Doctoral Program in Agricultural, Agri-Environmental
and Food Resources and Technologies

Introducing into Cultivation of the Medicinal Plant *Cistus albidus* L. for Optimized Production of Bioactive Compounds

A Dissertation

by

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In witness whereof, I sign this document for all pertinent purposes, in Orihuela, on 15 September 2025.

Dr. Juana Fernández López, Coordinator of the Doctoral Program

This dissertation is dedicated to my mother and to my late father, who would have loved to see this project completed; and to my wife, for her patience and support.

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“Gut Ding will Weile haben”

(Old German proverb: good results take time and are worth waiting for)

ABSTRACT

Cistus albidus L. is a traditionally used Mediterranean medicinal plant known for its extensive profile of bioactive secondary metabolites, particularly polyphenols and terpenoids, which exhibit pharmacological potential. However, its wild harvesting raises concerns regarding sustainability, standardization, and biodiversity conservation. This study aims to explore the domestication potential of *C. albidus* as a cultivated medicinal plant by optimizing agronomic practices to enhance biomass production and the yield of bioactive compounds. This study investigates the effects of controlled cultivation conditions, including organic fertilization, mycorrhizal inoculation, and harvest timing, on phytochemical profiles and evaluates the species' germination and survival strategies in an ecological context.

A multi-phase approach was adopted, comprising germination trials, experimental cultures, and phytochemical analyses. Seed germination was assessed under different treatments simulating natural disturbances (wildfire and water runoff) to determine key factors influencing establishment success. Cultivation trials included organic fertilization and mycorrhizal inoculation (with *Rhizophagus* and *Glomus* spp.) to evaluate their effects on plant growth and metabolite accumulation. Phytochemical profiling was conducted using Ultra-High-Performance Liquid Chromatography (UHPLC), focusing on flavanols, ellagitannins, flavonols, phenolic acids, and secoiridoids, as well as on total phenolic content and antioxidant capacity. Data were analyzed using statistical models to determine correlations between treatments, agronomic yields, harvest timing, and metabolite profiles.

The results indicate that germination success is significantly influenced by hydrological processes and seed coat scarification, highlighting the species' adaptation to disturbance-driven environments. In cultivation trials, organic fertilization enhanced vegetative growth, whereas mycorrhizal inoculation triggered a stress response, leading to increased accumulation of bioactive polyphenols. Notably, flavan-3-ols reach their peak concentrations during early harvest periods, whereas phenolic acids in autumn, and ellagitannins and flavonols peak later in the plant's developmental cycle. The combination of organic fertilization and early spring harvesting schedules was found to be the most effective strategy for optimizing both biomass and phytochemical yield.

These findings confirm that *C. albidus* can be successfully domesticated under controlled agricultural conditions while maintaining high concentrations of pharmacologically relevant compounds. The study demonstrates that agronomic factors significantly influence secondary metabolite biosynthesis, and that targeted cultivation strategies can enhance the production of specific bioactive compounds. The research highlights the potential of *C. albidus* as a sustainable source of plant-based pharmaceuticals, addressing both ecological conservation and industrial standardization challenges. Future research should focus on long-term cultivation effects, genetic regulation of metabolite biosynthesis, and further refinement of agronomic practices to maximize medicinal applications.

RESUMEN

Cistus albidus L. es una planta medicinal mediterránea empleada tradicionalmente y conocida por su amplio perfil de metabolitos secundarios bioactivos, en particular polifenoles y terpenoides, con un alto potencial farmacológico. Sin embargo, su recolección en estado silvestre plantea desafíos en términos de sostenibilidad, estandarización y conservación de la biodiversidad. Este estudio tiene como objetivo explorar el potencial para el cultivo de *C. albidus* como planta medicinal cultivada, mediante la optimización de prácticas agronómicas para mejorar tanto la producción de biomasa como el rendimiento de obtención de compuestos bioactivos. En particular, se ha investigado los efectos de condiciones de cultivo controladas, incluyendo la fertilización orgánica, la inoculación micorrízica y el momento de la cosecha, sobre los perfiles fitoquímicos, y se ha evaluado las estrategias de germinación y supervivencia de la especie en un contexto ecológico.

Durante el trabajo se ha adoptó un enfoque multifase que incluyó ensayos de germinación, cultivos experimentales y análisis fitoquímicos. La germinación de las semillas se evaluó bajo distintos tratamientos que simulaban perturbaciones naturales (incendios forestales y escorrentía) con el fin de identificar los factores clave que influyen en el éxito del establecimiento. Los ensayos de cultivo incluyeron la aplicación de fertilización orgánica y la inoculación con hongos micorrízicos (*Rhizophagus* y *Glomus* spp.) para evaluar sus efectos sobre el crecimiento vegetal y la acumulación de metabolitos secundarios. El perfil fitoquímico se determinó mediante cromatografía líquida de ultraalta resolución (UHPLC), centrándose en la cuantificación de flavanoles, elagitaninos, flavonoles, ácidos fenólicos y secoiridoides, así como en la determinación del contenido fenólico total y la capacidad antioxidante. Los datos fueron analizados mediante modelos estadísticos para evaluar las correlaciones entre los tratamientos, el rendimiento agronómico, el momento de la cosecha y la composición fitoquímica.

Los resultados indican que el éxito germinativo está significativamente influenciado por los procesos hidrológicos y la escarificación de la cubierta seminal, lo que subraya la adaptación de la especie a entornos caracterizados por condiciones ambientales alteradas. En los ensayos de cultivo, la fertilización orgánica promovió el crecimiento vegetativo, mientras que la inoculación micorrízica indujo una respuesta de estrés que favoreció una mayor acumulación de polifenoles bioactivos. Específicamente, se observó que los flavan-3-oles alcanzan sus concentraciones máximas en las primeras etapas de cosecha, mientras que los ácidos fenólicos aumentan en otoño, y los elagitaninos y flavonoles presentan su mayor acumulación en fases más avanzadas del desarrollo de la planta. La combinación de fertilización orgánica con cosechas programadas a inicios de la primavera resultó ser la estrategia más eficaz para optimizar tanto la producción de biomasa como el rendimiento fitoquímico.

Estos hallazgos confirman que *C. albidus* puede ser cultivado con éxito en condiciones agrícolas controladas, manteniendo elevadas concentraciones de compuestos farmacológicamente relevantes. El estudio demuestra que los factores agronómicos ejercen una influencia significativa sobre la biosíntesis de metabolitos secundarios y que la implementación de estrategias de cultivo dirigidas permite optimizar la producción de compuestos bioactivos específicos. La investigación resalta el potencial de *C. albidus* como fuente sostenible de productos farmacéuticos de origen vegetal, abordando tanto los desafíos asociados con la conservación ecológica como los requerimientos de estandarización industrial. Se recomienda que futuras investigaciones se centren en el impacto a largo plazo de las estrategias de cultivo, en la regulación genética de la biosíntesis de metabolitos y en el perfeccionamiento de las prácticas agronómicas para maximizar su aplicación en el ámbito medicinal.

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VI. LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ASA	Acetylsalicylic acid
ASD	Autism spectrum disorder
BBB	Blood brain barrier
CBF	Cerebral blood flow
CNB	Carbon/nitrogen balance
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
CONT	Control plants
COX	Cyclooxygenase
DA	Dopamine
DAD	Diode array detector
DAT	Dopamine Transporter
DDPH	2,2-diphenyl-1-picrylhydrazyl
DMEM/F12	Dulbecco's modified eagle medium: nutrient mixture
F-12 DMSO	Dimethylsulfoxide
ECM	Ectomycorrhizae
ELISA	Enzyme-linked immunosorbent assay
ESI	Electrospray ionization
ESI-MS	Electrospray ionization mass spectrometry
ESI-TOF-MS	Electrospray ionization time-of-flight mass spectrometry
FAAH	Fatty acid amide hydrolase
FERT	Fertilized plants
FERT+INOC	Fertilized and inoculated plants
GA	Gallic acid
GAE	Gallic acid equivalent
GA4	Gibberellic acid
GA24	Precursor of gibberellic acid GA4
HDAC1	Histon deacetylase 1
HHDP	Hexahydroxydiphenic acid
HHDP-Glc	Hexahydroxydiphenoyl-D-glucose
HPLC	High-performance liquid chromatography
IC_{50}	Median inhibitory concentration
IL-1	Interleukin 1
IL-6	Interleukin 6
INOC	Inoculated plants
iNOS	Inducible nitric oxide synthase

ITS	Internal transcribed spacer
JA	Jasmonic acid
JA-Ile	Jasmonoyl-isoleucine
LC	Liquid chromatography
MAO	Monoamine oxidase
MAPK	Mitogen-activated protein kinase
MC	Myricetin
MS	Mass spectrometer
m/z	Mass over charge ratio
NDD	Neurodegenerative disease
OXPHOS	Oxidative phosphorylation
PD	Parkinson Disease
PDA	Photo diode array
PGPR	Plant growth-promoting rhizobacteria
QC	Querecetin (3,3′,4′,5,7-pentahydroxyflavone)
QTRAP	Quadrupole ion trap
RCF	Relative centrifugal force
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RT	Retention time
SEM	Standard error of the mean
SIN-1	3-Morpholinosydnonimine (Peroxynitrite Donor)
TEAC	Trolox equivalent antioxidant capacity
TEFAM	Mitochondrial Transcription Factor A
TJ	Tight junctions
TNF-α	Tumor Necrosis Factor Alpha
TROLOX	6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (hydrophilic analogue of vitamin E)
UPLC	Ultra-performance liquid chromatography
WST-1	Water-soluble tetrazolium salt

0. FRAMEWORK OF THE DISSERTATION

0.1. MOTIVATION AND RELEVANCE

This thesis is part of an interdisciplinary project aimed at developing a plant-based medicine for the treatment of symptoms associated with Attention Deficit Hyperactivity Disorder (ADHD), with the wild-growing species *C. albidus* playing a central role. Historically, this plant has been successfully used in traditional Mediterranean medicine, particularly in treating children exhibiting symptoms similar to those of ADHD, such as inattention, impulsivity, and hyperactivity (Raus de Baviera et al., unpublished). Building on the significance of preliminary findings, this work is driven by the need to further explore the neuropharmacological properties of *C. albidus* laying the groundwork for future studies.

Therefore, this dissertation aims to provide foundation studies that further investigate and elucidate the pharmacological effects and their modulation by ecological and agronomic factors. The domestication of *C. albidus* presents an opportunity to address several critical challenges in both pharmaceutical and ecological domains. This plant has long been valued for its medicinal properties, and its phytochemical richness, particularly its high concentrations of phenolic compounds and terpenoids, has garnered increasing scientific interest. However, the growing demand for natural remedies places significant pressure on wild populations of medicinal plants, leading to concerns about overharvesting and habitat degradation.

Domestication offers a sustainable solution by enabling the controlled cultivation of *C. albidus*, ensuring a reliable and consistent supply of high-quality bioactive compounds. This approach not only addresses the pharmaceutical industry's need for standardized plant material but also helps conserve wild populations and maintain biodiversity. Additionally, *C. albidus* thrives in nutrient-poor soils and under drought conditions, making it an ideal candidate for sustainable cultivation in marginal lands, where conventional agriculture is less viable.

By advancing the domestication of *C. albidus*, this research provides a model for balancing commercial demands with ecological responsibility. It promotes sustainable agricultural practices that contribute to environmental conservation while also supporting the development of high-value medicinal products. Ultimately, this study seeks to ensure that medicinal plant resources remain available for future generations, meeting both present and future needs in a responsible and sustainable manner.

While this study focuses specifically on *C. albidus*, its findings have broader implications for the sustainable cultivation of other medicinal plants. The strategies developed for optimizing the cultivation of *C. albidus*, such as improving phytochemical and vegetative yield and managing environmental conditions, can serve as models for other species facing similar sustainability challenges. The approaches explored in this research are aimed to provide a framework for balancing the pharmaceutical industry's demand for high-quality plant material with the need of ecological sustainability.

0.2. RESEARCH OBJECTIVES

The primary objective of this dissertation is to explore the domestication potential of *C. albidus* as a sustainable medicinal plant, with a focus on optimizing its cultivation to enhance both its pharmacological properties and vegetative biomass. This study seeks to develop cultivation practices that not only improve the yield and quality of bioactive compounds but also promote a cultivation approach closely aligned with nature, such as agroforestry, to preserve the plant's genetic variability. By addressing both practical and scientific challenges, the study aims to contribute to the conservation of wild populations while also meeting the growing demand for high-quality, sustainable, plant-based medicines.

Specifically, the studies seek to:

1. **Pharmacological Assessment**: Review the pharmacological properties of *C. albidus*, with a particular focus on the pharmacological potential of this species for modern pharmaceutical applications.

2. **Optimize Cultivation Conditions:** Identify the ideal environmental and agricultural parameters, including AMF inoculation, organic fertilization, water management, and environmental stress, to enhance the growth of both vegetative biomass and key bioactive compounds in *C. albidus*, with a particular focus on polyphenols.

3. **Phytochemical Profiling**: Analyze the phytochemical composition of *C. albidus* cultivated under different conditions to assess the variability and consistency in the production of bioactive compounds during a vegetative cycle. Advanced analytical techniques, such as Ultra-High-Performance Liquid Chromatography (UHPLC) will be employed to ensure accurate identification of key compounds.

4. **Promote Sustainable Cultivation Practices**: Explore cultivation methods, such as organic farming, that maintain the plant's genetic variability and ensure ecological sustainability, thus aligning with natural growth conditions.

0.3. KEY RESEARCH QUESTIONS

- How do different environmental conditions affect germination of this species?
- How can cultivation conditions be optimized to increase both the yield and quality of vegetative biomass and bioactive compounds in *C. albidus*?

- What is the phytochemical variability of *C. albidus* under different cultivation environments, and which insights can be gained from this for the production of pharmacological interesting compounds?
- What are the key bioactive compounds in *C. albidus*, particularly in relation to biotic and abiotic stress, and optimal nutrient supply?

0.4. HYPOTHESES

1. *C. albidus* is not a strict pyrophyte but has developed a flexible survival strategy, where its adaptation to riparian habitats inherently includes pyrophytic traits. This enables the plant to adjust to changing environmental conditions. Its extensive phytochemical profile plays a key role in its resilience under extreme conditions, such as those found in the Mediterranean climate.

2. Controlled cultivation of *C. albidus* will enhance both vegetative biomass and the concentration of key bioactive compounds, with inoculation treatments expected to further boost phytochemical production with two important implications: (1) targeted agronomic practices offer a strategic means to modulate the plant's phytochemical composition, thereby enhancing its medicinal properties for specific therapeutic purposes; and (2) the pharmacological activity of *C. albidus* may depend on these cultural practices resulting in significant variations in therapeutic efficacy.

0.5. STRUCTURE

To answer the key questions and prove the hypothesis, this dissertation consists in three comprehensive phases and is organized into five chapters, each addressing different aspects of the domestication of *C. albidus* as a medicinal plant and its potential for pharmaceutical applications. The structure is designed to guide the reader through the research process, from the initial background to the experimental methods, results, and conclusions.

Chapter 1: General Introduction

This chapter provides a broad overview of the significance of medicinal plants in human history and the importance of domestication for sustainable use. It introduces *C. albidus* and its traditional uses, highlighting its phytochemical importance and pharmacological potential.

Chapter 2: Traditional and scientific background

In this chapter, a comprehensive review of the existing literature is presented, covering the phytochemical composition and known pharmacological properties of *C. albidus,* as well as its systematic classification and distribution. The review also examines the state of research on extraction methods of medicinal plants, focusing further on the pharmaceutical potential.

Chapter 3: Germination and survival strategies in an ecological context

The germination behaviour of *C. albidus* seeds is explored in detail in this chapter. The chapter reports the germination results of in vitro and outdoor conditions, such as water runoff and wildfire simulations, assessing the germination and viability of seeds and the establishment of seedlings. Furthermore, conclusions are presented that are crucial for the successful cultivation as well as the long-term survival of *C. albidus*.

Chapter 4: Relationships between agronomical factors and phytochemical profile

This chapter presents the results of vegetative and phytochemical analysis, focusing on the identification and quantification of key bioactive compounds. It compares the effects of different cultivation conditions on the concentrations of these compounds and vegetative yields and assesses their consistency across samples over one vegetative cycle.

Chapter 5: General Discussion and Conclusion

The final chapter synthesizes the findings from the previous chapters, discussing their implications for the domestication and use of *C. albidus* in modern medicine. It revisits the research questions and hypotheses, evaluating how well they were addressed by the study. The chapter concludes with recommendations for future research and practical applications of the findings in both agriculture and the pharmaceutical industry.

Chapter 1

General Introduction

Significance of Medicinal Plants in Human History and the Importance of Domestication for Sustainable Use – Introduction to *Cistus albidus* L.

1. GENERAL INTRODUCTION

1.1. BACKGROUND

Medicinal plants have supported human health since pre-history, providing valuable compounds for traditional remedies and modern phytotherapy. The use of medicinal plants dates back to the origins of humanity. There is evidence suggesting that approximately 50,000 years ago Neanderthals have possessed extensive knowledge of medicinal plants (Callaway, 2017).

For millennia, medicinal plants were gathered in the wild without major ecological consequences, but today, rising global demand and new sustainability concerns put many of these species under severe pressure (Hamilton, 2004; Sharma & Kala, 2018; van Wyk & Prinsloo, 2018). Nearly one-third of known vascular plant species are at risk of extinction, with medicinal plants particularly vulnerable due to habitat destruction and unsustainable harvesting practices (Asigbaase et al., 2023; Nic Lughadha et al., 2020). The 1988 Chiang-Mai Declaration highlighted the need for sustainable use of medicinal plants, leading to the 1993 “Guidelines on the Conservation of Medicinal Plants,” advocating for cultivation over wild collection and sustainable harvesting (Akerele et al., 1991; Brinckmann et al., 2022).

Despite these guidelines, cultivation still lags behind wild collection. Liu et al. reviewed 32 reports that included information on 193 plant species that are considered threatened being commercially cultivated. According to these reports, 82% of these species still rely on wild plant collection, either periodically or continuously, to maintain their cultivation (Liu et al., 2019).

Early surveys suggested that only ~900 of the world’s 72,000 medicinal species were under cultivation (Schippmann et al. 2006; Mulliken and Inskipp 2006). A 2022 update, however, lists 3,227 cultivated taxa from 235 different plant families are already being cultivated (Brinckmann et al., 2022). In Europe, approximately 90% of the 1,300 medicinal plant species used are at least still partially collected from the wild (Balunas & Kinghorn, 2005; Brinckmann et al., 2022; Chen et al., 2016; Ramawat, 2019; Ramawat & Goyal, 2019). In Spain, a biodiversity hotspot, 1,376 medicinal plant species are traditionally used, representing 22% of its native flora (Mateo-Martín et al., 2023) while most of these plants are abundant, with less than 10% being endangered (Moreno, 2010).

As the demand for natural remedies grows, the need to explore sustainable alternatives to wild harvesting becomes evident. Controlled cultivation of medicinal plants has become increasingly important to meet the increasing demand while protecting biodiversity (Chen et al., 2016). The process of adapting wild species to cultivation is known as domestication and has a deep-rooted history and is considered one of the most crucial advances in human evolution. Domestication began approximately 11,700 years ago, following the last major ice age, when human societies transitioned from a nomadic hunter-gatherer lifestyle to the deliberate cultivation of crops, marking the onset of agriculture (Diamond, 2002; Larson et al., 2014).

Against this backdrop of ecological strain and pharmacological demand, the Mediterranean shrub *C. albidus* offers a compelling case study.

1.2. *Cistus albidus* L.

C. albidus, commonly known as white rockrose, is a perennial shrub native to the Mediterranean region, widely distributed across Southern Europe and North Africa (Guzmán & Vargas, 2005). It thrives in dry, rocky soils characteristic of Mediterranean ecosystems and is well-adapted to harsh environmental conditions, including drought and nutrient-poor soils, making it resilient in the face of climate change and habitat degradation (Juhren, 1966; Munné-Bosch et al., 2003).

The genus name *Cistus* may derive from the ancient Greek term *kistē* (κίστη), later adopted as *cista* in Latin. It denotes a sacred container used in religious rites, particularly within mystery cults such as those of Demeter and Dionysus (Burkert, 1987). Its symbolic significance may be linked to the morphology of seed capsules, or alternatively, it may have originated from ritualistic practices associated with these religious traditions, with a plausible connection to the enclosure of a (sacred) area by *Cistus* spp., as these plants can form an impenetrable thicket. This hypothesis is reinforced by the frequent occurrence of *C. albidus* on elevated terrains historically linked to pre-Christian sanctuaries. Given that *C. albidus* primarily disperses downstream via hydrochory, its persistent presence on ridges suggests a strong likelihood of anthropogenic introduction, possibly reflecting its ritual or symbolic importance in ancient religious contexts. In addition to the plant's extense phytochemical profile and traditionally reported psychoactive properties, the fact that it was reported to be smoked traditionally as a substitute for tobacco (Ledesma, 2004; Maccioni et al., 2007; Segarra i Durà, 2008) suggests a long-standing cultural or ritualistic association, potentially linked to a former religious significance.

In traditional Mediterranean folk medicine, *C. albidus* has long been valued for its healing properties, particularly in regions with limited access to formal healthcare (Mulet Pascual, 1991). Its leaves and flowers have been used in rural communities in infusions and decoctions to treat ailments such as respiratory infections, gastrointestinal disorders, neurological alterations, and skin conditions (Bouyahya et al., 2017; Martínez-Lirola et al., 1996; Mulet Pascual, 1991; Pardo de Santayana, 2014).

The therapeutic effects of *C. albidus* are largely attributed to its rich phytochemical composition, particularly its concentrations of polyphenols and terpenoids. Especially flavonoids were shown to provide potent antioxidant effects (Gonçalves et al., 2013; Sousa et al., 2007), helping to neutralize free radicals and reduce oxidative stress, key factors in chronic diseases like cardiovascular and neurodegenerative disorders (Mattioli et al., 2020). In addition to its antioxidant properties, the plant also exhibits significant anti-inflammatory and antimicrobial activities, making it a valuable resource for both traditional and modern herbal medicine (Bechlaghem et al., 2019; Tahiri et al., 2017). Based on the underlying project of this dissertation, the neuropharmacological properties of *C. albidus* are hypothesized to result from the synergistic effects of various terpenoids combined with several phenolic compounds, including ellagitannins, flavan-3-ols, flavonols, and phenolic acids.

Building on its traditional uses, recent scientific studies have validated the therapeutic potential of *C. albidus*. Research has demonstrated its antimicrobial, anti-inflammatory, and antioxidant properties, confirming its effectiveness in treating infections and chronic diseases (Bouyahya et al., 2017; Mastino et al., 2021; Tahiri et al., 2017; Tomás-Menor et al., 2013). The plant’s extracts have shown activity against several microbial pathogens including *Staphylococcus aureus* and *Escherichia coli* and have proven antifungal effects, particularly against *Candida albicans* (Bechlaghem et al., 2019; Boy et al., 2021). These properties are particularly important in addressing contemporary health challenges, such as rising antibiotic resistance and chronic inflammatory diseases.

Beyond its medicinal applications, *C. albidus* offers significant ecological benefits. Its ability to thrive in drought-prone and nutrient-poor soils positions it as an important species for promoting environmental sustainability, particularly in the face of climate change and land degradation. As an autochthonous species, *C. albidus* contributes to soil stabilization, nutrient cycling, and biodiversity enhancement, forming a crucial part of Mediterranean ecosystem succession, as it helps create conditions that allow other plant species to establish over time (Castells et al., 2004; Castells & Peñuelas, 2003). By supporting pollinators, and protecting native flora and fauna, this species plays a vital role in enhancing ecosystem resilience (Hernández-Castellano et al., 2020; Parra et al., 2016; Pérez-Llorca et al., 2021). Its role in these ecosystems underscores its ecological significance in regenerating and maintaining Mediterranean habitats. Moreover, *C. albidus* enhances soil quality through its contribution to organic matter and nutrient cycling, supporting a diverse range of microorganisms and other plant species. Further, it was shown that this species is suitable for phytostabilization of heavy metal contaminated soils (El Mamoun et al., 2020; Parra et al., 2016). Its high adaptability and regeneration capabilities make this species an essential component in efforts to restore biodiversity and ecosystem functionality in Mediterranean shrublands, often serving as a keystone species in fire-prone and drought-affected habitats (Alguacil et al., 2003; Trabaud & Renard, 1999).

This dual role in healthcare and environmental conservation underscores its potential as a model species for the sustainable cultivation of medicinal plants.

1.3. DOMESTICATION

Purugganan described domestication as a co-evolutionary process where wild plants are brought into cultivation by humans, leading to new species or differentiated populations critical for human survival (Purugganan, 2019).

More generally, domestication may be described as the adaptation of wild species to promote new forms of plants to meet human needs through intentional selection. This process improves the adaptation of plants to cultivation, increases yields, and enhances other desirable traits.

Wild plant domestication has been primarily motivated by the need for food security, medicinal purposes, cultural preservation, economic benefit, and in some cases, aesthetic appreciation. This process is heavily influenced by ecological, cultural, and economic factors, which continue to shape the agricultural landscape worldwide (Gessert, 1997; Hawkes, 2008; Msuya et al., 2008; Vodouhè & Dansi, 2012).

Medicinal plant domestication involves the cultivation and selective breeding of wild plants with therapeutic properties to enhance desirable traits and ensure a consistent supply for medicinal use. This specialized form of agriculture has been crucial for both traditional and modern healthcare systems, addressing several critical needs.

Breeding programs typically start with mass selection, followed by individual selection to optimize species-specific traits (Bertoldo et al., 2014). Experience shows that, for medicinal plants, it takes several years to select individuals with desirable concentrations of secondary metabolites and to develop effective cultivation methods (Kumar et al., 2019; Singh et al., 2019). Given the high variability in wild plants, targeted selection can be informed by experimental results. Cultivation challenges are gradually resolved through experimental work in close collaboration with scientific institutions, relying on knowledge of plant biology, habitat requirements, and analogies from other cultivated species.

1.3.1. Advantages of domesticating *Cistus albidus*

The domestication of *C. albidus* marks a pivotal development in medicinal plant research. Transitioning from wild collection to systematic cultivation offers substantial benefits, ranging from enhanced pharmacological applications to contributions to environmental sustainability and biodiversity conservation.

1.3.1.1. Optimization of Phytochemical Quality

A primary advantage of domestication lies in the ability to optimize the phytochemical profile of *C. albidus*. Wild populations exhibit considerable variability in the concentration of key bioactive compounds, influenced by factors such as soil composition, microclimate, and seasonal dynamics (Fadel et al., 2020; Palá-Paúl et al., 2005). Controlled cultivation enables the stabilization, standarization and enhancement of these phytochemicals through the precise manipulation of growth conditions, including light intensity, temperature, humidity, and soil nutrients (Toscano et al., 2019).

Moreover, domestication facilitates the application of elicitation strategies, wherein mild abiotic stressors—such as controlled drought or UV exposure—are applied to stimulate secondary metabolite production (Cebulak et al., 2019; Jeyasri et al., 2023). These interventions can significantly enhance the concentration of pharmacologically active constituents.

Selective breeding further allows for the propagation of specific chemotypes, thereby concentrating desired compounds responsible for therapeutic effects (Grant et al., 2006; Grant & Incoll, 2005). Advances in plant breeding, including hybridization and molecular selection techniques, can improve the yield, potency, and stability of bioactive constituents (Caseys et al., 2015; Klčová et al., 2024).

Importantly, cultivation minimizes contamination risks from heavy metals, pesticides, and pathogens common in wild-harvested material (Hlihor et al., 2022), ensuring compliance with pharmaceutical-grade quality standards (Nasim et al., 2022; Wang et al., 2023).

Finally, domestication opens avenues to enhance the bioavailability of *C. albidus* compounds. By influencing the biosynthesis towards more soluble and absorbable forms, such as aglycones, therapeutic efficacy can be improved (Manach et al., 2005).

1.3.1.2. Standardization and Industrial Scalability

The pharmaceutical and nutraceutical industries require consistent, scalable production of plant material. Domestication addresses this need by enabling large-scale cultivation while maintaining batch-to-batch uniformity in pharmacological properties (Arden et al., 2021). Standardized production is critical for clinical research, regulatory approval processes, and the formulation of reliable herbal medicines.

Furthermore, cultivation practices can be tailored to optimize synergistic phytochemical interactions. For instance, while curcumin alone exhibits limited antibacterial activity, its efficacy is greatly enhanced in combination with EGCG (Betts & Wareham, 2014). Such synergistic principles, also observed in related species (Tomás-Menor et al., 2015), can be harnessed through selective breeding and cultivation strategies.

1.3.1.3. Contributions to Environmental Sustainability and Biodiversity

The domestication of *C. albidus* presents significant ecological advantages. Wild harvesting exerts pressure on natural populations, leading to habitat degradation and genetic erosion. Cultivation alleviates this pressure, supporting the conservation of native ecosystems (El Mamoun et al., 2020; Pérez-Llorca et al., 2021).

Moreover, *C. albidus* is well-suited for the restoration of degraded or marginal lands. Its robust root system stabilizes soils, prevents erosion, and enhances soil fertility, facilitating the recovery of native vegetation (Alguacil et al., 2003; Parra et al., 2016). The species also supports pollinator biodiversity through its highly attractive flowers (Blasco & Mateu, 1995; Hernández-

Castellano et al., 2020). By integrating *C. albidus* into agricultural landscapes, pollinator habitats can be strengthened, promoting broader ecosystem health.

As a resilient Mediterranean native, *C. albidus* can help counteract the spread of invasive species, particularly through allelopathic interactions that suppress competitor growth (Brasseur et al., 2024; Robles et al., 1999). Additionally, its capacity for carbon sequestration contributes to climate change mitigation efforts (Oliveira & Peñuelas, 2002; Shang et al., 2024), while its drought tolerance positions it as a valuable resource for climate-resilient agriculture (Casadesús et al., 2021, 2022). Establishing buffer zones with *C. albidus* around protected areas can further enhance landscape connectivity and safeguard ecological integrity (Kuglerová et al., 2014). Integration into agroforestry systems offers complementary benefits for soil health, water retention, and biodiversity conservation (Willmott et al., 2023). Lastly, domestication initiatives should be accompanied by ex-situ conservation strategies, such as seed banking, to preserve the species' genetic diversity and ensure long-term adaptive capacity (Salgotra & Chauhan, 2023).

1.3.1.4. Advancing Scientific Research and Innovation

The domestication of *C. albidus* provides a robust platform for advancing scientific research across disciplines. With a rich history in traditional medicine (Alarcón et al., 2015; Carrió & Vallès, 2012), the species offers opportunities to scientifically validate and optimize its ethnopharmacological uses (Turner, 2007).

Domesticated populations enable detailed investigations into phytochemical pathways, genetic adaptations, and mechanisms of action, supporting innovation in drug development, sustainable agriculture, and plant biology (Bechlaghem et al., 2019; Elbouzidi et al., 2024; Parra et al., 2016).

Moreover, *C. albidus* serves as an ideal model for systems biology approaches, integrating genomics, transcriptomics, proteomics, and metabolomics to elucidate complex biochemical networks (Luo et al., 2022).

Ultimately, promoting the domestication and scientific exploration of *C. albidus* fosters greater awareness of the ecological and medicinal importance of native plant species. As Davis and Choisy (2024) aptly stated, “medicinal plant species are not just chemical factories for extraction and exploitation. Rather, they may be symbiotic partners that have shaped modern societies, improved human health, and extended human lifespans.”

1.3.2. Challenges in the Cultivation of *Cistus albidus*

While the domestication of *C. albidus* offers considerable advantages, it also presents several specific challenges related to the plant’s ecological requirements, sensitivity to environmental changes, and the impact of these factors on the production of bioactive compounds.

One primary challenge is replicating the natural conditions in which *C. albidus* thrives. As a native to the Mediterranean region, this plant is highly adapted to specific environmental conditions (Munné-Bosch et al., 2003), including poor, rocky soils and long periods of drought (Durán et al., 2024). This adaptability, while beneficial in the wild, complicates cultivation in agricultural systems that may not easily replicate these conditions, particularly in regions outside the Mediterranean. Inadequate soil conditions or improper irrigation can negatively affect the plant's growth and reduce its yield. Furthermore, the plant's need for prolonged dry periods poses challenges for irrigation practices, which may lead to root rot or other diseases if overwatering occurs. Thus, optimizing soil and water management in cultivation is essential but challenging.

Another critical issue is maintaining genetic diversity in domesticated populations. Wild populations of *C. albidus* exhibit a high degree of genetic variability (Grant et al., 2006; Lukas, Jovanovic, et al., 2021), which is critical for the plant's resilience to environmental changes and diseases. However, during domestication, selective breeding for certain traits—such as higher yields of bioactive compounds or faster growth—can lead to genetic homogenization (Li et al., 2012). This loss of genetic diversity may make cultivated populations more vulnerable to pests, diseases, or climate variations, ultimately threatening the long-term viability of the crop (Fu, 2006).

The production of key bioactive compounds, such as polyphenols and terpenoids, is heavily influenced by environmental stressors in the wild, such as nutrient deficiency, drought, and interactions with other species (Kumar et al., 2023; Šamec et al., 2021). Controlled cultivation, by mitigating these stressors, may inadvertently reduce phytochemical concentrations and thus compromise the pharmacological quality of the plant. Achieving a balance between optimal growth and the induction of bioactive compound production remains a central challenge.

Despite these obstacles, the domestication of *C. albidus* holds substantial promise. With careful management of soil conditions, genetic resources, and cultivation strategies, the species can meet the increasing demand for high-quality medicinal products while contributing to sustainable agricultural practices and ecological conservation.

1.3.3. Legislation

The domestication and cultivation of *C. albidus* must comply with the European Union's regulatory framework governing medicinal plants. This framework is designed to ensure the safety, quality, and efficacy of herbal medicines through a combination of legal classifications, good practice guidelines, and quality standards (European Parliament and Council, 2001; European Parliament and Council, 2004).

A critical requirement is the adherence to Good Agricultural and Collection Practices (GACP) for starting materials of herbal origin (EMA, 2006). Compliance with GACP ensures the traceability, purity, and consistency of raw plant materials, thereby aligning cultivation practices with pharmaceutical industry expectations. In addition, domesticated *C. albidus* must meet the quality specifications established by the European Pharmacopoeia, particularly regarding the content of active ingredients and limits for contaminants (Council of Europe, 2023).

These regulatory standards not only facilitate the standardized production of high-quality medicinal plants but also promote sustainable and environmentally responsible cultivation practices. For *C. albidus*, aligning domestication efforts with these requirements is essential for successful integration into the pharmaceutical and nutraceutical sectors.

1.3.4. Outlook - Economic Impact and Market Potential

The market for natural and plant-based medicinal products has been growing rapidly, driven by rising health consciousness, a strong consumer preference for organic and eco-friendly alternatives, and the increasing popularity of holistic healthcare solutions and traditional medicine systems (Chupina et al., 2023). There is also a notable rise in the adoption of herbal medicines for their perceived safety, fewer side effects compared to synthetic drugs (Lynch & Berry, 2007). Technological advancements in extraction and formulation processes have also contributed to the growth of this sector by enhancing the quality and efficacy of these products (Capaldi et al., 2024; Usman et al., 2023).

The global herbal medicine market was valued at approximately USD 216.40 billion in 2023 and is expected to reach around USD 437 billion by 2032 (Fortune Business Insights, 2024). Another estimate suggests a different starting point at USD 70.57 billion in 2023 reflecting differences in definitions and segmentation within the herbal medicine sector (Grand View Research, 2024). The global botanical and plant-derived drugs market is also projected to grow by USD 20.93 billion between 2023 and 2028 (Technavio, 2024), indicating robust expansion across related markets.

The market for herbal products and other natural remedies is expected to see considerable growth at a compound annual growth rate (CAGR) between 8.17% and 20.91% (Fortune Business Insights, 2024; Grand View Research, 2024; Technavio, 2024). The increasing trend toward organic and clean-label products will likely support the sustained demand for plant-based medicines globally (Chupina et al., 2023). Furthermore, enhanced regulatory frameworks and increased research and development activities targeting the improvement of herbal medicine formulations are key drivers expected to promote innovation and sustain market expansion (Trisilawati et al., 2020).

Nevertheless, the market faces challenges such as stringent regulations regarding product claims and quality standards, which can lead to higher compliance costs for manufacturers. At the same time, these regulatory demands promote the production of higher-quality and safer products, ultimately enhancing consumer trust and benefiting the industry in the long term (Singh, 2019; Wang et al., 2023).

The domestication of *C. albidus* could tap into this market trend with multiple economic benefits. The economic impact and market potential of *C. albidus* domestication are significant and multifaceted. Its role as a high-value ingredient in the cosmetics, nutraceutical, pharmaceutical and essential oils industries, combined with its contribution to sustainable agriculture, rural development, and ecological restoration, positions it as a versatile and profitable crop. With growing global demand for natural products and increasing focus on ecological sustainability, *C. albidus* has the potential to become a player in the modern economy, driving innovation and creating economic opportunities in multiple sectors.

The antioxidant and antimicrobial properties of *C. albidus* extracts make them highly desirable for the cosmetics and skincare industry (Gonçalves et al., 2013). Its active compounds, such as polyphenols, and within them flavonoids, are effective in anti-aging formulations, skin-soothing products, and natural preservatives (Domaszewska-Szostek et al., 2021). The demand for natural and plant-based ingredients in personal care products is growing rapidly (Ferreira et al., 2021) and may positioning *C. albidus* as a premium ingredient in this expanding market.

The global nutraceutical industry is witnessing significant growth as consumers increasingly seek dietary supplements derived from natural sources (Srivastava, 2018). *C. albidus* has promising potential in this sector due to its rich content of polyphenols, which are known for their health-promoting effects, such as boosting the immune system, reducing inflammation, and protecting against oxidative stress (Hussain et al., 2016). Its extracts could be developed into a range of nutraceutical products.

The essential oil of *C. albidus* only is obtained in low yields (Bechlaghem et al., 2019; Robles & Garzino, 1998). Domestication efforts that focus on enhancing the quality and yield of this oil may tap into the lucrative market for natural fragrances and aromatherapy products, where demand is steadily increasing (Reisch, 2019).

Cultivating *C. albidus* aligns well with the principles of sustainable and organic agriculture, which are becoming more important to consumers and regulatory bodies (Mohan et al., 2022; Pilipavičius et al., 2014). Organic farming of this species not only meets consumer demand for clean and eco-friendly products but also may increase profit margins for farmers and producers who focus on environmentally responsible practices. The cultivation of this species can contribute significantly to rural economic development, particularly in Mediterranean regions where agriculture is a primary source of income (Franklin-Lyons, 2021; Grandi et al., 2023). As the plant can grow in poor or even degraded soils and harsh conditions, it provides an alternative crop that does not compete with traditional agricultural products. Its production can lead to the creation of new jobs in farming, processing, and distribution, revitalizing rural communities and reducing the migration of people from these areas to urban centres (Khesht et al., 2021).

Further, the domestication may offer opportunities for crop diversification in agricultural systems, reducing farmers' reliance on a single crop and mitigating risks associated with market volatility or climate-related challenges. Diversified production systems are more resilient to economic and environmental stresses, providing stable income sources even in times of crop failure or market fluctuations (Vigani & Berry, 2018; Zampieri et al., 2020).

Given the increasing global demand for natural remedies and herbal products, *C. albidus* has significant export potential. Countries that cultivate this plant can position themselves as key suppliers in the international herbal medicine and phytotherapy markets. This can lead to increased foreign exchange earnings and strengthen the economic standing of countries where the plant is grown extensively.

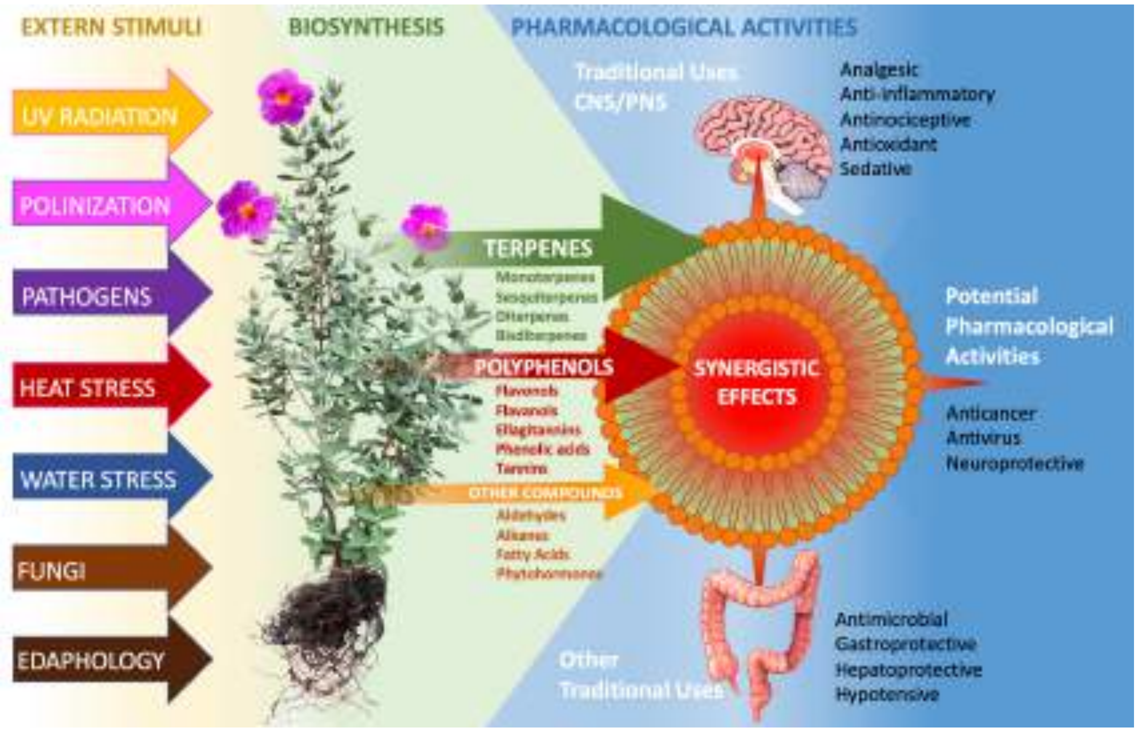
Chapter 2

Traditional and Scientific Background

Cistus albidus L.

A Traditional Mediterranean Medicinal Plant with Pharmacological Potential

2. TRADITIONAL AND SCIENTIFIC BACKGROUND



Graphical Abstract 1 *C. albidus*, is a Mediterranean medicinal plant rich in terpenes and polyphenols, whose traditional use is supported by scientific evidence indicating promising pharmacological potential, especially for neurodegenerative diseases, without reported toxicity.

Abstract

C. albidus L. (Cistaceae) is a medicinal plant that has been used therapeutically since ancient times in the Mediterranean basin for its important pharmacological properties. The ability of *C. albidus* to produce large quantities of a wide range of natural metabolites makes it an attractive source of raw material. The main constituents with bioactive functions that exert pharmacological effects are terpenes and polyphenols, with more than 200 identified compounds. The purpose of this review is to offer a detailed account of the botanical, ethnological, phytochemical, and pharmacological characteristics of *C. albidus* with the aim of encouraging additional pharmaceutical investigations into the potential therapeutic benefits of this medicinal plant.

This review was carried out using organized searches of the available literature up to July 2023. A detailed analysis of *C. albidus* confirms its traditional use as a medicinal plant. The outcome of several studies suggests a deeper involvement of certain polyphenols and terpenes in multiple mechanisms such as inflammation and pain, with a potential application focus on neurodegenerative diseases and disorders. Other diseases such as prostate cancer and leukaemia have already been researched with promising results for this plant, for which no intoxication has been reported in humans.

Keywords

C. albidus; phytochemistry; pharmacology; polyphenols; terpenes; traditional uses.

2.1. INTRODUCTION

C. albidus L., is one of the approximately 20 species of the *Cistus* genus (B. Guzmán & Vargas, 2005). The genus' name is derived from the ancient Greek term *kistos* (Schubert & Wagner, 1984). It is supposed that the name alludes to the woody capsule fruits. Evergreen in its Mediterranean homeland and between 50 and 250 centimetres tall (Schmidt & Schmidt, 1999), this shrub is called *albidus,* not because of the colour of its flowers, but because its leaves are finely covered with white hair (trichomes) (Coombes, 1994). For its optimal development, it needs calcareous, sandy or siliceous soils, as occurs in the *garrigue* of the Mediterranean (Barrajón-Catalán et al., 2011; Ormeño et al., 2008). Here it can grow in large groups (known as *jarales* in Spanish; Figure 2-1) and sometimes invade adjoining areas. It does not make high demands on the soil in terms of nutrients (Ormeño et al., 2008), but it needs permeability as it does not tolerate stagnant soils.

The characteristic feature of *C. albidus* is that its leaves are covered on both sides with dense hairiness made up of a combination of glandular and non-glandular trichomes (Figure 2-2). The glandular trichomes can be stellate or solitary elongated and produce and secrete a resin rich in metabolites of pharmacological interest (Gülz et al., 1996), such as flavonoid aglycones, glycosides and terpenoids, including the characteristic labdane-type diterpenes as described in Table 2-1. It is because of these compounds that this species was traditionally used in popular medicine according to its pharmacological action as anti-inflammatory, antimicrobial, antinociceptive and sedative (Mulet Pascual, 1991; Pardo de Santayana, 2014; Verde et al., 2008).

Figure 2-1 Typical Mediterranean landscape with a predominance of *C. albidus*, called jaral (left). Detail of flowers and leaves of *C. albidus* in spring (right) (Raus et al., 2023).

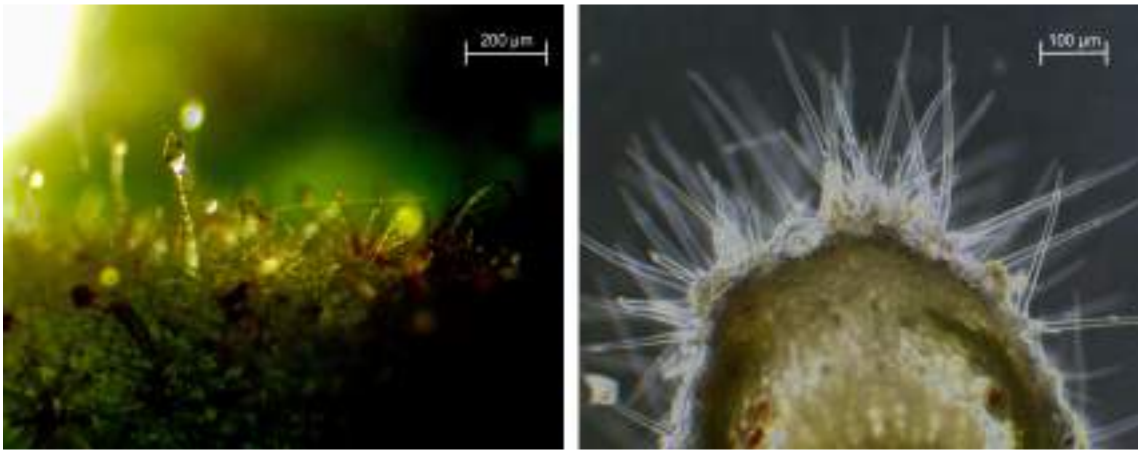


Figure 2-2 Trichomes: Glandular trichomes with secretion of bioactive compounds on their tops (left). Stellar trichomes covering the central vein of a leave (right). Images were captured by Raus et al. (2023) using a Swift microscope, model SW380T-SC500-5PBC (M TEC USA Inc., Tschertz, TX, USA).

Currently its use as a medicinal plant is vestigial, however, its phytochemical composition, especially the combination between some terpenoids and polyphenols, makes it a promising species with many pharmacological activities. Pharmacological studies on extracts of *C. albidus* have shown their antioxidant, antibacterial and antifungal (Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021; Mastino et al., 2021), antinociceptive (Tahiri et al., 2017) and anticarcinogenic (Barrajón-Catalán et al., 2011; Makabe et al., 2016) activity, in addition to other potential activities discussed later in this review.

But nowadays *C. albidus* is known more for its ability to withstand severe summer stress situations to repopulate degenerate areas (Centenaro et al., 2023; Civeyrel et al., 2011; El Mamoun et al., 2020; Lucas-Borja et al., 2022), than for its important pharmacological properties. Due to its ability to produce large amounts of secondary metabolites, it becomes an attractive model for the elucidation of the biosynthetic pathways involved in resisting climatic adversities (Brossa et al., 2015; Casadesús et al., 2021; B. Guzmán et al., 2009; Hernández et al., 2015). The pathways that lead to the production of terpenes and polyphenols have been investigated on many occasions and the substances were analysed in isolation. However, in the author´s opinion, the potential of *C. albidus* does not lie in the independent substances that compose it, but in the interaction among them.

2.2. DISTRIBUTION

Cistus is a characteristic genus of the Mediterranean flora. The rockrose family has spread throughout the western Mediterranean. The genus is now believed to comprise approximately 20 species, of which 16 are native to Europe (Guzmán & Vargas, 2005). Some species of *Cistus* are endemic, others are widespread in the Iberian Peninsula, the Canary

Islands, Northwest Africa, Italy, Greece, France or Turkey (B. Guzmán et al., 2009; B. Guzmán & Vargas, 2005).

The often coexisting species *C. albidus* L., *Cistus crispus* L., *Cistus creticus* L. and *Cistus heterophyllus* Desf. are native only to the western part of the Mediterranean with the exception of *Cistus creticus*, which also reaches the eastern Mediterranean and the Black Sea coasts and the Crimean peninsula (Civeyrel et al., 2011). As can be seen in Figure 2-3, the currently known distribution of *C. albidus* includes the Iberian Peninsula, the Canary Islands and the western Mediterranean. The northernmost population, by far, of *C. albidus* is found near Lake Garda in Italy (Bertolasi et al., 2019). It grows from sea level to 1,300 m (Grant et al., 2006) and tolerates temperatures down to -12°C, having an even lower thermal threshold (Bertolasi et al., 2019).

Figure 2-3 Natural distribution of *C. albidus* in the western Mediterranean basin (distribution map compiled using Google Earth (https://www.google.com/earth/download/), accessed 19 April 2022). Highlighted in pink, the known natural distribution of *C. albidus* (Raus et al.,2023).

2.3. SYSTEMATICS

Cistus is one of eight genera found within the rockrose family (Cistaceae), which is a part of the Malvales order. The Cistaceae encompasses approximately 180 species (B. Guzmán & Vargas, 2009). Within this family, genera that are native to the Mediterranean basin include *Cistus, Halimium, Fumana, Tuberaria*, and *Helianthemum,* while *Crocanthemum, Hudsonia*, and *Lechea* are endemic to the American continent (Arrington & Kubitzki, 2003). The *Cistus* genus is further categorized into the subgenus *Cistus*, which includes nine species. In the Iberian Peninsula, this subgenus contains species such as *C. albidus* L*., C. crispus* L., *C. creticus* L., and *C. heterophyllus* Desf., which often coexist. Among the species *C. crispus, C. creticus,* and *C. heterophyllus, C. albidus* represents one of the four paraphyletic species within the subgenus *Cistus* (Civeyrel et al., 2011) (Figure 2-4). DNA sequence and pollen analysis showed a close evolutionary relationship of *C. creticus* and *C. albidus*, being *C. crispus* and *C. heterophyllus* more distantly related taxa (Guzmán et al., 2009; Guzmán & Vargas, 2005; Lukas, Jovanovic, et al., 2021). Calculations have determined that the species *C. albidus, C. creticus* and *C. heterophyllus* separated 0.19 Ma ago (Guzmán et al., 2009).

All representatives of this genus have a similar chromosome number (2n=18), which has facilitated hybridization between species (Lukas, Jovanovic, et al., 2021). Nowadays, more than twenty natural interspecific hybrids are known, in addition to numerous cultivars of hybrid origin used for ornamental purpose (Civeyrel et al., 2011; Guzmán & Vargas, 2005). As a consequence of this scenario, although the main characteristics of *C. albidus* are easily identifiable, they can be confused with these species due to their similarity of characteristics, especially the inflorescences.

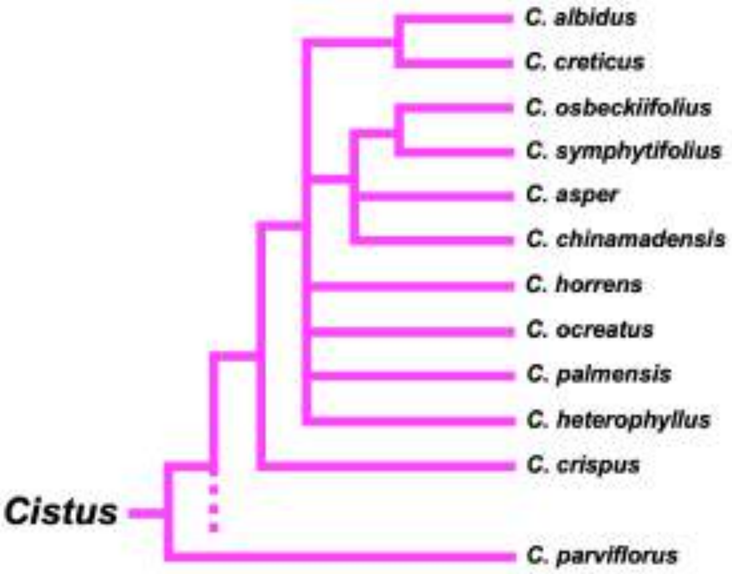


Figure 2-4 Systematics of the pink-purple flowered species of *Cistus* genus based on Guzmán and Vargas (Guzmán & Vargas, 2005) and Civeyrel et al. (Civeyrel et al., 2011).

2.4. BOTANICAL CHARACTERISTICS

From the morphological point of view, *C. albidus* is characterized by having five sepals, five pink to purple petals, up to 150 yellow stamens, pollen with a thin exine up to 1.4 *µ*m thick, a long style that reaches or exceeds the stamens and three-celled, polyspermous capsules. The hermaphroditic, actinomorphic and hypogynous flowers, which appear from February to July, reach normally a diameter of four to six centimetres and develop individually or in umbels of usually five to seven (Guzmán & Vargas, 2009). The five sepals are ovate-lanceolate and hairy. The five petals, on the other hand, are delicate and slightly wrinkled. The flowers open in the morning and after a few hours the plant loses its petals. The flowers rarely last more than a day.

A single adult bush can produce more than 1000 flowers per flowering period, depending on age (Müller et al., 2014).

The ovate-lanceolate leaves are arranged opposite each other and are usually 20-50 mm long and 8-30 mm wide. But specimens with leaves exceeding 100 mm long with more than 50 mm wide have also been found by the authors. They are sessile with a smooth margin, but may occasionally have a slightly wavy edge. Foliar veins are composed of three to five principal veins with a strong central vein. Adaxis veins are sunken while veins on the abaxial surface are raised (Figure 2-2).

Due to its morphological adaptation to extremely dry climate within Mediterranean regions and a pronounced resistance to abiotic stress in general, *C. albidus* could be considered a malacophilous xerophyte. During dry periods, these plants reduce the growth of relatively long and wide hairy leaves until only short, narrow leaves remain. At the same time, the hairiness (trichomes) of the leaves of these plants is increased. In general, these processes significantly reduce respiration, which is an effective protection mechanism against dehydration (Pérez-Llorca, Casadesús, Müller, et al., 2019; Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019).

2.4.1. Vegetative development

C. albidus has developed mechanisms that allow it to withstand severe summer droughts. These mechanisms consist in part of a reduction in leaf area and angle (Pérez-Llorca, Casadesús, Müller, et al., 2019) combined with an increase in root mass per leaf area and modification of stomatal conductance (Munné-Bosch et al., 2003). On the other hand, the link between tocopherols and jasmonates appears to be primarily responsible for the regulation of biotic and abiotic stress responses (Casadesús et al., 2021). It was observed that, under water stress, *C. albidus* increases enzymes related to redox homeostasis, such as oxidized ascorbate reductase, glyoxalase, superoxide dismutase and isoflavone reductase, which was related to a reduction in oxidative stress in *C. albidus* exposed to drought and the ability to recover quickly after re-irrigation (Brossa et al., 2015). The interaction of these mechanisms allows this species to resist the adverse Mediterranean climate conditions with only little photoinhibition (Casadesús et al., 2021).

Further *C. albidus* belongs to the nanophanerophytes (a subgroup of phanerophytes). These are plants whose overwintering buds are above the level of the snow cover. In contrast to the macrophanerophytes, they do not rise above the level of the surrounding vegetation, conditioned by this, and are therefore partially sheltered from the wind. Due to this fact, a more than 2 m high specimen was discovered in the Valle y Carrascoy Regional Park in Murcia, surrounded by shrubs up to 3 m high.

The vegetative development of this species, which lives normally for about 14 years (Roy & Sonie, 1992) and was found to reach 17 (Casadesús et al., 2022) or even 25 years (Müller et al., 2014), is characterized by two types of lateral shoots, dolichoblasts and brachyblasts.

Dolichoblasts are long shoots with large leaves, which are produced when climatic conditions are benign (availability of water and absence of frost), this is usually between the end of February to May and from September to December. Brachyblasts are short shoots that develop throughout the year in the axils of leaves of dolichoblast shoots (Cabezudo et al., 1993). The fall of the leaves of this marcescent species is acropetic.

Sexual reproduction begins at about the age of one year. The flowers of this partially self-incompatible species (Blasco & Mateu, 1995), normally last around 12 hours but may last up to two days on the plant, especially in rainy weather with high relative air humidity. This seems to be due to the fact that the apoidea, its main pollinators (Blasco & Mateu, 1995), do not fly in humid environmental conditions. It has been further shown that zeatin is the substance that modulates the speed of floral development depending on the age of the plants (Hernández et al., 2015).

Fruiting takes place from May to August. The capsules contain an average of about 80 seeds, with exceptions found by the authors from less than ten seeds to more than 140, and generally mature from August to December (Blasco & Mateu, 1995; Cabezudo et al., 1993), but in warmer regions such as the Spanish Levant, for example, the first capsules usually mature at the end of May. Mature capsules spread their seeds close to parent plants as they lack expansion mechanisms. Studies suggest that *C. albidus* seeds experience a combination of physical and physiological dormancy (Siles et al., 2017). Although physical dormancy was broken and water was available, the seeds seemed able to partially control their dormancy and germination capacity (Siles et al., 2017). Under optimal conditions, germination takes between five and ten days and is epigeal (Rizzotto, 1979).

Like other plants typical of fire-prone regions, *C. albidus* is generally considered pyrophytic (Robles et al., 1998), especially since the heat generated by fire is thought to facilitate breaking physical dormancy due to the hard seed coat (Roy & Sonie, 1992; Thanos et al., 1993; Trabaud & Oustric, 1989), thus being one of the first shrubs to emerge after a fire. Thus, development is rapid within the first five years and then progressively slows down (Roy & Sonie, 1992). But also the scarification of the seeds, by soil particles, (through dragging by water flow) softens the hard cover of the seed, making them permeable to water (Trabaud & Renard, 1999), thus overcoming physical dormancy (Baskin & Baskin, 2004; Trabaud & Renard, 1999). In addition, it is common to find this species along the edges of watercourses with temporary flows. This seems to be its dispersal strategy since forest fires do not facilitate the spatial expansion of this species. Very specific conditions must be met for the seeds to viably survive forest fires and also break the integument. For this reason, *C. albidus* could be considered an opportunistic pioneer plant.

Regarding the influence of the soil on the development of *C. albidus*, together with *C. creticus*, it is the only taxon of the purple-pink clade capable of growing independently in calcareous and acidic soils. However, *C. albidus* grows best on calcareous soils in Mediterranean climates (Barrajón-Catalán et al., 2011; Polunin et al., 1971). Studies reported that no significant qualitative or quantitative differences were found in the polyphenolic profile between the cultivation of *C. albidus* in different types of soil (Barrajón-Catalán et al., 2011; Ormeño et al., 2008), while the concentration of terpenes was influenced by soil conditions, showing lower yields in calcareous soils (Robles & Garzino, 1998). However, higher concentrations of polyphenols were not associated with lower soil fertility (Castells & Peñuelas, 2003). This suggests that the genetic influence of this species on the biosynthesis of phytochemicals may be stronger than the influence of soil parameters. This is confirmed by a recent study, where *C. albidus* exhibited a low translocation of Pb and Cd to aerial parts from heavy metal contaminated soil (El Mamoun et al., 2020), making this species also suitable for plantations under problematic soil conditions.

2.5. PHYTOCHEMICAL CONSTITUENTS

The main constituents of *C. albidus* derived products belong to the groups of terpenes and polyphenols. Other organic compounds have also been detected. To date, more than 200 secondary metabolites have been reported in *C. albidus* samples. In this review, it has been found 153 terpenoids, including 31 monoterpenes, 109 sesquiterpenes, 9 diterpenes and 3 tetraterpenes and their respective derivatives. In addition, 58 polyphenols including 19 phenolic acids, 17 flavonols, 11 flavanols, 3 ellagitannins, 3 anthocyanins, 2 flavones, 1 anthocyanidin, 1 flavanone and 1 hydrolysable tannin. Moreover 8 fatty acids, 7 alkanes and various other compounds were found in the literature and discussed in the present study.

The irregular presence of reported compounds – analyses were often very heterogeneous – is possibly due to seasonal variation and the analytical methods used. Secondary metabolites reported so far have been determined under a wide variety of conditions, making it sometimes difficult a comparison among the studies. For example, some metabolites, such as punicalagin derivatives or some diterpenes, were only found in a small number of studies (Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021) since the results depend on multiple factors such as the method of analysis, the season and hours of the day of collection, the type of processing among others and some of them are not detailed in many studies. However, on the other hand, there are a number of compounds that practically all authors found in significant amounts, being thus characteristic of this specie. These more common compounds will be highlighted along the following sections.

The various compound structures detected in *C. albidus* are described below, headed by the terpenes, paying particular attention to the essential oils (mono- and sesquiterpenes). Phenylpropanoids detected in essential oils are also briefly discussed. Furthermore, di- and tetraterpenes were described. The second large group of substances, polyphenols, are examined more closely, especially flavonols, flavanols, ellagitannins and phenolic acids. The carbonyl compounds and alkanes found so far are then listed. Finally, proven phytohormones and various fatty acids are described. However, the latter is not part of the secondary metabolism but is included here for its supposed importance as a potential bioavailability enhancer.

2.5.1. Terpenes

2.5.1.1. Mono- and sesquiterpenes from the essential oils

Terpenes, a very large but heterogeneous group of naturally occurring secondary metabolites in *C. albidus*, representing the group with the most compounds identified in this species. And among them, the most abundant were the sesquiterpenes, being these in addition, the largest class of identified compounds in *C. albidus*. While monoterpenes found contribute, to a certain extent, together with aldehydes to the characteristic odour of this species (they are among the main components of floral aromas), the sesquiterpenes play a signalling role in the defence mechanisms of this species and act as herbivore repellents or through the attraction of predators. Diterpenes are also synthesized for defence purposes and serve as precursors for vitamins and hormones such as tocopherols and gibberellins. Finally, tetraterpenes contribute to the pigmentation of flowers and fruits, playing an essential role in pollination and distribution of seeds. As an antioxidant, it protects *C. albidus* from oxidative stress caused by adverse growing conditions (Munné-Bosch et al., 2003).

The ISO definition for essential oils is “Product obtained from a natural raw material of plant origin, by steam distillation, by mechanical processes from the epicarp of citrus fruits, or by dry distillation, after separation of the aqueous phase — if any — by physical processes.” (International Organization for Standardization, 2013).

Essential oils from fresh aerial parts of *C. albidus* were generally obtained in low yields of 0.01–0.1% (w/w) (Bechlaghem et al., 2019; Llusià et al., 2010; Palá-Paúl et al., 2005) by steam distillation. Especially the seeds contain very small amounts of essential oil, sometimes insufficient to be analysed, with a yield of less than 0.01% (Palá-Paúl et al., 2005). The concentration of terpenes depends fundamentally on soil conditions – the more calcareous the lower the yield – climatic factors and the season (Robles & Garzino, 1998). Analysis of seasonal variation in terpene composition show strong interannual variability with the highest emission rates in autumn and spring and the lowest in summer and winter, leading to maximum values of stored terpenes in autumn and winter, while the spring and summer values showed minimum levels (Llusià et al., 2010).Table 2-1 shows the list of the terpenoids identified in *C. albidus* samples, including information about their previously published pharmacological activity. The compounds most frequently found in the analyses of the extracted terpenes (w/w) and therefore representative of this species, whether in leaves, pollen, flowers, flowering tops or stems, are α-zingiberene (7.4-20.7%), aromadendrene (1.0-10.6%), ar-curcumene (8.3-13.2%) and germacrene D (1.0-7.9%) (Bechlaghem et al., 2019; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008). Among the terpenes in leaves, flowering tops and flowers, monoterpenes were only present in small quantities and sometimes only in traces while sesquiterpenes were the most abundant (Bechlaghem et al., 2019; Maccioni et al., 2007; Palá-Paúl et al., 2005).

The following quantities refer to the w/w of the extracted oil. Oxygenated sesquiterpenes ranged from 44.8% in aerial parts (twigs, leaves, flowers) (Bechlaghem et al., 2019) to 67.1% in leaves (Maccioni et al., 2007). Hydrocarbon sesquiterpenes were found from 22.5% in flowers (Maccioni et al., 2007) to 48.6% in aerial parts including flowers (Bechlaghem et al., 2019). Within representative sesquiterpenes in leaves, *α*-zingiberene is the most abundant and was extracted from 5.9% (Maccioni et al., 2007) to 14.8% (Palá-Paúl et al., 2005), followed by *α*-bisabolol with values ranging from 1.9% (Palá-Paúl et al., 2005) to 11.4% (Bechlaghem et al., 2019). Further ar-curcumene was obtained from 8.3% (Bechlaghem et al., 2019) to 10.6% (Palá-Paúl et al., 2005) and *β*-bourbonene showed a presence from a residual 0.1% (Palá-Paúl et al., 2005) up to 8.7% (Bechlaghem et al., 2019).

The essential oil compositions of the aerial parts (stems and leaves) of *C. albidus* showed only quantitative differences. However, the flowers (petals) essential oil has different composition with mainly *α*-zingiberene, *α*-cadinol, ar-curcumene and *δ*-cadinene (Maccioni et al., 2007; Palá-Paúl et al., 2005) while the composition of the isolated pollen contained *α*-zingiberene, *δ*-cadinene and germacrene D within the most abundant compounds (Maccioni et al., 2007).

Since the analysed samples come from different places with different climatic and soil conditions, and were collected on different dates and, sometimes were analysed by different methods, comparison of their compositions is only possible to a very limited extent. In addition to these limitations, it must also be taken into account that the species of the *C.* subgenus hybridize with each other, which may also have an impact on the composition of the synthesized compounds if species purity has not been ensured beforehand.

Table 2-1 Identified terpenes in *C. albidus*. Table includes the structure for each compound along with the references in which it was identified and its pharmacological activity (including the references for this activity). 🌱: aerial parts, including leaves and twigs; ✿: flowering tops, flowers, petals, and sepals; ❃: pollen. n/a: reliable data are not available.

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
1	*cis*-*α*-Bergamotene	polycyclic monoterpene hydrocarbon	🌱✿	(Maccioni et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008)	n/a
2	*trans*-*α*-Bergamotene		🌱	(Llusià et al., 2010; Palá-Paúl et al., 2005)	
3	Borneol	polycyclic monoterpene alcohol	🌱	(Ormeño, Bousquet-Mélou, et al., 2007)	blood brain barrier (BBB) permeability improvement, intercellular tight junction (TJ) loosening (Gao & Gao, 2019)
4	Camphor	oxygenated polycyclic monoterpene	🌱	(Morales-Soto et al., 2015)	analgesic, antinociceptive (H. Xu et al., 2005); antimicrobial, antiviral (Chen et al., 2013); anticancer (Banerjee et al., 1995); antitussive (Laude et al., 1994); skin penetration enhancer (Liu et al., 2011);
5	Carene	polycyclic monoterpene hydrocarbon	🌱✿	(Ormeño, Bousquet-Mélou, et al., 2007)	antiviral (Patra et al., 2020); enhances bone mineralization (Jeong et al., 2008); anti-inflammatory (Gil et al., 1989);
6	Carvacrol	monocyclic monoterpene alcohol	🌱✿	(Maccioni et al., 2007)	antibacterial (64); antifungal (Pina-Vaz et al., 2004); antioxidant (Aeschbach et al., 1994); anticancer (Jayakumar et al., 2012); anti-inflammatory, analgesic (Hotta et al., 2010); antiobesity (Cho et al., 2012); hepatoprotective (Decker & Keppler, 1972); spasmolytic (Boskabady & Jandaghi, 2003); vasorelaxant (Peixoto-Neves et al., 2010);

Nº	**Compound**	**Structure/class**	**Presence in**	**Analytical Reference**	**Pharmacology**
7	*β*-Cyclocitral	oxygenated monocyclic monoterpene	🌱	(Paolini et al., 2008)	n/a
8	*p*-Cymene	monocyclic monoterpene hydrocarbon	🌱	(Maccioni et al., 2007; Morales-Soto et al., 2015)	anti-inflamatory, antinociceptive, antioxidant (Quintans-Júnior et al., 2013); antidiabetic (Arabloei Sani et al., 2022);
9	*p*-Cymenene	monocyclic monoterpene hydrocarbon	🌱✿	(Morales-Soto et al., 2015)	n/a
10	Isobornyl formate	oxygenated polycyclic monoterpene	🌱	(Morales-Soto et al., 2015)	n/a
11	(D-)Limonene	monocyclic monoterpene hydrocarbon	🌱✿	(Llusià et al., 2010; Maccioni et al., 2007; Morales-Soto et al., 2015; Palá-Paúl et al., 2005)	anticancer, anticholesterol (Sun, 2007); antidepressant (Lorigooini et al., 2021);
12	Linalool	acyclic monoterpene alcohol	🌱✿	(Ormeño, Bousquet-Mélou, et al., 2007; Ormeño, Mévy, et al., 2007)	antibacterial, antifungal (Pattnaik et al., 1997); anxiolytic (Linck et al., 2010); anticancer, antioxidant (Jana et al., 2014); analgesic (Sugawara et al., 2000); anti-inflammatory (Peana et al., 2002);
13	*cis*-linalool oxide	oxygenated heteromonocyclic monoterpene		(Ormeño, Mévy, et al., 2007)	n/a
14	Myrcene	acyclic monoterpene hydrocarbon	🌱	(Maccioni et al., 2007; Ormeño, Mévy, et al., 2007)	analgesic, antinociceptive (Jansen et al., 2019);
15	Neryl acetate	acyclic monoterpene hydrocarbon	🌱✿	(Paolini et al., 2008)	n/a
16	(E)-Ocimene	acyclic monoterpene hydrocarbon	🌱✿	(Maccioni et al., 2007)	anticancer (Bomfim et al., 2016); anticonvulsant (Sayyah et al., 2004);

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
17	(*Z*)- *β* -Ocimene			(Maccioni et al., 2007)	anticancer (Bomfim et al., 2016); antibacterial (Pulaj et al., 2016);
18	*α*-Phellandrene	monocyclic monoterpene hydrocarbon	🌱	(Maccioni et al., 2007)	antifungal (Zhang et al., 2017); antidepressant (Piccinelli et al., 2015); anti-inflammatory, antihyperalgesic (Lima et al., 2012; Piccinelli et al., 2015), analgesic, antinociceptive (Lima et al., 2012); anticancer (Lin et al., 2014);15/09/2025 12:49:00
19	*β*-Phellandrene		✿	(Maccioni et al., 2007)	n/a
20	*α*-Pinene	polycyclic monoterpene hydrocarbon	🌱	(Llusià et al., 2010; Maccioni et al., 2007; Ormeño, Mévy, et al., 2007)	antifungal, anti-inflammatory, antioxidant (Karthikeyan et al., 2018); anticancer (Hou et al., 2019); anti-Leishmania (Rodrigues et al., 2015); gastroprotective (Matthews Jucá et al., 2011; Pinheiro et al., 2015); antibacterial (Utegenova et al., 2018); antiviral (Yang et al., 2011); neuroprotective (Zamyad et al., 2019); 15/09/2025 12:49:00
21	*β*-Pinene		🌱✿	(Llusià et al., 2010)	anticancer (Wang et al., 2019); antimicrobial (Liao et al., 2016); gastroprotective (Matthews Jucá et al., 2011); neuroprotective (Felipe et al., 2019);
22	Piperitone	oxygenated monocyclic monoterpene	❁	(Maccioni et al., 2007)	n/a
23	Sabinene	polycyclic monoterpene hydrocarbon	🌱	(Maccioni et al., 2007)	n/a
24	*cis*-Sabinene hydrate	oxygenated polycyclic monoterpene		(Maccioni et al., 2007)	

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
25	Safranal	oxygenated monocyclic monoterpene	🌱	(Paolini et al., 2008)	antioxidant (Assimopoulou et al., 2005); antimicrobial (Pintado et al., 2011); anticonvulsant (Hosseinzadeh & Talebzadeh, 2005); antidepressant, anxiolytic (Hosseinzadeh & Noraei, 2009); gastroprotective (Kianbakht & Mozaffari, 2009);
26	*α*-Terpinene	monocyclic monoterpene hydrocarbon	🌱	(Maccioni et al., 2007)	antioxidant (Rudbäck et al., 2012); antimicrobial (Baldissera et al., 2016);
27	*Δ*-Terpinene		🌱✿	(Ormeño, Bousquet-Mélou, et al., 2007)	n/a
28	*γ*-Terpinene		✿	(Maccioni et al., 2007)	antimicrobial (Baldissera et al., 2016);
29	*α*-Terpineol	monocyclic monoterpene alchohol	✿❁	(Fadel et al., 2020; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Paolini et al., 2008)	antioxidant, anticancer, antinociceptive, anticonvulsant, sedative, antibronchitis, antihypertensive, vasorelaxant, cardioprotective (Khaleel et al., 2018);
30	4-Terpineol		🌱	(Maccioni et al., 2007; Paolini et al., 2008)	antimicrobial (Couladis et al., 2003); gastroprotective (Souza et al., 2011);
31	Thymol	monocyclic monoterpene hydrocarbon	🌱✿	(Maccioni et al., 2007; Morales-Soto et al., 2015)	anti-inflammatory, antioxidant, antimicrobial, immunostimulatory, anticancer (Nagoor Meeran et al., 2017); cardioprotective (Nagoor Meeran et al., 2016); antihypertensive (Peixoto-Neves et al., 2010); antihyperglycemic (Saravanan & Pari, 2015); antinociceptive (Mendes et al., 2010); gastroprotective (Bukovská et al., 2007); anxiolytic (Bhandari & Kabra, 2014);

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
32	Abscisic acid	oxygenated monocyclic sesquiterpene	🌱	(López-Carbonell et al., 2009; Pérez-Llorca et al., 2021)	antidiabetic (Bassaganya-Riera et al., 2010); antinociceptive (Mollashahi et al., 2018);
33	*α*-Amorphene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015; Paolini et al., 2008)	n/a
34	Aromadendrene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Llusià et al., 2010; Palá-Paúl et al., 2005; Paolini et al., 2008)	
35	allo-Aromadendrene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Bechlaghem et al., 2019; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	antimicrobial (Mulyaningsih et al., 2010);
36	allo-Aromadendrene epoxide	oxygenated polycyclic sesquiterpene	🌱	(Paolini et al., 2008)	
37	Bisabola-2,10-diene(1-9)oxide	oxygenated polycyclic sesquiterpene	🌱	(Paolini et al., 2008)	n/a
38	*β*-Bisabolene	monocyclic sesquiterpene hydrocarbon		(Palá-Paúl et al., 2005)	anticancer (Yeo et al., 2016)
39	epi-*α*-Bisabolol	monocyclic sesquiterpene alcohol	🌱✿	(Bechlaghem et al., 2019; Maccioni et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008)	anti-inflammatory (Maurya et al., 2014); antimicrobial (van Zyl et al., 2006); anticancer (Seki et al., 2011);
40	*α*-Bisabolol		🌱	(Paolini et al., 2008; Robles & Garzino, 1998)	
41	*β*-Bisabolol		🌱✿	(Palá-Paúl et al., 2005)	n/a15/9/25 12:49:00

Nº	**Compound**	**Structure/class**	**Presence in**	**Analytical Reference**	**Pharmacology**
42	*β*-Bourbonene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Bechlaghem et al., 2019; Llusià et al., 2010; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Paolini et al., 2008; Robles & Garzino, 1998)	n/a
43	1,5-di-epi-Bourbonene (*α* or *β*)		🌱	(Paolini et al., 2008)	
44	Bulnesol	polycyclic sesquiterpene alcohol	🌱✿	(Maccioni et al., 2007)	n/a
45	Cadalene	polycyclic sesquiterpene hydrocarbon	🌱	(Paolini et al., 2008)	n/a
46	Cadina-1,4-diene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Palá-Paúl et al., 2005; Paolini et al., 2008)	n/a
47	*α*-Cadinene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015; Paolini et al., 2008)	n/a
48	*cis*-*γ*-Cadinene		🌱✿⁘	(Maccioni et al., 2007)	
49	*trans*-*γ*-Cadinene		🌱	(Bechlaghem et al., 2019)	
50	*γ*-Cadinene		🌱	(Ormeño, Bousquet-Mélou, et al., 2007; Ormeño, Mévy, et al., 2007; Paolini et al., 2008)	
51	*δ*-Cadinene		🌱✿⁘	(Bechlaghem et al., 2019; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	
52	*α*-Cadinol	polycycylic sesquiterpene	🌱✿	(Maccioni et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	antifungal (Ho et al., 2011);

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
53	T-Cadinol	alcohol		(Bechlaghem et al., 2019; Maccioni et al., 2007; Mastino et al., 2017; Paolini et al., 2008)	anticancer (Takei et al., 2006)
54	*α*-Calacorene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015; Paolini et al., 2008)	n/a
55	*β*-Calacorene			(Paolini et al., 2008)	
56	Calamenene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015; Paolini et al., 2008)	anticancer (Takei et al., 2006);
57	Caryophylladienol I	polycyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
58	Caryophylladienol II			(Paolini et al., 2008)	
59	*β*-Caryophyllene	polycyclic sesquiterpene hydrocarbon	🌱✿❁	(Bechlaghem et al., 2019; Llusià et al., 2010; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	antioxidant, antimicrobial, antitumor, anticancer (Dahham et al., 2015); anti-inflammatory, neuroprotective (Ojha et al., 2016); anxiolytic, antidepressant (Bahi et al., 2014); anticonvulsant (de Oliveira et al., 2016); analgesic (Fidyt et al., 2016);
60	*β*-Caryophyllene epoxide	oxygenated polycyclic sesquiterpene	🌱	(Bechlaghem et al., 2019; Maccioni et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	anticancer, analgesic (Fidyt et al., 2016);
61	Caryophyllenol II	polycyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
62	8,14-Cedranoxide	oxygenated sesquiterpene	🌱	(Bechlaghem et al., 2019)	n/a
63	*α*-Cedrene	polycyclic sesquiterpene hydrocarbon	🌱	(Llusià et al., 2010)	n/a

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
64	*α*-Copaene	polycyclic sesquiterpene hydrocarbon	🌱	(Bechlaghem et al., 2019; Llusià et al., 2010; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Paolini et al., 2008)	antioxidant, anticancer (Türkez et al., 2014); neuroprotective (Turkez et al., 2014);
65	*β*-Copaene		🌱✿❁	(Bechlaghem et al., 2019; Morales-Soto et al., 2015; Paolini et al., 2008)	
66	*α*-Corocalene	polycyclic sesquiterpene hydrocarbon	🌱	(Paolini et al., 2008)	n/a
67	*α*-Cubebene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Maccioni et al., 2007; Ormeño et al., 2008; Paolini et al., 2008)	antioxidant, neuroprotective (Park et al., 2013); antimicrobial (Lee et al., 2012); anti-inflammatory (Baek et al., 2022);
68	*β*-Cubebene		🌱	(Bechlaghem et al., 2019; Maccioni et al., 2007; Ormeño et al., 2008)	
69	Cubebol	polycyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
70	4-epi-Cubebol			(Paolini et al., 2008)	
71	1,10-di-epiCubenol	polycyclic sesquiterpene alchohol	🌱✿	(Bechlaghem et al., 2019; Maccioni et al., 2007; Paolini et al., 2008)	n/a
72	Cubenol		🌱	(Paolini et al., 2008)	
73	1-epi-Cubenol		🌱✿	(Bechlaghem et al., 2019; Maccioni et al., 2007; Paolini et al., 2008)	
74	ar-Curcumen-15-al	oxygenated monocyclic sesquiterpene	🌱	(Bechlaghem et al., 2019; Paolini et al., 2008)	n/a
75	ar-Curcumene	monocyclic sesquiterpene hydrocarbon	🌱✿	(Bechlaghem et al., 2019; Llusià et al., 2010; Maccioni et al., 2007; P. M. Mastino et al., 2017; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	n/a

Nº	**Compound**	**Structure/class**	**Presence in**	**Analytical Reference**	**Pharmacology**
76	*β*-Curcumene		✿	(Palá-Paúl et al., 2005)	
77	*γ*-Curcumene		🌱✿	(Maccioni et al., 2007; Palá-Paúl et al., 2005)	
78	Curcuphenol	monocyclic sesquiterpene alcohol	🌱✿	(Palá-Paúl et al., 2005; Paolini et al., 2008)	anticancer (Rodrigo et al., 2010);
79	Cyclosativene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Maccioni et al., 2007)	n/a
80	Dehydrosesquicineole	oxygenated polycyclic sesquiterpene	🌱	(Paolini et al., 2008)	n/a
81	Bicyclo-Elemene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015)	n/a
82	*β*-Elemene	monocyclic sesquiterpene hydrocarbon	🌱	(Palá-Paúl et al., 2005; Paolini et al., 2008)	anticancer, anti-inflammatory (Bai et al., 2021);
83	*γ*-Elemene		🌱	(Palá-Paúl et al., 2005)	
84	*δ*-Elemene		🌱✿	(Maccioni et al., 2007; Morales-Soto et al., 2015; Palá-Paúl et al., 2005)	
85	Elemol	monocyclic sesquiterpene alcohol	🌱	(Maccioni et al., 2007; Palá-Paúl et al., 2005; Robles & Garzino, 1998)	n/a
86	*β*-Eudesma 4(15), 7 dien-1*β*-ol	polycyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
87	*α*-Eudesmol		🌱	(Bechlaghem et al., 2019)	neuroprotective (Asakura et al., 2000);
88	*β*-Eudesmol		🌱✿	(Bechlaghem et al., 2019; Palá-Paúl et al., 2005)	anti-allergic, anti-inflammatory (Moon et al., 2018); anticancer (Narahara et al., 2020);
89	*γ*-Eudesmol		🌱✿	(Maccioni et al., 2007; Palá-Paúl et al., 2005)	n/a

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
90	10-epi-γ-Eudesmol			(Maccioni et al., 2007; Palá-Paúl et al., 2005)	
91	Kunseaol	monocyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
92	Bicyclo-Germacrene	polycyclic sesquiterpene hydrocarbon	🌱	(Paolini et al., 2008)	n/a
93	Germacrene B	monocyclic sesquiterpene hydrocarbon	🌱	(Llusià et al., 2010; Palá-Paúl et al., 2005)	anticancer (Dhyani et al., 2022); anti-inflammatory, analgesic (Guedes et al., 2023); antioxidant (Casiglia et al., 2017);
94	Germacrene D		🌱✿❁	(Llusià et al., 2010; Maccioni et al., 2007; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	
95	Iso-Germacrene D		🌱	(Paolini et al., 2008)	
96	*β*-Germacrenol	monocyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
97	Globulol	polycyclic sesquiterpene alcohol	🌱✿	(Bechlaghem et al., 2019; Palá-Paúl et al., 2005)	n/a
98	*α*-Guaia-6,10(14)-diene-4*β*-ol	polycyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
99	Guaiene	polycyclic sesquiterpene hydrocarbon	🌱	(Bechlaghem et al., 2019)	n/a
100	Guaiol	polycyclic sesquiterpene alcohol	🌱✿	(Maccioni et al., 2007; Palá-Paúl et al., 2005)	n/a

Nº	**Compound**	**Structure/class**	**Presence in**	**Analytical Reference**	**Pharmacology**
101	*α*-Gurjunene	polycyclic sesquiterpene hydrocarbon	🌱✿	(Llusià et al., 2010; Maccioni et al., 2007; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño, Mévy, et al., 2007)	n/a
102	*β*-Gurjunene			(Maccioni et al., 2007)	
103	*β*-Himachalene	polycyclic sesquiterpene hydrocarbon	✿ ❀	(Maccioni et al., 2007)	n/a
104	*α*-Humulene	monocyclic sesquiterpene hydrocarbon	🌱✿	(Bechlaghem et al., 2019; Llusià et al., 2010; Maccioni et al., 2007; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	antitumor, anti- inflammatory, antimicrobial (Mendes De Lacerda Leite et al., 2021);
105	Iso-Calamendiol	polycyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
106	Iso-Italicene	polycyclic sesquiterpene hydrocarbon	🌱	(Bechlaghem et al., 2019)	n/a
107	Juniper camphor	polycyclic sesquiterpene alcohol	🌱✿	(Maccioni et al., 2007)	n/a
108	Ledol	polycyclic sesquiterpene alcohol	🌱	(Fadel et al., 2020; Paolini et al., 2008)	n/a
109	*α*-Longipinene	polycyclic sesquiterpene hydrocarbon	🌱	(Bechlaghem et al., 2019)	n/a
110	*cis*-Muurola-4(14),5-diene	polycyclic	🌱✿	(Maccioni et al., 2007; Paolini et al., 2008)	n/a

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
111	*α*-Muurolene	sesquiterpene hydrocarbon		(Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Palá-Paúl et al., 2005)	
112	*γ*-Muurolene			(Bechlaghem et al., 2019; Maccioni et al., 2007; Paolini et al., 2008)	
113	14-hydroxi-α-Muurolene	polycyclic sesquiterpene alcohol	🌱	(Bechlaghem et al., 2019)	n/a
114	*α*-Muurolol		🌱✿	(Maccioni et al., 2007)	
115	epi-*α*-Muurolol			(Palá-Paúl et al., 2005)	
116	T-Muurolol			(Bechlaghem et al., 2019; Maccioni et al., 2007, 2007; Paolini et al., 2008; Robles & Garzino, 1998)	
117	E-Nerolidol	acyclic sesquiterpene alcohol	🌱✿	(Palá-Paúl et al., 2005)	antihyperlipidemic, anti-inflammatory, anti-uterine fibroids (Sabir et al., 2022); anticancer (Dong et al., 2021);
118	(E)-Nuciferol	moncyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
119	*β*-Oplopenone	oxygenated polycyclic sesquiterpene	🌱	(Paolini et al., 2008)	n/a
120	Salvial-4(14)-en-1-one	oxygenated polycyclic sesquiterpene	🌱	(Paolini et al., 2008)	n/a
121	*α*-Santalene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015)	n/a
122	cis-*α*-Santalol	polycyclic sesquiterpene alcohol	🌱	(Bechlaghem et al., 2019)	antihyperglycemic, antioxidant (Misra & Dey, 2013);

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
123	Selin-11-en-4-*α*-ol	polycyclic sesquiterpene alcohol	🌱	(Fadel et al., 2020)	anxiolytic, sedative (Garlet et al., 2019);
124	Selina-3,7(11)-diene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015)	n/a
125	*α*-Selinene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015)	n/a
126	*β*-Sesquiphellandrene	monocyclic sesquiterpene hydrocarbon	🌱✿	(Llusià et al., 2010; Maccioni et al., 2007; Paolini et al., 2008; Robles & Garzino, 1998)	anticancer (Tyagi et al., 2015); antioxidant (Zhao et al., 2010);
127	*trans*-Sesquisabinene hydrate	polycyclic sesquiterpene alcohol	🌱	(Palá-Paúl et al., 2005)	n/a
128	Shyobunone	oxygenated monocyclic sesquiterpene	🌱	(Ormeño et al., 2008; Paolini et al., 2008)	neuroprotective, acetyl-cholinesterase inhibition (Martins et al., 2021);
129	6-epi-Shyobunone			(Paolini et al., 2008)	
130	iso-Shyobunone			(Paolini et al., 2008)	
131	Spathulenol	polycyclic sesquiterpene alcohol	🌱✿	(Bechlaghem et al., 2019; Maccioni et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008)	neuroprotective (Manjima et al., 2021); antibacterial, antioxidant, anti-inflammatory, anticancer (do Nascimento et al., 2018);
132	Spathulenol isomer		🌱	(Palá-Paúl et al., 2005)	
133	ar-Turmerol	monocyclic sesquiterpene alcohol	🌱✿	(Bechlaghem et al., 2019; Palá-Paúl et al., 2005)	n/a
134	Valerianol	polycyclic sesquiterpene alcohol	🌱✿	(Maccioni et al., 2007)	n/a

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
135	Viridiflorol	polycyclic sesquiterpene alcohol	🌱✿	(Palá-Paúl et al., 2005; Paolini et al., 2008)	anti-arthritic, analgesic, antinociceptive (de Matos Balsalobre et al., 2023); anticancaer (Akiel et al., 2022); antioxidant, antibacterial, anti-inflammatory (Trevizan et al., 2016);
136	Xanthorrhizol	monocyclic sesquiterpene alcohol	🌱	(Bechlaghem et al., 2019; Paolini et al., 2008)	anticancer (Oon et al., 2015); antimicrobial, antibacterial (Yogiara et al., 2020); antihypolipidemic (Oon et al., 2016); anti-inflammatory (Cho et al., 2011);
137	*α*-Ylangene	polycyclic sesquiterpene hydrocarbon	🌱	(Morales-Soto et al., 2015)	n/a
138	*β*-Ylangene		🌱	(Paolini et al., 2008)	
139	*α*-Zingiberene	monocyclic sesquiterpene hydrocarbon	🌱✿❁	(Bechlaghem et al., 2019; Llusià et al., 2010; Maccioni et al., 2007; Morales-Soto et al., 2015; Ormeño, Bousquet-Mélou, et al., 2007; Ormeño et al., 2008; Ormeño, Mévy, et al., 2007; Palá-Paúl et al., 2005; Paolini et al., 2008; Robles & Garzino, 1998)	analgesic, neuroprotective (Borgonetti et al., 2023); anticancer (Bou et al., 2013); anti-inflammatory (Ferreira et al., 2022);
140	Zingiberenol	monocyclic sesquiterpene alcohol	🌱	(Paolini et al., 2008)	n/a
141	15,16-Dinorlabd-8(20)-en-13-one	oxygenated diterpene	🌱	(Fadel et al., 2020)	n/a
142	Geranyl-*p*-cymene	monocyclic diterpene hydrocarbon	🌱	(Paolini et al., 2008)	n/a
143	Geranyl *α*-terpinene	monocyclic diterpene hydrocarbon	🌱	(Paolini et al., 2008)	n/a

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
144	Geranyl linalool	acyclic diterpene alcohol	🌱	(Paolini et al., 2008)	n/a
145	Gibberellin	oxygenated polycyclic diterpene	🌱	(Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019)	n/a
146	Manool	polycyclic diterpene alcohol	🌱	(Fadel et al., 2020)	antioxidant, anti-inflammatory (Ravera et al., 2021); anticancer (Nicolella et al., 2014); antihypertensive (Monteiro et al., 2020); cardioprotective (Castro & Pontes, 2020);
147	Manoyl oxide	polycyclic oxygenated diterpene	🌱	(Mastino et al., 2017)	anticancer (Angelopoulou et al., 2001);
148	13-epi-Manoyl oxide			(Llusià et al., 2010; Mastino et al., 2017; Paolini et al., 2008)	
149	Methyl Neoabietate	oxygenated polycyclic diterpene	🌱	(Llusià et al., 2010)	n/a
150	lutein	oxygenated polycyclic tetraterpene	🌱	(Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019)	antioxidant, anti-inflammatory, neuroprotective (Kim et al., 2008); anticancer (Zhang et al., 2018); hepatoprotective (Li et al., 2015); cardiopreotective (Ouyang et al., 2019);
151	neoxanthin	oxygenated polycyclic tetraterpene	🌱	(Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019)	antihyperlipidemic (Okada et al., 2008);
152	zeaxanthin	oxygenated polycyclic tetraterpene	🌱	(Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019)	n/a

2.5.1.2. Phenylpropanoids from the essential oils

Phenylpropanoids are compounds that are built from an aromatic benzene ring and a chain of three carbon atoms, and often have hydroxyl and methoxy groups on the aromatic ring. Many phenylpropanoids are natural substances that are formed in plants and microorganisms through the shikimate biosynthetic pathway with phenylalanine and tyrosine as intermediate compounds (Teuscher, 2020). In addition to terpenes, phenylpropanoids are a frequent component of essential oils and represent the majority of natural phenolic substances or their precursors. The phenolpropanoids identified so far in *C. albidus* are eugenol (Maccioni et al., 2007; Paolini et al., 2008; Tomás-Menor et al., 2013) and chavicol (Morales-Soto et al., 2015).

2.5.1.3. Diterpenes

As for the diterpenes present in *C. albidus*, these are not usually detected in most analyses, because they belong to the non-volatile terpenes. This is mainly because the analytical methods described are not suitable for detecting non-volatile substances and not because of the absence of these compounds. The diterpenes detected so far are geranyl linalool, geranyl α-terpinene, geranyl p-cymene and 13-epi-mannoyloxide, (Paolini et al., 2008), methyl neoabietate (Llusià et al., 2010), 15,16-dinorlabd-8(20)-en-13-one, manool (Fadel et al., 2020) and manoyl oxide (Mastino et al., 2017). The latter was found in the aerial parts, including the stems, unlike 15,16-dinorlabd-8(20)-en-13-one and manool, which were obtained only from the leaves.

2.5.1.4. Tetraterpenes

Tetraterpenes are vital for plant growth, protection against stress, and successful reproduction, so far lutein, neoxanthin and zeaxanthin were identified in *C. albidus* (Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019).

2.5.2. Phenolic compounds

Phenolic compounds are based on the phenol structure. In general, these compounds can be divided into seven subgroups: simple phenols, hydroxybenzoic acids, hydroxycinnamic acids, coumarins, flavonoids, lignans, and lignins (Sticher et al., 2015). The concentration of these phenolic substances in plant foods depends, in part, on the plant species, the climate and the degree of maturity (Belitz et al., 2008). In the present work, the analytical focus of phenolic compounds lies on the group of hydroxybenzoic acids (basic structure C6-C1), hydroxycinnamic acids (basic structure C6-C3) (Figure 2-5) and flavonoids (basic structure C6-C3-C6) as they are the most frequent polyphenolic groups present in *C. albidus* samples (Figure 2-6).

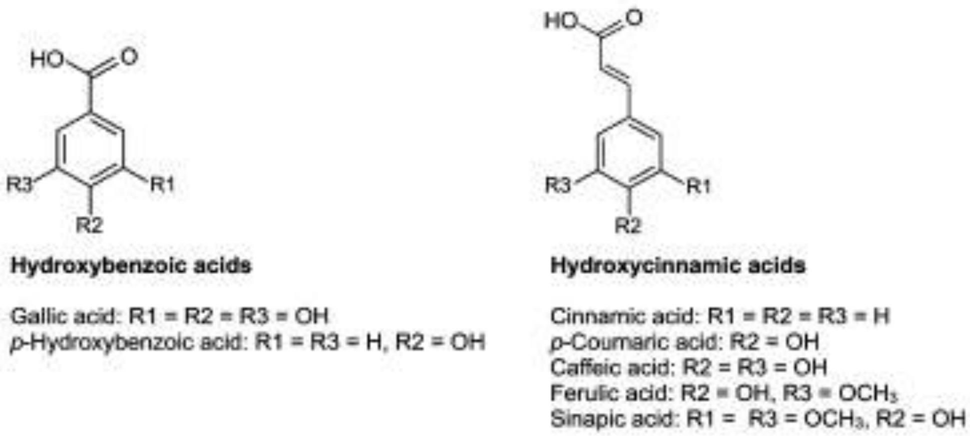


Figure 2-5 Structures of hydroxybenzoic and hydroxycinnamic acids. These acids are two major subclasses of phenolic acids, characterized by a hydroxylated benzene ring, with hydroxybenzoic acids (e.g., gallic acid) derived from benzoic acid and hydroxycinnamic acids (e.g., caffeic acid) derived from cinnamic acid, both widely found in plants and known for their antioxidant and bioactive properties.

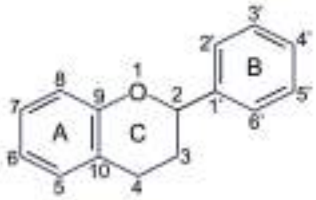


Figure 2-6 Basic structure of flavonoids with its three characteristic rings, highlighting the central C-ring that connects the benzopyran (A and C rings) with the phenyl (B ring) moiety. The general backbone allows for various substitutions, leading to different flavonoid subclasses such as flavonols, flavones, flavanones, isoflavones, anthocyanins, and flavan-3-ols.

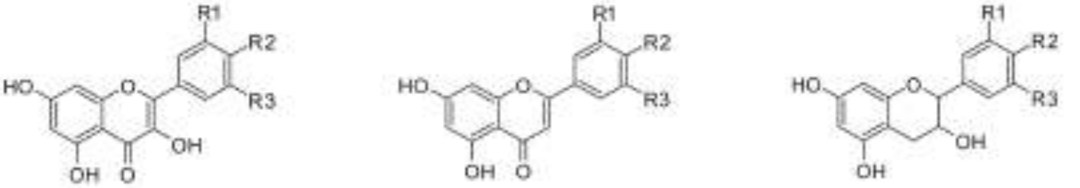
In general terms, the polyphenolic composition of *C. albidus*, listed in Table 2-1, is very similar to that of other members of the *Cistus* subgenus, such as *C. crispus* and *Cistus x incanus* (hybrid of *C. albidus x C. creticus*) (Barrajón-Catalán et al., 2011). A semi-quantitative analysis of the composition of extracts from *C. albidus, Cistus clusii, Cistus ladanifer,* and *Cistus salviifolius* revealed small differences between them (Tomás-Menor et al., 2013) with a series of substances that occur exclusively in *C. albidus*, namely caftaric acid, prunin, and 5-O-caffeoylquinic acid glucoside (Mastino et al., 2021).

2.5.2.1. Flavonoids

Flavonoids contribute to overall fruit colour and flavour in plants (Sticher et al., 2015). In form of flavones they are responsible for the yellow hues of the inner petals in the flowers and of the stamens and, in form of anthocyanidins, for the purple-pink coloured petals of *C. albidus*. Flavones often appear as co-pigments of anthocyanins. The interaction of both types of dye explains the simultaneous appearance of yellow and red in different flowers. Flavonoids found so far are flavonols, flavones, flavanols and tannins (Figure 2-7).

Flavonols and flavones occur in *C. albidus'* aerial parts as free aglycones and glycosides. They are responsible for yellow colour nuances and are usually tasteless. Flavonols are distinguished from flavones by the presence of a 3-hydroxyl group (Figure 2-7). Phenolic substances of the flavonol subclass are present in all plant organs of *C. albidus*. Characteristic representatives of these compounds in *C. albidus* are kaempferol, quercetin, myricetin, myricitrin (myricetin-3-O-rhamnoside) and quercitrin (quercetin-3-O-rhamnoside) (Barrajón-Catalán et al., 2011). High contents of myricetin glycoside (7 mg/g dry weight) were detected in *C. albidus* aerial parts, with myricetin-3-*O*-rhamnoside being the primary derivative of myricetin with an 83% of total myricetin composition, followed by quercetin glycoside (2 mg/g dry weight), being quercetin-3-*O*-rhamnoside the most abundant derivative of quercetin constituting an 80% of the total quercetin composition (Lukas, Jovanovic, et al., 2021). The only flavones detected so far are diglycosylated apigenin (Barrajón-Catalán et al., 2011) and the isoflavone glycitin 6"-*O*-malonate (Mastino et al., 2021).

Flavanols are found predominantly in the leaves of *C. albidus* and contributes particularly to the astringent taste of extracts. Compounds belonging to this subclass have two asymmetrically substituted carbon atoms and can therefore exist as diastereomeric 5,7,3-,4-tetrahydroxyflavanols, catechin and epicatechin. A third hydroxyl group on ring B also results in 5,7,3,4,5-pentahydroxyflavanol gallocatechin, or correspondingly epigallocatechin (Figure 2-7). Among the polymeric flavanols, the most relevant compounds in *C. albidus* are prodelphinidins such as (epi-)gallocatechins. Procyanidins are other representative flavanols contained in *C. albidus* leaves. Within these oligomeric compounds, (epi-)catechins are most common in *C. albidus* aerial parts (Barrajón-Catalán et al., 2011). But also combinations of prodelphinidins and procyanidins were detected. So far the following flavan-3-ol compounds have been found: (+)-catechin, (-)-epicatechin, (-)-(epi)gallocatechin, (-)-(epi)gallocatechin-(epi)catechin dimer, and (-)-(epi)gallocatechin, (-)-(epi)gallocatechin-(epi)gallocatein dimer (Barrajón-Catalán et al., 2011; Qa'dan et al., 2003).



Flavonols

Quercetin: R1 = R2 = OH, R3 = H
Kaempferol: R1 = R3 = H, R2 = OH
Myricetin: R1 = R2 = R3 = OH

Flavones

Apigenin: R1 = R2 = R3 = OH
Luteolin: R1 = R2 = OH, R3 = H

Flavanols

Catechins: R1 = R2 = OH, R3 = H
Gallocatechins: R1 = R2 = R3 = OH

Figure 2-7 Structure of flavonoids (flavonols, flavanols, flavanones) with their three characteristic rings, illustrating the common flavan backbone and the structural variations that distinguish these subclasses. Flavonols contain a hydroxyl group at the 3-position, flavanols (also known as flavan-3-ols) lack a double bond in the C-ring and often occur as monomers or polymers, while flavanones are characterized by a saturated C-ring, influencing their distinct biochemical properties and functions.

Tannins are water-soluble, slightly acidic oligomers of polyphenols. They are able to form water-insoluble complexes with protein molecules. In the past, this property of *C. albidus* was used to tan animal skin in leather production (Wiesner, 1921). Based on the chemical structure of the monomeric building blocks, tannins present in *C. albidus* could be divided into two groups, the condensed and the hydrolysable tannins.

The first group includes the proanthocyanidins (flavanols) already described, which are also known as condensed tannins. They consist of polymerized flavonoid phenols such as catechins, epicatechin, anthocyanins, etc. They are correspondingly polymers whose monomeric units consist of phenolic flavans, mostly catechin (flavan-3-ol).

The second group represents hydrolysable tannins, which are hydrolysed by the action of acids. These compounds exist as various polyhydroxy compounds, for example as sugar esterified with a phenolic acid (Sticher et al., 2015). Within this group, hexahydroxydiphenoyl-D-glucose (HHDP-Glc) was detected in *C. albidus* (Barrajón-Catalán et al., 2011). When the phenolic acid is gallic acid, the compound is called gallotannin. If, on the other hand, esterification with hexahydroxydiphenic acid occurs, this compound is called ellagitannin. Ellagitannins were not found in *C. albidus* aerial parts, except for a residual presence of glucogallin, pedunculagin and punicalagin gallate (Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021).

2.5.2.2. Phenolic acids

Phenolic acids are being understood as the hydroxylated derivatives of benzoic acids (hydroxybenzoic acids) and cinnamic acids (hydroxycinnamic acids). Their highest concentration in plants is found in the outer leaves. In *C. albidus* aerial parts, glucogallin (Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021) and gallic acid (Barrajón-Catalán et al., 2011; Gonçalves et al., 2013) was found. Within the category of phenolic acid derivatives, 5-*O*-caffeoyl quinic acid glucoside, caffeoylquinic glycoside (Mastino et al., 2021), uralenneoside and rhamnoside of hydroxyferulic acid (Barrajón-Catalán et al., 2011) were also detected.

Table 2-2 Phenolic compounds identified in *C. albidus*. 🌱: aerial parts, including leaves and twigs. n/a: reliable data are not available.

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
1	Apigenin diglucoside	flavone	🌱	(Barrajón-Catalán et al., 2011)	anticancer, anti-inflammatory, antimicrobial, antioxidant (Wang et al., 2019); anxiolytic (Salgueiro et al., 1997);
2	Caffeic acid	phenolic acid	🌱	(Lukas, Jovanovic, et al., 2021)	anticancer (Alam et al., 2022; Magnani et al., 2014; Tyszka-Czochara et al., 2017); antimutagenic, antihyperglycemic, anti-inflammatory, antioxidant, (Agunloye et al., 2019; Lopes et al., 2021); antmicrobial (Magnani et al., 2014); cardioprotective (Agunloye et al., 2019); hepatoprotective (Yang et al., 2013); neuroprotective (Alam et al., 2022; Kulkarni et al., 2021);
3	Caftaric acid	phenolic acid	🌱	(Mastino et al., 2021)	anticancer, antidiabetic, antihypertensive, anti-inflammatory, antimutagenic, antioxidant, hepatoprotective, (Khaled & Koriem, 2020);
4	Cynarin	phenolic acid	🌱	(Mastino et al., 2021)	anticancer, antidiabetic antiulcer, antivirus, antioxidant, hepatoprotective, hypocholesterolemic (Gezer, 2017); cardioprotective (Xia et al., 2014);
5	(-)-(Epi)catechin	flavanol	🌱	(Barrajón-Catalán et al., 2011; Qa'dan et al., 2003; Tomás-Menor et al., 2013)	neuroprotective (Sebastiani et al., 2021);

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
6	(-)-(Epi)gallocatechin		🌱	(Barrajón-Catalán et al., 2011; Qa'dan et al., 2003; Tomás-Menor et al., 2013)	antioxidant (Jakubek et al., 2023; Sebastiani et al., 2021); antimicrobial (de Oliveira Caleare et al., 2017); anti-inflammatory, antiallergenic, antivirus, anticancer, skin penetration enhancer, UV-protection (Bae et al., 2020);
7	Epigallocatechin-(4*β*-->8)-gallocatechin- (4α-->8)-gallocatechin trimer		🌱	(Barrajón-Catalán et al., 2011; Qa'dan et al., 2003)	
8	Epigallocatechin-(4*β*-->8)-gallocatechin-(4*α*-->8)-catechin trimer		🌱	(Barrajón-Catalán et al., 2011; Qa'dan et al., 2003)	
9	(-)-(Epi)catechin-(epi)gallocatechin dimer		🌱	(Barrajón-Catalán et al., 2011)	
10	(-)- (Epi)gallocatechin-(epigallocatechin dimer		🌱	(Barrajón-Catalán et al., 2011)	
11	(-)-(Epi)gallocatechin gallate		🌱	(Barrajón-Catalán et al., 2011)	
12	4,3',4'-Trimethyl catechin		🌱	(Mastino et al., 2021)	
13	Ferulic acid oligomer	phenolic acid	🌱	(Mastino et al., 2021)	antioxidant (Zduńska et al., 2018); antimicrobial (Pinheiro et al., 2022); anti-inflammatory (Liu et al., 2022); neuroprotective (Ren et al., 2017); antiviral (Antonopoulou et al., 2021); antiallergic (Lee et al., 2015); hepatoprotective (Esmat et al., 2022); anticancer (Gao et al., 2018); antithrombotic (Choi et al., 2018); antidiabetic (Narasimhan et al., 2015);
14	Hydroxy-ferulic acid rhamnoside	phenolic acid glycoside	🌱	(Barrajón-Catalán et al., 2011)	
15	Feruoyl quinic glucoside		🌱	(Mastino et al., 2021)	n/a
16	Gallic acid	phenolic acid	🌱	(Barrajón-Catalán et al., 2011; Gonçalves et al., 2013)	anti-inflammatory (Kroes et al., 1992; Ojeaburu & Oriakhi, 2021); antiobesity, antioxidant (Dludla et al., 2018);

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
					hepatoprotective (Ojeaburu & Oriakhi, 2021); anticancer ; antifungal (Li et al., 2017);
17	Galloyl glucose	flavanol	🌱	(Mastino et al., 2021)	antiviral (Ahn et al., 2002);
18	Glucogallin	flavanol	🌱	(Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021)	antioxidant, anti-inflammatory, antidiabetic, cataract-preventing, antiglaucoma, UV-protective (Khan et al., 2022);
19	Glycitin 6"-*O*-malonate	isoflavone (flavonoid glycoside)	🌱	(Mastino et al., 2021)	n/a
20	Hexahydroxydiphenoyl-D-glucose	hydrolysable tannin		(Barrajón-Catalán et al., 2011)	antioxidant (Jacob et al., 2018)
21	Kaempferol diglucoside	flavonol	🌱	(Barrajón-Catalán et al., 2011)	antidiabetic (Habtemariam, 2011); anxiolytic, antidepressant, antiepileptic, anti-inflammatory, neuroprotective, analgesic (Silva dos Santos et al., 2021);
22	Kaempferol 3-O-rutinoside		🌱	(Barrajón-Catalán et al., 2011; Tomás-Menor et al., 2013)	
23	Luteolin-7-*O*-rutinoside	flavonol	🌱	(Mastino et al., 2021)	antioxidant, anti-inflammatory (Tian et al., 2021);
24	Myricetin hexoside	flavonol	🌱	(Barrajón-Catalán et al., 2011; Tomás-Menor et al., 2013)	anticancer, antidiabetic, antiobesity, cardioprotective, osteoporosis protective, anti-inflammatory,
25	Myricetin glycoside		🌱	(Lukas, Jovanovic, et al., 2021)	
26	Myricetin 3-*O*-rutinoside		🌱	(Mastino et al., 2021)	
27	Myricetin-*O*-galloyl-hexoside		🌱	(Mastino et al., 2021)	
28	Myricitrin		🌱	(Barrajón-Catalán et al., 2011)	

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
					hepatoprotective (Imran et al., 2021);
29	Oenin	anthocyanin (flavonoid glycoside)	🌱	(Mastino et al., 2021)	anticancer (Oliveira et al., 2016); neuroprotective (Shih et al., 2011); anti-inflammatory (Decendit et al., 2013); antioxidant (Rossetto et al., 2002);
30	Pedunculagin	ellagitannin	🌱	(Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021)	antioxidant, anti-inflammatory, dermatoprotective (M. Kim et al., 2020); anticancer (Chang et al., 1995); antibacterial (Silva Fernandes et al., 2022);
31	Pelargonidin 3-*O*-(6"malonylglucoside)	anthocyanin (flavonoid glycoside)	🌱	(Mastino et al., 2021)	cardioprotective, neuroprotective (Ma et al., 2021; Mattioli et al., 2020);
32	Peonidin 3-*O*-(6"-p-coumaroyl) glucoside	anthocyanin (flavonoid glycoside)	🌱	(Mastino et al., 2021)	cardioprotective, neuroprotective (Ma et al., 2021; Mattioli et al., 2020);
33	Petunidin	anthocyanidin (O-methylated flavonoid)	🌱	(Mastino et al., 2021)	antioxidant ; cardioprotective, neuroprotective (Ma et al., 2021; Mattioli et al., 2020; Zheng et al., 2020);
34	Procyanidin	flavanol	🌱	(Mastino et al., 2021)	antioxidant (Wang et al., 2020); antibacterial (Nawrot-Hadzik et al., 2021); anticancer (Choy et al., 2016); anti-inflammatory (Tian et al., 2019; Wang et al., 2020);
35	Prunin	flavanone	🌱	(Mastino et al., 2021)	antihyperlipidemic, antihyperglycemic, antidiabetic (Jung et al., 2017);
36	Punicalagin	ellagitannin	🌱	(Lukas, Jovanovic, et al., 2021)	anti-inflammatory, antioxidant, neuroprotective, hepatoprotective, cardioprotective, antiviral,
37	Punicalagin gallate		🌱	(Lukas, Jovanovic, et al., 2021)	

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
					antimicrobial, anticancer, antidiabetic, antihyperlipidemic, gastroprotective (Rozadi et al., 2022);
38	Quercetin	flavonol	🌱	(Mastino et al., 2021)	anticancer, antitumor, anti-inflammatory, antiviral, antihypercholesterolemia, antihyperglycemic, antioxidant, antibacterial, cardioprotective, gastroprotective, hepatoprotective, antihypertensive, nephroprotective, neuroprotective (Kim & Park, 2018); antidepressant (Chimenti et al., 2006); antimicrobial (Nguyen & Bhattacharya, 2022), antifungal (Rocha et al., 2019); antiallergic (Kempuraj et al., 2005) antiobesity (Zhao et al., 2017);
39	Quercetin glucoside		🌱		
40	Quercetin 3-*O*-glucoside		🌱	(Mastino et al., 2021)	
41	Quercetin 3-*O*-(2’-cumaroyl)-rutinoside		🌱	(Mastino et al., 2021)	
42	Quercetin 3,4-diglucoside		🌱	(Mastino et al., 2021)	
43	Quercetin 3-*O*-(2’-caffeoyl)-rutinoside		🌱	(Barrajón-Catalán et al., 2011)	
44	Quercitrin		🌱	(Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021)	
45	Rutin		🌱	(Barrajón-Catalán et al., 2011; Lukas, Jovanovic, et al., 2021; Mastino et al., 2021; Tomás-Menor et al., 2013)	
46	Quinic acid	phenolic acid	🌱	(Mastino et al., 2021; Tomás-Menor et al., 2013)	radioprotective (Cinkilic et al., 2013); neuroprotective (Hur et al., 2001); anti-inflammatory (Jang et al., 2017); 5antiviral (Zanello et al., 2015);
47	3*p*-Coumaroylquinic acid		🌱	(Mastino et al., 2021)	n/a
48	3-Caffeoylquinic acid		🌱	(Lukas, Jovanovic, et al., 2021)	antioxidant, anti-inflammatory (Alcázar Magaña et al., 2021);
49	Caffeoylquinic glycoside	phenolic acid glycoside	🌱	(Mastino et al., 2021)	enzyme inhibition, hepatoprotective (Hou et al., 2023);
50	Isorhamnetin-*O*-rutinoside	flavonol	🌱	(Barrajón-Catalán et al., 2011)	anti-atherosclerosis, cardioprotective,

Nº	Compound	Structure/class	Presence in	Analytical Reference	Pharmacology
					neuroprotective, anticancer, antihypertensive, antioxidant antihyperglycemic, hepatoprotective, anti-inflammatory, anti-osteoporosis, antiobesity, UV-protection (Gong et al., 2020); antimicrobial (Jnawali et al., 2016);
51	3-*O*-Methylrosmarinic acid	caffeic acid ester	🌱	(Mastino et al., 2021)	anti-inflammatory, antioxidant, antidiabetes, antivirus, antitumor, neuroprotective, hepatoprotective (Guan et al., 2022);
52	Methoxy dihydroferuoyl methyl rosmarinic acid		🌱	(Mastino et al., 2021)	
53	Dihydroxy-dihydro feruoyl methyl rosmarinic acid		🌱	(Mastino et al., 2021)	
54	*p*-Hydroxy benzil rosmarinic acid		🌱	(Mastino et al., 2021)	
55	Shikimic acid dimer	phenolic acid	🌱	(Mastino et al., 2021)	anticoagulant (Tang et al., 2009); antithrombotic (Veach et al., 2016);
56	6'-O-Sinapoyl sucrose	hydroxy-cinnamate sucrose esters	🌱	(Mastino et al., 2021)	antioxidant (Fabre et al., 2000);
57	Syringyl shikimic acid dimer	phenolic acid	🌱	(Mastino et al., 2021)	n/a
58	Uralenneoside	p-hydroxy-benzoic acid alkyl ester	🌱	(Barrajón-Catalán et al., 2011)	n/a

2.5.3. Carbonylic compounds

Aldehydes are odoriferous aromatic substances in plants. These often arise from substances containing linolenic acid during harvesting, crushing or preparation (Legrum, 2011). The aliphatic aldehydes, octanal (Maccioni et al., 2007), nonanal and decanal (Maccioni et al., 2007; Paolini et al., 2008), were exclusively identified in pollen and may be responsible for the typical sweet smell of the flowers (Fahlbusch et al., 2003). On the other hand, tetradecanal, undecanal and dodecanal were present in the aerial parts (Paolini et al., 2008). These compounds may contribute to the typical sweetish odour of *C. albidus* with its undertone of oranges, lemons and roses (Fahlbusch et al., 2003; Fenaroli & Burdock, 2002).

2.5.4. Phytohormones and vitamin E

Tocopherols and tocotrienols are also present in leaves and seeds. More than 75% of the vitamin E present in the seeds was in the form of *α*-tocopherol followed by *α*-tocotrienol and *γ*-tocopherol (Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019; Pérez-Llorca et al., 2021; Siles et al., 2017), which is the immediate precursor of *α*-tocopherol. Phytohormone and vitamin studies revealed further the presence of the jasmonates 12-oxo-phytodienoic acid (OPDA), jasmonic acid (JA) and jasmonoyl-isoleucine (JA-Ile) and plastochormanol-8 (Casadesús et al., 2021), carotenoids and abscisic acid, with *α*-tocopherol being the most abundant (Müller et al., 2014). A negative correlation was revealed between vitamin E and OPDA accumulation in *C. albidus* under winter conditions, while a positive correlation was found between JA and *α*-tocopherol (Casadesús et al., 2021). A significant positive correlation was also detected between hydration and total leaf chlorophylls due to the protection mechanism of tocopherols from the photosynthetic apparatus. Therefore, higher levels of *α*-tocopherol were observed under abiotic stress conditions and when the leaves showed an orientation more perpendicular to the solar rays (Casadesús et al., 2021; Müller et al., 2014; Oñate & Munné-Bosch, 2010; Pérez-Llorca, Casadesús, Müller, et al., 2019).

Drought stress can induce an increase in the concentrations of abscisic acid and H_2O_2 in the leaves, inducing an increase in ascorbic acid, maintaining and even decreasing the oxidative state of ascorbate, thus protecting plants from oxidative damage (Jubany-Mari et al., 2008; Munné-Bosch et al., 2003). In addition, cytokinins that act as nitric oxide scavengers and are involved in the modulation of the abscisic acid response have been reported (Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019).

C. albidus seeds obtained from mature plants showed higher concentrations of *α*-tocopherol, JA and salicylic acid than those obtained from younger plants. Auxin (indole-3-acetic acid) content was also significantly higher in seeds from older plants. Gibberellic acids GA4 and its precursor GA24 were also found in seeds (Müller et al., 2014). No differences were detected between the concentration of cytokinins in seeds from older and younger plants, except for zeatin, which was significantly higher in seeds from older plants. Zeatin was the main form of cytokinin found in the seeds of *C. albidus* (Müller et al., 2014).

2.5.5. Alkanes

Among the volatile compounds isolated from aerial parts of *C. albidus*, tricosan (Paolini et al., 2008), tetracosan (Llusià et al., 2010), pentacosan (Robles & Garzino, 1998), octacosan (Llusià et al., 2010) and docosan (Llusià et al., 2010; Robles & Garzino, 1998) were found. n-Tridecane was present in petals, n-tetradecane was identified in both petals and pollen, while n-hexadecane was detected only in pollen, and n-pentadecane was found in leaves (Llusià et al., 2010; Paolini et al., 2008; Robles & Garzino, 1998).

2.5.6. Other compounds: fatty and carboxylic acids

Although fatty acids are products of the primary metabolism, they are described here for the role they may play in the bioavailability of pharmacologically active compounds as described below. Among the fatty acids found in the aerial parts of *C. albidus* are tetradecanoic, primaric and pentadecanoic acid (Llusià et al., 2010), nonanoic acid (Fadel et al., 2020), palmitic acid (Paolini et al., 2008) and butanoic acid (Maccioni et al., 2007). The fatty acid composition of the seeds showed significantly higher levels of polyunsaturated fatty acids as well as very long-chain saturated fatty acids for older plants due to their higher levels of linoleic acid (Müller et al., 2014). In addition the carboxylic acids methacrylic acid (Fadel et al., 2020) and quinic acid (Mastino et al., 2021; Tomás-Menor et al., 2013) were identified.

2.6. PREPARATION METHODS OF THE *CISTUS ALBIDUS* EXTRACTS

Studies of the pharmacological properties of traditional medicines based on *C. albidus* preparations are related to the presence of terpenoids and polyphenols. In order to understand the use that has been given to *C. albidus* traditionally, it is necessary to previously review the preparation methods used in popular medicine of this plant due to its influence on the pharmacological effect.

2.6.1. Traditional preparations

For the different applications, traditionally only the aerial parts of *C. albidus* were harvested, mainly the leaves, but also flowers, flower buds and, to a lesser extent, stems. The traditional preparation of *C. albidus* varies from an infusion to a prolonged decoction, while the dose usually used is around 3 g per 100 mL of water, taking a cup (150 mL) two or three times a day (Mulet Pascual, 1991).

Within traditional preparations, decoction is the most used technique. It consists of boiling the plant material for a certain period of time and letting them rest afterwards. This method is primarily suitable for thermostable and water-soluble phytochemicals. During decoction, several compounds expect chemical modifications. For example, catechins undergo epimerization, which is a change in their configuration relative to one of their stereogenic centres. Epimers, specifically epicatechins and epigallocatechins, have been shown to have important health benefits. It has been found that this epimerization occurs more readily in water with alkaline pH-values than in purified water (Wang, 2000). In addition, it has been shown that at temperatures greater than 98°C, epimerization occurs faster than its degradation (Wang et al., 2008), so it can be deduced that the traditional preparation of *C. albidus* is the most effective way to extract catechins and their epimers. However, for green tea, the levels of epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate were reported to increase only during the first 3 to 5 minutes of preparation (infusion at 85°C) and the proportion of these flavonoids decreased as time increased. In contrast, another study found that levels of catechin, gallocatechin, and gallocatechin gallate increased continuously with the length of preparation time (Saklar et al., 2015). Taking these results into account, the pharmacological activities referred to in traditional use could be optimized by limiting the decoction time. Nonetheless, thermolabile compounds are lost in the decoction process. As a result, monoterpenes should not be contained in the resulting extract. Whereas sesquiterpenes would not be affected by extracting temperatures around 100 degrees but by low solubility in water due to their lipophilic character. It can therefore be assumed that terpenes play a minor role in the traditional decoction of plant material.

On the other side, probably in order to use the entire compound spectrum of the plant, based on both terpenes and polyphenols, the dried and crushed leaves sometimes were used directly (orally) (Ajjoun et al., 2022; Alami Merrouni et al., 2021; Fajardo et al., 2000; Fernández Ocaña, 2000; Verde et al., 2008). This usage ensures that the resulting medicine is rich in polyphenols terpenes and other volatiles. But a loss of several terpenes and oxidative reactions could be induced by the drying process, as reported for other species as *Cannabis sativa* (Fiorini et al., 2019; Ross & ElSohly, 1996).

2.6.2. Actual and alternative extraction methods

In general, solid liquid extraction is the most commonly used method for extractive purposes. When using water as a solvent, the extraction is carried out at temperatures ranging between 20 and 50°C. For extraction with solvents such as ethanol, methanol, and acetone, temperatures commonly used range from 60 to 80°C (Antony & Farid, 2022). For temperatures above 80°C, a decrease in the yield of total polyphenols and proanthocyanidins has been reported, suggesting that it is due to their degradation, accelerating this process with temperatures above 70-80°C (Al Juhaimi et al., 2018; Larrauri et al., 1998). However, other studies have shown that the higher the temperature the more efficient the extraction is, since the heat makes the cell walls permeable, increasing the solubility and the diffusion coefficients of the compounds to be extracted and the viscosity of the solvent decreases (Alara et al., 2021). The extraction temperature has a significant effect on the types of polyphenols that are extracted. However, the thermal degradation of different types of polyphenols varies according to the pre-treatment, type of solvent, pH and time used (Antony & Farid, 2022).

On the other hand, a mixture of polar and nonpolar solvents should result in an efficient extraction of both, polyphenols and terpenes at the same time. But with a few exceptions, in its traditional use, *C. albidus* has not been extracted by solvents with combined properties, like EtOH. Studies revealed low efficiency of the these extraction methods as well as environmental problems due to the requirement of large volumes of solvents, especially if they are organic (Zhang et al., 2018). Furthermore, traditional extraction processes involve often an intermediate step before extract concentration that is a time and energy consuming process.

The compounds of *C. albidus* listed in this review were obtained from the aerial parts of the plant by means of distillation or extraction (water, ethanol, chloroform, pentene). **Essential oils** were isolated from fresh aerial parts by hydro-distillation using a Clevenger's apparatus for between 2 h and 8 h. The isolated oil was dried over anhydrous sodium sulphate and the essential oils were stored at +4°C, in glass vials at dark, until analyses (Bechlaghem et al., 2019; Maccioni et al., 2007; Mastino et al., 2017; Palá-Paúl et al., 2005). But also pentane extracts (Llusià et al., 2010) and a mixture of pentane/diethyl oxide (Paolini et al., 2008) were used to isolate essential oils.

To analyse the **polyphenols** of *C. albidus*, aerial parts were usually air dried and grounded into powder to a size between 2-5 mm and then extracted by ethanol maceration (1:4, w/v) up to 72 h or acidified (0.1% HCl) methanol (1:3, w/v) for 24 h. The plant extracts were filtered or decanted (< 24 h) and dried under vacuum using a rotary evaporator at temperatures ≤ 50°C. Extracts were stored at dark between 2-8°C until used for the assessment (Bouyahya, 2016; Mastino et al., 2021; Tomás-Menor et al., 2013).

A special case of polyphenol extraction is the flavonol-enriched *C. albidus* chloroform extract as described by Tahiri et al. (Tahiri et al., 2017). Here the supernatant of the ethanol extract was further partitioned in ethyl acetate and water (1:3:1, w/v/v) and then separated into an organic and an aqueous phase. The organic phase of ethyl acetate was further partitioned in chloroform and water (1:3:1, w/v/v), yielding an organic and an aqueous phase of chloroform, respectively.

For the aqueous extracts, fresh aerial parts were grounded to a maximum size of 5 mm and macerated for 2 h with distilled water (1:5-20, w/v) at temperatures between 60 and 90°C. The filtered extract was then centrifuged and concentrated by rotatory evaporation, and kept at 4°C until use (Barrajón-Catalán et al., 2011; Gonçalves et al., 2013; Lukas, Jovanovic, et al., 2021; Tomás-Menor et al., 2013).

Alternative methods may consist in supercritical CO_2 extraction, microwave-assisted extraction, ultrasound-assisted extraction, enzyme-assisted extraction, pressurized fluid extraction, or a combination of these approaches. These methods need less solvent volume and extraction time, at the same time producing higher yields and reducing toxic residues. Although these methods have not yet been described with *C. albidus*, they may be an interesting alternative that should be further explored as it has been done for other vegetal matrices from *Rosmarinus officinalis* (Reverchon & Senatore, 1992) or *Salvia miltiorrhiza* (He et al., 2019).

2.7. BIOAVAILABILITY OF COMPOUND GROUPS FOUND IN EXTRACTS

Bioavailability is a pharmacokinetic concept that refers to the proportion and the pace at which a served dose of a drug reaches its therapeutic target, considering the tissue on which it acts. According this definition, this term includes the absorption, metabolism and distribution of a single compound. In general, secondary plant substances are absorbed, distributed and metabolized in a similar way to xenobiotics (Teuscher, 2020).

Apart from the fact that it has not yet been proven that extracts from *C. albidus* will be bioavailable, in this subsection an attempt will be made to derive the bioavailability theoretically.

The structure of flavonoids affects their solubility in water, which in turn affects their absorption and bioavailability. Flavonoids with a more hydrophobic structure such as flavonols may have lower bioavailability compared to those that are more hydrophilic like flavanols. Flavonols contain a high proportion of hydrophobic groups such as aromatic rings and aliphatic chains, which make them less soluble in water and more soluble in lipids (Sticher et al., 2015). Flavonoids with a more hydrophobic structure present in *C. albidus* are apigenin, quercetin, myricetin and kaempferol. They must undergo metabolism in the gut to be absorbed (Manach et al., 2005).

On the other hand, the bioavailability of flavanols and condensed tannins is related to its catechol ring structure with hydroxyl groups that can form hydrogen bonds with water molecules, which makes them more soluble in water and more readily absorbed by the body. They cannot be hydrolyzed in the stomach and are therefore broken down into phenolic acids by microorganisms in the large intestine. The latter are then resorbed in the large intestine (Manach et al., 2005). Thus, flavanols, such as catechins are relatively soluble in water and can be absorbed by the body through passive diffusion in the small intestine (Scalbert et al., 2002).

The gut microbiota plays a crucial role in the metabolism and absorption of flavonoids by breaking them down into smaller metabolites that can be absorbed and utilized by the body. Flavonoids are not readily absorbed in their native form and must therefore undergo extensive metabolism in the gut to be absorbed and utilized (Manach et al., 2005). The gut microbiota contains a diverse community of microorganisms, including bacteria, fungi, and viruses, that can metabolize flavonoids through various pathways. Some bacterial species have specialized enzymes that can break down flavonoids into smaller metabolites that are more bioavailable, such as phenolic acids and aromatic compounds (Scalbert et al., 2002; Thilakarathna & Rupasinghe, 2013).

Phenolic acids are generally more water-soluble than flavonoids and can be absorbed by the body through passive diffusion in the small intestine. Overall, the bioavailability of unesterified phenolic acids is high. These can be absorbed quickly in the small intestine without prior hydrolysis. However, phenolic acids are mainly present in esterified form, so that due to the lack of esterases in the human digestive tract, there is no absorption in the small intestine. Esterified phenolic acids are therefore first hydrolysed by microorganisms in the large intestine and the resulting metabolites are then resorbed (Scalbert et al., 2002).

Ellagitannins found in *C. albidus* are considered to have relatively low bioavailability. This is because they are highly complex molecules that require microbial metabolism in the colon to be broken down into smaller, absorbable metabolites (Scalbert et al., 2002).

Regarding the terpenes and other poorly absorbed compounds, it is described that both, their low permeability across absorption barriers and reduced solubility in biological fluids, decreases their bioavailability (Sticher et al., 2015). However, it might be increased through the natural presence in *C. albidus* of certain unsaturated fatty acids by enhancing micellarization during the digestion process. (Failla et al., 2014). These compounds might increase the absorption of terpenoids and polyphenols present in *C. albidus* samples.

Furthermore, phenolic and terpenoid compounds, in the presence of *α*-tocopherol, have been shown to promote transport through the blood brain barrier (BBB) (Ferri et al., 2015). Moreover, studies have shown that borneol could increase the permeability of BBB by significantly losing the intercellular tight junctions (TJ) and increasing the number and volume of fluid endocytosis (pinocytosis) in *in vitro* models, thus enhancing the bioavailability of drugs (Chen et al., 2013; Yin et al., 2017; Yu et al., 2013; Zhou et al., 2010). Thus, several compounds of *C. albidus* may induce potential mechanisms resulting in an increased bioavailability. Further, the absorption and bioavailability of *C. albidus’* compounds can be influenced by other factors such as food matrix, processing (extraction), and individual variations.

2.8. THERAPEUTICAL USES

2.8.1. Traditional uses

Plant resources have always been an integral part of human society throughout history. Until the middle of the last century, traditional medicines provided an alternative and inexpensive source of primary health care for the rural population. However, with access to synthetic drugs, a large number of medicinal plants became obsolete, the memory of which in the population, after only two generations, is being lost.

One of these medicinal plants is *C. albidus*, which has been used in traditional folk medicine for a variety of illnesses (Alcaraz Ariza & Le Houérou, 2002; Mulet Pascual, 1991; Segarra i Durà, 2008; Stübing & Peris, 1998), especially for the treatment of fever, diarrhoea, and other gastrointestinal illnesses (Pardo de Santayana, 2014), skin diseases, rheumatism, and various inflammatory diseases (Gonçalves et al., 2013). For the sake of completeness, it is mentioned here that *C. albidus* has also been used as a tanning agent (Wiesner, 1921), as an insect repellent and as a substitute for tobacco, highly appreciated, moreover, for its hypotensive effect (Ledesma, 2004; Maccioni et al., 2007; Segarra i Durà, 2008).

The decoction of leaves was traditionally used in the Spanish Levant as a tranquilizer. Thus, for example, in the Baixa Plana as a sedative (Mulet Pascual, 1991) and as a remedy against Parkinson's symptoms in Mallorca (Carrió Cabrer, 2013; Carrió & Vallès, 2012). To relieve toothache, mouthwashes were made with a decoction of its leaves and flowers. A sip of the resulting liquid, once cold, was kept in the mouth for some time (Belda et al., 2013; Fernández Ocaña, 2000; Martínez-Lirola et al., 1996; Torres-Montes, 2004). In addition, the decoction of the aerial parts was used as an external antiseptic, for wounds and skin infections (Alarcón et al., 2015; Martínez-Lirola et al., 1996; Ortuño Moya, 2004; Torres-Montes, 2004). In the Spanish Basque Country several uses were reported. For example, decoction was applied for the treatment of ulcers and for the treatment of gangrene and fresh leaves were used directly on the wound for disinfection (Goicoetxea Marcaida, 2017).

In the Mediterranean region, the decoction of the aerial parts (leaves, stems and flowers) has been used to regulate blood pressure (González-Tejero García, 1989; Rivera et al., 2008). It has also been a frequent remedy for haemorrhoids, to treat bruises and varicose veins (Carrió Cabrer, 2013). The decoction of flowers and leaves has also been popularly used as an analgesic for oral infections (Martínez-Lirola et al., 1996) and for hepatoprotection in Granada and Mallorca (Carrió Cabrer, 2013; González-Tejero García, 1989). The decoction of the fresh aerial parts, including the flowers, was used as a remedy against colds and flu infections, against bronchitis (Carrió Cabrer, 2013; Rivera et al., 2008; Verde et al., 2008) and whooping cough (Mulet Pascual, 1991). In the Spanish Peninsula*, C. albidus* decoction has also been used as a remedy for osteoarthritis in the Province of Jaen (Fernández Ocaña, 2000) and rheumatism in the Valencian Community and the Province of Jaen (Belda et al., 2013; Guzmán, 1997). In addition, it was used as an external antiseptic for wound healing and skin infections in the Provinces of Castellon, Mallorca and Almería (Carrió Cabrer, 2013; Martínez-Lirola et al., 1996; Mulet Pascual, 1991) and in Morocco (Ajjoun et al., 2022; Alami Merrouni et al., 2021). In Sardinia (Italy), a traditional use is reported in poultices and ointments where it was applied directly to the wound (Atzei, 2003).

In cases of gastrointestinal infections, in Almería (Spain), an infusion of dried leaves was prepared to reduce abdominal pain (González-Tejero García, 1989; Martínez-Lirola et al., 1996). Against colic, in Castilla-La Mancha and Murcia (Spain) an infusion of young and tender shoots was administered, but it was also supplied by oral ingestion of the powder of dry leaves for its treatment (9,264). The dried leaf powder also served as an antidiarrheal in Jaen (Fernández Ocaña, 2000).

Infusions of fresh flowers and leaves have been used as an antiseptic for the urinary tract in Murcia (Rivera et al., 1994) and also as an anti-inflammatory for orchitis in Valencia (Pellicer, 2000).

2.8.2. Scientific evidences confirming traditional uses

2.8.2.1. Antimicrobial activity

The antimicrobial activity of *C. albidus* is attributed to two main compound classes, terpenes, and polyphenols. Studies have shown that both terpenes and polyphenols have potent antibacterial and antifungal activities (Bechlaghem et al., 2019; Bouyahya, 2016; Mastino et al., 2021; Tomás-Menor et al., 2013). However, there are few studies on the antimicrobial activity of *C. albidus*.

The terpenoid fraction of *C. albidus* extracts has been found to exhibit antimicrobial activity against *S. aureus, Bacillus subtilis, Listeria monocytogenes, Klebsiella pneumoniae*, and *Candida albicans* (Bechlaghem et al., 2019). Gram-positive bacteria are more affected by terpenoids than gram-negative bacteria (Bechlaghem et al., 2019). The inhibitory activity against *B. subtilis, S. aureus, L. monocytogenes, K. pneumoniae*, and *C. albicans* is seen at a minimum inhibitory concentration (MIC_{50}) of 20 µ/mL, while *E. faecalis, E. coli*, and *E. freudii* are not affected (Bechlaghem et al., 2019).

The polyphenolic compounds, such as gallic acid and some glycosylated derivatives of myricetin and quercetin, are found in *C. albidus* extracts that exhibit strong antimicrobial activity against *S. aureus* (Bechlaghem et al., 2019; Tomás-Menor et al., 2013). However, the specific role of polyphenols in the antimicrobial capacity of *C. albidus* extracts against several bacteria, including *S. aureus* and *E. coli*, is not yet clear. Some studies suggest a positive correlation between the higher content of polyphenols and higher antibacterial activity against both Gram-positive and Gram-negative bacteria (Tomás-Menor et al., 2013). The antimicrobial activity may be attributed to a synergistic effect of different compounds, including phenolic and terpenoid. The polar fraction of *C. albidus* extracts, including the butanol extract, the spray-dried aqueous extract, and the ethyl acetate extract, all exhibit strong antimicrobial activity against *S. aureus* with MIC_{50} of 2.5 mg/mL (Mastino et al., 2021), 60.0 µg/mL (Tomás-Menor et al., 2013) and 1.25 mg/mL (Mastino et al., 2021) respectively. The hydroalcoholic extract of *C. albidus* also shows strong activity against *E. coli* with MIC_{50} of 233 µg/mL (Tomás-Menor et al., 2013).

2.8.2.2. Anti-inflammatory, antinociceptive, analgesic and sedative activity

The anti-inflammatory, antinociceptive, analgesic and sedative effects reported in the traditional use of this species are probably based on both, terpenes and polyphenols and, may be the result of a synergy of both groups of compounds, each with different effects on the Central Nervous System (CNS). Among single compounds of the terpenoid class, present in *C. albidus* with a reported neurophysiological activity, are the monoterpenes bicyclogermacrene, borneol, *p*-cymene, germacrene-D, linalool, myrcene, α-phellandrene, safranal, thymol and the sesquiterpenes abscisic acid, α-bisabolol, *β*-caryophyllene, caryophyllenol, guaiol, selin-11-en-4-*α*-ol, *β*-sesquiphellandrene and α-zingiberene (Table 2-1).

A recent study with α-zingiberene, one of the principal compounds in *C. albidus*, showed a significant anti-inflammatory activity resulting in a reduction in angiogenesis, macrophage activation, as well as in the activity of metalloproteinases (Ferreira et al., 2022). In a mice model, α-zingiberene was found to reduce neuroinflammation through Histone deacetylase 1 (HDAC1) inhibition. Neuropathic pain results from microglia-spinal overexpression of HDAC1 and α-zingiberene was found to be a promising HDAC1 inhibitor, with an IC_{50} of 2.3 ± 0.1 μM. Further, the administration of α-zingiberene reduced thermal hyperalgesia and mechanical allodynia (Borgonetti et al., 2023). Moreover, germacrene-D, another principal compound, was shown to have the potential for the development of pharmaceutical formulations with anti-inflammatory, antinociceptive and analgesic activities in non-toxic concentrations (Ascari et al., 2019; Guedes et al., 2023).

Due to the polyphenolic composition, significant anti-inflammatory and antinociceptive activities were observed in *C. albidus* extracts, especially for several flavonols (Tahiri et al., 2017; Yatoo et al., 2018). Anxiolytic and analgesic properties have also been observed for apigenin diglucoside (Salgueiro et al., 1997), which selectively binds with high affinity to $GABA_A$ receptors. Similarly, kaempferol, myricetin and quercetin derivatives are potentially responsible for anxiolytic, antinociceptive, and anti-inflammatory activity without exerting psycho-modulatory effects (Gertsch et al., 2008; Salgueiro et al., 1997; Tahiri et al., 2017; Viola et al., 1995; Vissiennon et al., 2012). In addition, quercetin and kaempferol exhibited antidepressant effects. It has been demonstrated in several studies that both compounds act as monoamine oxidase inhibitors (Chimenti et al., 2006; Sloley et al., 2000).

In a murine model, a flavonol-enriched *C. albidus*-extract exhibited a substantial reduction in paw oedema and significantly inhibited nitrite generation without affecting the cell viability of lipopolysaccharide-stimulated murine peritoneal macrophages (Tahiri et al., 2017). The same study observed a downregulation of the proinflammatory enzymes cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS) in macrophages treated with the *C. albidus* extract, as well as a decrease in *p*38 mitogen-activated protein kinases (MAPK) phosphorylation. Furthermore, a high antinociceptive activity was observed at a concentration of 100 mg/kg and proved to be as efficient as acetylsalicylic acid at concentrations of 200 mg/kg. An HPLC-DAD-ESI-MS/MS analysis of the used chloroform extract revealed that kaempferol and quercetin derivatives were potentially responsible for such effects (Tahiri et al., 2017). It is suggested that these compounds may act through a CNS mediated analgesic mechanism. Both effects suggest that the polyphenolic composition of this species may act on the central and peripheral nervous system through inhibition of the mechanisms of pain acting as a sedative (Coppin et al., 2013; Tahiri et al., 2017).

2.9. POTENTIAL PHARMACOLOGICAL APPLICATIONS AND THEIR MECHANISMS

The pharmacological activity of traditional preparations of *C. albidus* is mainly based on the antimicrobial, anti-inflammatory, antinociceptive and analgesic effects of several of its compounds. Most of these activities have been confirmed by recent studies as described in previous section, but taking into account the whole spectrum of bioactive substances included in *C. albidus* samples, new applications derived from the above-mentioned pharmacological activities can be suggested, opening the field for future research and uses. In this context, labdane-type diterpenes are promising compounds which were shown to exert strong antiviral activity. For example, manoyl oxide showed a high capacity to suppress the dengue virus. In a fraction of labdanum diethyl ether extract at a concentration of 31.25 μg/mL from *C. creticus*, the proliferation of this virus was suppressed by 100% (Kuchta et al., 2020).

In the field of cancer research, evidence suggests that 13-epi-manoyl oxide, a characteristic labdane-type diterpene of *C. albidus,* may play a pivotal role in antitumor activity inducing apoptosis in leukemic cell lines through multiple pathways (Angelopoulou et al., 2001; Dimas, Demetzos, et al., 1999; Dimas et al., 1998; Dimas, Kokkinopoulos, et al., 1999). But also flavanols like prodelphinidins and epigallocatechin-gallocatechin-catechin oligomers were shown to exert a significant growth inhibitory activity against human prostate cell lines by blocking cell cycle partly at the G1/G0 phase and activating caspase-3 as it was shown for prodelphinidins extracted from *C. albidus* (Makabe et al., 2016), synthetic prodelphinidins (Fujii et al., 2013) and oligomeric proanthocyanidins from *Vigna angularis* (Kawahara et al., 2019). The cytotoxic effect was suggested to be related with the presence of the pyrogallol moiety (Makabe et al., 2016). However, due to the composition of *C. albidus*, future applications could focus on the prevention of neurodegenerative diseases.

2.9.1 Prevention of neurodegenerative diseases

A potential field of application, regarding phenolic compounds from *C. albidus*, is the prevention of neurodegenerative diseases (NDDs). The potential application of the phenolic compounds of *C. albidus* for NDD prevention is suggested to be based on a combination of properties like free radical scavenging and heavy metal chelation.

2.9.1.1 Free radical scavenging

Pathogenesis of NDD is influenced by oxidative stress (Scalbert et al., 2005). Studies have shown the preventive effects of antioxidants in this regard, and in particular, an improvement in cognitive and neural functions was observed (Joseph et al., 1999). In addition, human CNS studies found that antioxidants can improve cerebral blood flow (CBF) (Francis et al., 2006; Sorond et al., 2008). This effect is particularly significant since it influences the maintenance of cognitive performance through adult neurogenesis (Gage, 2019) by improving vascularity (Boldrini et al., 2018). *C. albidus* is rich in antioxidants of both, terpenes and polyphenols – especially the phenolic content with high amounts of flavonols, phenolic acids, flavanols, anthocyanins and tannins. However, although phenolic compounds are the most abundant and potent antioxidants in *C. albidus*, there are also non-phenolic compounds, such as terpenes, that contribute to the overall antioxidant activity of this species.

Within polyphenols, the flavonols, myricetin and quercetin, both a hydroxylated form of kaempferol, are capable of inducing the enzyme glutathione-S-transferase, which is involved in resistance to oxidative stress. Myricetin and quercetin and their glycosides, especially the rhamnosides, act directly as free radical scavengers (Mahmoudi et al., 2016). They are capable of preventing DNA, protein, and membrane damage due to their aromatic hydroxyl groups (Limasset et al., 1993). Especially, quercetin acts as a potent radical scavenger based on three structural parts – an *O*-dihydroxy structure (catechol in ring B), a 2,3-double bond in combination with a 4-oxo group and the additional presence of a 3- and 5-hydroxyl group (Sticher et al., 2015).

Furthermore, it was demonstrated that flavanols like epicatechins and phenolic acids like gallic acid exert strong neuroprotective effects. They are able to block neurotoxic effects caused by oxidized proteins. For example, some HIV proteins are known to cause neurotoxicity in humans through mechanisms that activate macrophages and glial cells inducing the production of oxidative stress. Epicatechins have been shown to neutralize this effect (Huang et al., 2006). In another study, prior to gamma radiation exposure, epicatechin treatment prevented liver and testicular damage due to oxidative stress produced by free radical formation as a result of radiation (Cheng et al., 2020), suggesting that epicatechin may present protective effects in patients undergoing radiotherapy. It was further shown, that epicatechins decrease the susceptibility of low-density lipoproteins to oxidation, thus preventing the onset of atherosclerosis (Lavanchy, 2011). In addition, neuroinflammation in a PD-induced mouse model was significantly reduced when animals were given gallic acid (100 mg/kg) by attenuating heme oxygenase-1 (a redox-regulated protein) and α-synuclein aggregation (an indicator of neurodegeneration of the CNS), suggesting that gallic acid is capable of inhibiting lipopolysaccharide-induced oxidative stress and protein conjugation (Liu et al., 2020).

In general, several studies demonstrated a positive correlation between the total phenolic content of *C. albidus* and its antioxidant activity (Casadesús et al., 2021; Gonçalves et al., 2013; Jubany-Mari et al., 2008; Mastino et al., 2021; Munné-Bosch et al., 2003). Bouyahya et al (Bouyahya, 2016) determined the total phenolic content for an ethanolic extract of *C. albidus* as high as 112.48 ± 1.78 mg gallic acid equivalents per gram extract. The antioxidant activity (2,2-diphenyl-1-picrylhydrazyl radical scavenging assay, DDPH) was determined also with high values between 27,26 and 142 mg Trolox equivalents per gram dry weight by Gonçalves et al. (Gonçalves et al., 2013) and Lukas et al. (Lukas, Jovanovic, et al., 2021) respectively. A study of *C. albidus* from Sardinia showed the ability to scavenge DPPH radicals from *C. albidus*-extracts with EC_{50} values of 31.93 μg mL^{-1} for the butanol fraction, 22.23 μg mL^{-1} for the ethyl acetate fraction and 33.24 μg mL^{-1} for water (Mastino et al., 2021).

Regarding the antioxidant activity of terpenes in *C. albidus*, these compounds are present in smaller but not negligible quantities and may be responsible for a synergistic effect. They may improve symptoms caused by inflammation processes, inhibiting them in different steps of the inflammatory process, as demonstrated by a series of studies (Bahi et al., 2014; Benito et al., 2008; Gertsch et al., 2008; Walter et al., 2003). Terpenes present in *C. albidus* with potential activity on oxidative stress are *α*-bisabolol, *α*-pinene, *α*-zingiberene, *β*-caryophyllene, *δ*-limonene, myrcene, p-cymene, linalool and humulene (Gonzalez-Burgos & Gomez-Serranillos, 2012). The mechanisms of action involved in the antioxidant activity are mainly the reduction of lipid peroxidation induced by H_2O_2, decreasing the formation of ROS and the release of NO. Furthermore, terpenes can increase catalase, superoxide dismutase, peroxidase activities and reduce glutathione content, and restore the mitochondrial membrane (Kim et al., 2020). On the other hand, α-pinene, limonene and *β*-caryophyllene are GABA receptor agonists, decreasing the activities of acetylcholinesterase and lipoxygenase. They can arrest the cell cycle in the G2/M phase (Kim et al., 2020).

It has been claimed that α-bisabolol exhibits antioxidant activity in chemical and/or biological assays. Studies indicated that α-bisabolol significantly inhibits luminol-amplified chemiluminescence at concentrations ranging from 7.7 to 31 μg/mL for *Candida albicans* and N-formyl-methionyl-leucyl-phenylalanine, respectively. A similar effect was observed in the SIN-1 and H_2O_2/HOCl systems, suggesting that *α*-bisabolol is a means of enhancing antioxidant capacity (Braga et al., 2009).

Limonene, one of the most abundant terpenes in nature, was found to exert antidepressant-like effects in mice caused by reduced nitrite levels in the hippocampus (Lorigooini et al., 2021). In addition, it has been shown that limonene reduced the inflammatory response and decreased the levels of inflammatory cytokines such as IL-1, IL-6 and TNF-α, which are related to depressive symptoms (d'Alessio et al., 2014).

In relation to linalool, there are several in vitro and in vivo studies that show a strong anti-inflammatory and antioxidant activity that confers it an important neuroprotective activity (Batista et al., 2010; Y. Li et al., 2015). Its mechanism of action consists in reducing the activation of NF-*κ*B and preventing its nuclear translocation (Del Prado-Audelo et al., 2021).

2.9.1.2. Heavy metal chelation

Another factor associated with ROS is the accumulation of heavy metals in the CNS, which can be treated with chelation. These metals are essential for biological functions in plants and animals, but their chemical properties can cause toxicity by interfering with homeostasis. They may bind to inappropriate protein sites, displacing natural binding sites and causing cellular malfunction. Heavy metals have been found to cause oxidative damage to biological macromolecules, primarily by binding to DNA and nuclear proteins. Exposure to heavy metals is related to proinflammatory cytokines resulting in neuronal damage through neuroinflammation and can lead to various disorders and diseases (Cicero et al., 2017).

Numerous studies have demonstrated a connection between AD, PD and dementias, and an exposure to heavy metals due to oxidative stress caused by the formation of free radicals (Bakulski et al., 2020; Pyatha et al., 2022). Results from several studies suggest even associations between the levels of metals during pregnancy and autism spectrum disorder (ASD) in children (Adams et al., 2009; Arora et al., 2017; Grove et al., 2017). In a recent study, arsenic, cadmium, copper, mercury, manganese, magnesium and lead were identified in the development of ASD. The results of this study suggest that the impact of these metals may be related, in addition, with Attention deficit hyperactivity disorder (ADHD), sharing neurochemical and neurodevelopmental pathways (Skogheim et al., 2021).

Chelation is a process in which a molecule, known as a chelating agent, forms a complex with a metal ion by surrounding it and holding it in a stable, water-soluble form. Chelation can occur through the formation of coordinate covalent bonds between the metal ion and the chelating agent (Hider et al., 2001). The metal chelation potential of polyphenols is highly dependent on catechol moieties and combinations of hydroxyl and carbonyl groups (Fraga et al., 2010). Combinations of these groups and moieties define metal binding sites. Chelating agents are compounds that bind to metal ions and prevent them from participating in reactions that can generate reactive oxygen species (ROS). Metal ions can catalyse the production of ROS by participating in reactions that generate highly reactive oxygen species. By binding to these metal ions, chelating agents can prevent them from participating in these reactions, reducing the amount of ROS that are produced. Several polyphenols, present in *C. albidus,* may exert both, antioxidant and chelating properties as it was shown for isolated polyphenols (Jomova et al., 2017; Lakey-Beitia et al., 2021) and can form stable five- or six-membered rings with oxophilic transition metal ions such as iron, copper, and zinc which are abundant in the CNS (Lakey-Beitia et al., 2021; Savelieff et al., 2014).

Flavonoids such as kaempferol, quercetin, myricetin, luteolin, as well as flavanols like catechins have multiple oxygen-containing functional groups, such as hydroxyl (-OH) and carboxyl (-COOH) groups, as shown in Figure 2-8, which are capable of binding to metal ions and forming chelates (Lakey-Beitia et al., 2021). The chelating effect of these compounds may also be enhanced by their ability to form hydrogen bonds with metal ions, which further stabilizes the complex (Fernandez et al., 2002).

There is evidence that the free radical scavenging and metal chelating effects of aqueous extracts of *C. albidus* could contribute to the prevention of Fe^{2+}-induced lipid peroxidation (Gonçalves et al., 2013). Infusions of *C. albidus* showed a high capacity to form complexes with Fe^{2+} of 66.63% at a concentration of 1.6 mg mL^{-1}. This is especially noteworthy because Fe^{2+} chelation was suggested to be a more important mechanism than direct free radical scavenging for the prevention of lipid peroxidation (Gonçalves et al., 2013).

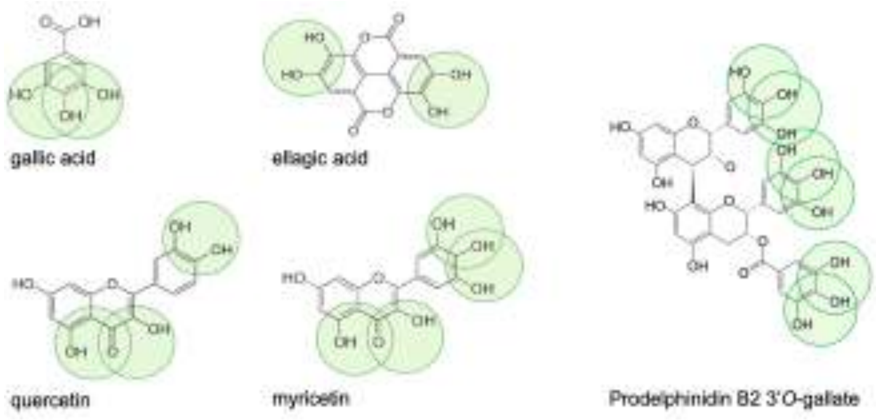


Figure 2-8 Structural formula of gallic and ellagic acids, as well as quercetin, myricetin and prodelphinidin B2 3'O-gallate. In green, the binding sites responsible for the chelating activity.

2.10. TOXICITY

Aside from the fact that this species has been used as an insect repellent and its dead leaves are allelopathic to other plant species, to date, no intoxication produced by *C. albidus* has been reported for mammals. Studies to evaluate the toxicity of *C. albidus* extracts have not yet been performed.

For the genus *C.,* in general, there is no evidence of toxicity. However, isolated cases of intoxication in bovines have been associated with a possible ingestion of *C. salvifolius* (Mignacca et al., 2020; Yeruham et al., 2002). However, the responsible substances contained in some species of the genus *C.*, especially in *C. salvifolius*, which could cause toxic effects, are not yet clear (Bruno-Soares et al., 2004) and may be related to their tannins. Tannins differ from other phenolic compounds by their ability to precipitate proteins, exerting a direct inhibition of digestive enzymes that lead to the formation of indigestible complexes for ruminants. Bacterial fermentation converts tannins into gallic acid and pyrogallol, both of which are nephrotoxic to cattle (Mignacca et al., 2020). It is noteworthy that *C. albidus* was widely used in ethno-veterinary for a variety of diseases (Chaachouay et al., 2022; Rivera et al., 2008; Verde et al., 2008). For example, a decoction of leaves and flowers of *C. albidus* was popularly used to treat rumination syndrome in horses (Verde et al., 2008).

2.11. CONCLUSIONS

The composition of secondary metabolites of *C. albidus*, with more than 200 identified compounds, supports the widespread use of this species in folk medicine and indicate the therapeutic potential with mainly anti-inflammatory, antimicrobial, antinociceptive and analgesic properties.

The broad-spectrum antimicrobial effects of the *C. albidus* extracts, summarized in this review, support further exploration of the extracts and their components for novel approaches. Furthermore, its potential to regulate physiological processes in the nervous system, makes this species an interesting candidate to be used for neurodegenerative disorders and diseases, especially in those diseases with an inflammatory or oxidative implication.

No references to metabolites that could exhibit toxicity have been found, nor are there known episodes of intoxication in humans. Based on ethnobotanical research, the paraphyletic varieties of the *Cistus* subgenus, especially *C. creticus* and *C. albidus*, were traditionally used for direct consumption of their leaves (dried and ground) or their extracts (as infusions and decoctions). Therefore, and based on its long traditional use, this plant could be considered safe.

In this work, it has been argued that the success of the effectiveness of traditional preparations based on *C. albidus* may be based mainly on three factors. On the one hand, there is the pharmacological activity that derives from certain terpenes and polyphenols naturally present in *C. albidus*. On the other hand, increased bioavailability of phenolic and terpenoid compounds is suggested due to the presence of *α*-bisabolol, tocopherols and fatty acids.

And finally, since they are present in the same drug (aerial parts), all the compounds coexist in an equilibrium, which suggests a natural synergism. Hence the entire drug should be more effective than the isolated substances that compose it. This natural composition of all the compounds found in this species makes *C. albidus* a medicinal plant with high potential, especially for treating and preventing neurodegenerative diseases and disorders.

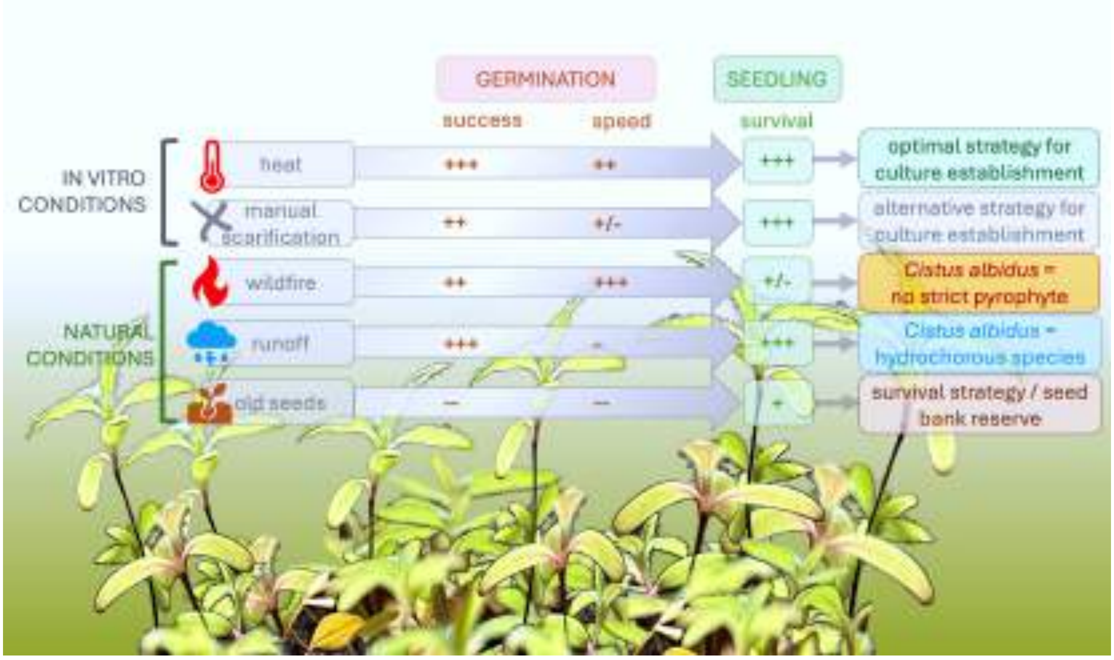
We hope that this review will help lay the groundwork for further comprehensive pharmacological and pharmaceutical studies to better understand the clinical relevance and use of *C. albidus* and improve its legal status as a traditional medicinal plant.

Chapter 3

Germination and Survival Strategies in an Ecological Context

Comparative Effects of Wildfires and Torrential Rains on the Germination and Dispersal of *Cistus albidus* L. in Mediterranean Ecosystems

3. GERMINATION AND SURVIVAL STRATEGIES IN AN ECOLOGICAL CONTEXT



Graphical Abstract 2 *C. albidus*, traditionally classified as a pyrophyte, shows optimal germination under runoff conditions rather than after wildfires, suggesting that its reproductive strategy is more strongly linked to riparian traits than to fire adaptation, challenging conventional ecological assumptions.

Abstract

The white rockrose (*C. albidus* L.), a semideciduous species of the Cistaceae family, is native to the Mediterranean region and plays a crucial role in the functioning of the ecosystem. Most research on *C. albidus* reproduction has focused on the role of fire and high-summer temperatures in breaking seed dormancy, leading to its classification as a pyrophyte. However, this focus overlooks the spatial distribution patterns of the species. In our study, we broaden the scope to examine both its reproductive and dispersal strategies, aiming for a more comprehensive understanding of how *C. albidus* adapts to environmental changes.

Our hypothesis is that *C. albidus* employs a complex survival strategy rooted in its riparian traits, with adaptations to changing environmental conditions, particularly shifts in climate, that may have facilitated a transition from riparian specialization to the development of pyrophytic traits. To test this hypothesis, we investigated the ideal conditions for its germination by simulating two common natural effects in the Mediterranean: wildfires and runoff from torrential rains.

Our results indicate that runoff conditions are the most favourable for the germination of *C. albidus*, explaining its frequent occurrence along temporary waterways. While wildfire simulation significantly accelerated germination, the variability of factors in and after actual wildfire scenarios reduces the probability of successful germination. Summer wildfires do not contribute to the spatial dispersal of *C. albidus* seeds and may even reduce survival rates by destroying seed banks thus challenging the common view that *C. albidus* is a pyrophyte by definition.

Keywords

Cistus albidus, Dispersal, Germination, Mediterranean Region, Runoff scarification, Seed dormancy, Wildfire simulation.

3.1. INTRODUCTION

The Mediterranean region, characterized by hot, dry summers and mild, wet winters, experiences a highly variable climate with frequent disturbances such as wildfires and torrential rains (Rundel et al., 2018; Senciales-González & Ruiz-Sinoga, 2021). *C. albidus* has adapted to these conditions, playing a crucial role in stabilizing the soil, preventing erosion, and supporting biodiversity. (El Mamoun et al., 2020; Hernández-Castellano et al., 2020; Parra et al., 2016; Pérez-Llorca et al., 2021). Its extensive and deep root system effectively binds soil on steep slopes and in areas prone to heavy rainfall, reducing the impact of flash floods and mitigating soil erosion. By stabilizing the soil, *C. albidus* helps prevent the loss of fertile topsoil and contributes to overall improvement in soil quality (Alguacil et al., 2003; El Mamoun et al., 2020; Pérez-Sanz et al., 2023).

It's remarkable adaptability to extreme conditions such as drought, high temperatures, and nutrient-poor soils makes *C. albidus* an ideal species to restore severely degraded land. Its resilience allows it to thrive in harsh environments, creating the foundation for the colonization of other plant species (Gómez-Aparicio et al., 2004). As a pioneer species, *C. albidus* facilitates natural succession by modifying soil and microclimate, paving the way for less resilient species to establish (Castells et al., 2004; Castells & Peñuelas, 2003). This process promotes long-term ecological recovery, leading to stable and healthy ecosystems (Saura-Mas et al., 2020).

In addition to its role in soil stabilization, *C. albidus* enhances local biodiversity. Its abundant spring-to-summer blooms (Figure 3-1) attract a wide range of pollinators, including bees and other apoidea, which are vital for the reproductive cycles of both the rockrose and nearby plant species (Blasco & Mateu, 1995; Hernández-Castellano et al., 2020). *C. albidus* also supports the larger ecosystem by providing habitat and food for various insect and bird species, contributing to the complexity and resilience of Mediterranean ecosystems (Hernández-Castellano et al., 2020). Its production of organic matter through leaf litter and its role in improving soil structure further underscore its ecological importance.

Figure 3-1 The study area: a typical *C. albidus* stand called Jaral in Valle y Carrascoy regional park in Murcia (Spain): healthy plants in full bloom (April 2022) (left); dead plants after a prolonged dry period (October 2024) (right).

Given the central role that *C. albidus* plays in Mediterranean ecosystems, understanding its reproductive strategies and survival mechanisms is crucial. Specifically, its ability to regenerate after environmental disturbances, such as wildfires and heavy rains, is of particular interest. The survival and dispersal of *C. albidus* in fire-prone environments have been well documented, leading to its classification as a pyrophyte, a species whose reproduction is enhanced or facilitated by fire (Roy & Sonie, 1992; Thanos et al., 1993; Trabaud & Oustric, 1989). This classification comes from the observation that the heat of wildfires breaks the dormancy of the *C. albidus* seed, enabling rapid germination after a fire.

According to the Spanish Society of Forest Sciences a pyrophyte is a “species adapted to survive large fires, or in areas with frequent recurrence of fires” and “a plant species whose reproduction is favoured by fire” (Sociedad Española Ciencias Forestales, 2017). Following this definition, a pyrophytic plant is one that is adapted to resist or achieve a competitive advantage from wild fires (Allaby, 2006), meaning that its life cycle and physical characteristics are influenced by fire.

However, while this pyrophytic characteristic is widely recognized, the reliance of *C. albidus* on fire for its propagation is not exclusively (Trabaud, 1995). Unlike typical pyrophytic species such as *Pinus halepensis* or *Quercus suber*, which have well-documented adaptations to survive and regenerate after fires, *C. albidus* shows a distinct reproductive strategy. Although it can germinate after fire exposure due to heat-breaking seed dormancy, its primary mode of dispersal appears to be through runoff from torrential rains.

Field observations by the authors suggest that *C. albidus* colonizes not only disturbed areas, but also forests that have been free from disturbances, such as wildfires, for decades. *C. albidus* grows particularly in regions with north-facing slopes or along temporary waterways. In these environments, the species thrives in microhabitats shaped by runoff from seasonal torrential rains. These watercourses provide ideal conditions for seed scarification, where the physical process of runoff abrades the seed coat, making it permeable to water and enabling germination (Trabaud & Renard, 1999). This observation challenges the traditional view that *C. albidus* is mainly dependent on fire for regeneration. In fact, in several regions such as the Valle y Carrascoy regional park in Murcia and Barranco de la Sal in Santa Pola, Spain, *C. albidus* populations have flourished despite the absence of wildfires in decades. This suggests that the species may employ a more nuanced reproductive strategy, one that is adaptable to various environmental disturbances.

Our hypothesis is that *C. albidus* employs a complex survival strategy rooted in its riparian traits, with adaptations to changing environmental conditions, particularly shifts in climate, that may have facilitated a transition from riparian specialization to the development of pyrophytic traits. As such a species, *C. albidus* is capable of rapidly colonizing disturbed landscapes, including areas cleared by human activity or natural events (Trabaud, 1995). However, its ability to regenerate without fire, particularly along temporary waterways, suggests a broader survival strategy that goes beyond pyrophytism. This is especially important for understanding how *C. albidus* adapts to the Mediterranean climate, where fire seasons are increasingly decoupled from periods of rain due to climate change (Ali et al., 2012). The resilience of the species in these environments is likely to be a critical factor in ensuring its persistence under the pressures of a rapidly changing climate.

To test this hypothesis, we conducted four controlled experiments to simulate two key environmental conditions typical of the Mediterranean region: wildfires and heavy rains followed by torrential water runoff. By comparing the germination rates of *C. albidus* seeds exposed to heat treatments that simulate wildfire conditions with those subjected to mechanical scarification that mimics the effects of runoff, our aim is to elucidate the conditions most conducive to successful germination and establishment of the species. Additionally, we investigated the germination behavior of untreated one year old seeds to gain further insight into the survival strategy of this species. This study aims to provide information on the primary dispersal mechanisms of the species and to assess its adaptability to various environmental stressors. The findings have important implications for conservation efforts, habitat restoration, and sustainable cultivation practices.

3.2. MATERIALS AND METHODS

3.2.1. Study area and seed collection

The seeds used in this study were collected from wild *C. albidus* plants that grow in the Valle y Carrascoy regional park, located in Murcia, Spain (37.925889°N, 1.128056°W; Figure 3-1). The area is characterized by a semiarid climate, with an average precipitation of 187 mm during the flower formation and fruiting period of 2021 (January to May) (Figure A1) and an average temperature during this period of 15.9°C. In 2020, annual precipitation reached 266 mm with an average temperature of 18.9°C. The study plot was located at an altitude of 290 m above sea level, covering an area of approximately 250 m², on calcium rich luvisol soil with a loam texture (Table A1).

Six plants of *C. albidus* that grow uniformly were selected from the plot. These plants, according to Siles et al. (2017), had an estimated age of around 12 years and a perimeter of 6.1 ± 0.4 cm. The plants grew distanced 1-2 m and were north oriented. Water input came exclusively from natural rainfall. From January to May 2021, the average soil moisture at a depth of 0.25 m was 28.6 % (Figure A2). The surrounding vegetation included *Anthyllis cytisoides*, *Salsola genistoides*, and *Stipa tenacissima*, bordered by a *Pinus halepensis* forest (Figure 3-1).

3.2.2. Flowering, seed selection, and preparation

The flowering of the mother plants was determined based on a daily count from February to July 2021. Seed-containing capsules (fruits) were collected from plants that bloomed in March and early April 2021. Their maturity was assessed using prior field experience: capsules exhibiting a light brown color, easy detachment from the plant, a minimum diameter of 0.8 cm at the equator, and initial apex openings were considered mature (Figure 3-2).

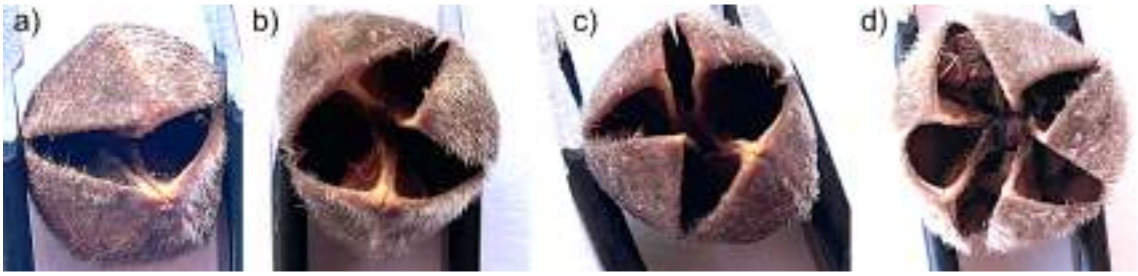


Figure 3-2 The images depict the characteristic loculicidal capsules of *C. albidus*, which open at the apex and separate into five valves that contain the seeds. On the far left is a mature capsule. These woody, hairy capsules, measuring 6–8 mm in length, are covered by a persistent five-valve calyx. The capsules are arranged in cymes, with one to seven individual capsules per cyme, opening gradually over the vegetative cycle of the plant, typically from the end of May to April of the following year. The opening process of each capsule can take anywhere from a few days to months.

The capsules were harvested manually at the end of May 2021, and the trials were conducted in June and July 2021. A separate trial began in May 2022 using one-year-old seeds harvested in March 2022. These seeds came from capsules formed by spring 2021 flowers that had remained unopened and were left on the mother plants until collection, all sourced from the same six mother plants.

Table 3-1 Overview of seed germination trials conducted on *C. albidus*. The seeds of six different mother plants were grouped by their respective plants, with each plant representing a distinct plot. The seeds from each plot were subjected to five different treatments. The seeds were hydrated for 12 hours or 24 hours.

trial	**number of seeds**	**treatment**	**post-treatment hydration time (h)**
dry heat	978	oven dry heat (100°C; 5 min)	12, 24
wild fire simulation	465	fire heat	12
controlled scarification	1018	manual scarification	12, 24
runoff scarification simulation	208	random scarification	12
one-year-old seeds	317	no treatment	12, 24

The capsules were broken manually to extract the seeds, which were then stored in dry and dark conditions at 20°C. Using a digital microscope (Digital Microscope Pro, Celestron, Torrance, California, USA), the seeds were classified by size and color before the trials. A total of 2,986 *C. albidus* seeds underwent various treatments, as shown in Table 3-1, to examine their germination responses. Seeds were subjected to manual scarification, dry heat treatment, runoff, and wildfire simulation. After these treatments, the seeds were soaked in water for distinct hydration periods of 12 and 24 hours. A total of 48 trials were conducted. Seed viability was assessed prior to germination trials using a 1% tetrazolium solution.

3.2.3. Dry Heat

A total of 978 seeds were subjected to dry heat treatment. The seeds were subjected to a 100°C heat shock for 5 min in an air-forced oven, following the method outlined by Müller et al. (2014).

3.2.4. Wildfire Simulation

The wildfire simulation was carried out using a controlled burn on a 10 × 10 m plot surrounded by protective barriers at the Rausenbach Foundation's experimental site. The soil was predominantly clay with numerous stones of varying sizes. Temperature measurements were taken in a 1 m² area in the center of the plot, where six lots containing a total of 465 seeds were placed, spaced equidistantly. Seeds were weighed beforehand. Each lot consisted of a clay container of 10 cm diameter filled with sieved soil (diameter 0.5 mm) from the plot, moistened to about 25% humidity. The seeds were covered with 3 ± 1 mm of soil, lightly compacted, and kept in the dark for 24 hours at 25°C.

Six temperature sensors (ThermoPro, Model TP-16, iTronics GmbH, Willich, Germany) were placed equidistantly: three at 0.3 m from the center at a depth of 2 ± 1 mm below the surface and three at a depth of 50 mm. The plot was then covered with Mediterranean forest debris (dry leaves of *C. albidus,* pine needles, cones, fine branches, etc.). At the beginning of the simulation, the outside temperature was 35.5°C, with soil temperatures of 41°C at 2 mm and 20°C at 50 mm. Once the plot had cooled, the seeds were retrieved and soaked in Milli-Q® water at 25°C for 12 hours.

3.2.5. Runoff simulation

A total of 398 seeds from one capsule from each mother plant were subjected to a simulated runoff test. A 1.5-liter cylindric plastic bottle was filled with 1.75 kg of pea gravel (6 to 12 mm in diameter) and 1.0 L of water at 20°C. The seeds were then introduced into the bottle. The bottle was shaken gently for 10 minutes, after which the seeds were left to rest (in the bottle) for 12 hours. We recovered a total of 208 intact seeds by sieving for germination testing.

3.2.6. Controlled scarification

A total of 1,018 seeds were manually scarified using 120-grit sandpaper. Scarification was applied to ensure partial removal of the seed coat, which was verified under a digital microscope. Seeds were divided into two groups: one soaked for 12 hours and the other for 24 hours in 25°C Milli-Q® water before germination tests. The seeds were weighed before and after scarification and after hydration.

3.2.7. Seeds of one year old

The capsules containing seeds, which had remained unopened in the mother plants for approximately one year, were collected before ripening of the capsules from the new flowering period in March 2022. A total of 317 seeds were divided into two groups. One group was soaked in Milli-Q® water for 12 hours and the other group for 24 hours.

3.2.8. Germination testing

All seeds, except those in the runoff simulation, were sterilized in a bleach solution for 10 minutes before the germination tests. Seeds were placed in Petri dishes lined with sterilized 6 mm diameter glass beads and filter paper. The setup ensured continuous moisture supply via capillary action. The Petri dishes were kept in darkness and the daily temperatures inside the test box fluctuated between 14.1 and 29.5°C. Germination was monitored daily for 50 days, with seeds removed once their radicles reached approximately 2 mm.

3.2.9. Seedling establishment trial

In July 2021, 2,880 seeds from the six mother plants were subjected to a dry heat treatment (as described in 3.2.3) and transferred to forest trays filled with peat-based substrate. The trays, consisting of 96 cells (0.75 cm³ per cell), were watered to maintain field capacity. Germination and seedling survival were recorded on a daily basis for 60 days.

3.2.10 Statistical Analysis

Germination rates and treatment effects were analyzed using ANOVA, followed by the Mann-Whitney U-Test for post hoc comparisons. Spearman's rank correlation was used to assess the relationships between seed characteristics and germination success. A significance level of $p < 0.05$ was applied to all tests.

3.3. RESULTS

3.3.1 Flowering and fruit production

The average cumulative flower production per plant across the six mother plants was 1,374 ± 138.6 flowers (Figure 3-3) over a period of 131 days, corresponding to an average flowering rate of 10.5 flowers per day. The flowering commenced on February 21 and ended on July 1, 2021. Two distinct flowering phases were observed: the first phase involved the main shoots, beginning at the end of February and ending mid-May, while the second phase, involving the lateral shoots, began in early to mid-May and ended at the end of June, with the final flower appearing on July. During this second phase, the lateral shoots surpassed the main shoots in length, though they produced significantly fewer flowers (Figure 3-4).

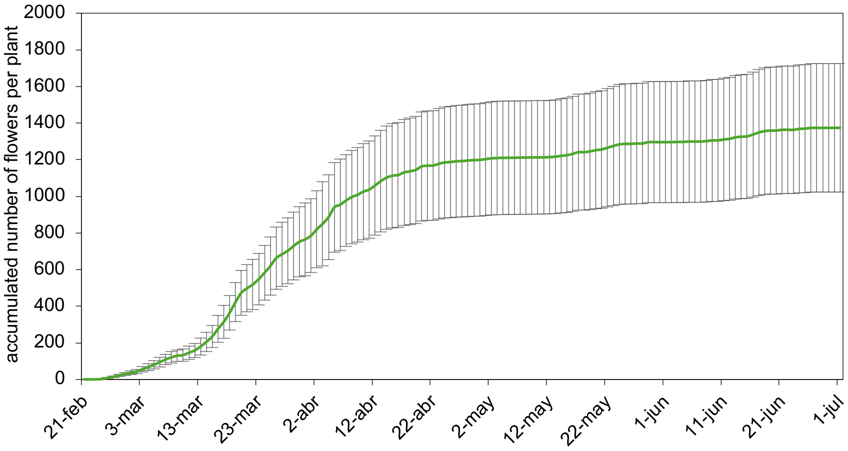


Figure 3-3 Average accumulated number of flowers per plant for mother plants during the flowering period from 21 February to 1 July 2021 (n = 6 ± SD).

In March 2021, before the onset of the new flowering season, an average of 4.7% ± 0.2 of the previous year's capsules remained intact on the six mother plants. These capsules, in contrast to fresh ones, contained an average of 26.4 ± 7.2 seeds, a significantly ($p < 0.05$) lower number compared to the 84.1 ± 26.9 seeds found in capsules that had opened during the same vegetative period. However, this phenomenon was not consistently observed in all plants in the study area and may be influenced by local environmental conditions. Some plants did not retain fruits from the previous year.

Flower and fruit abortion rates were practically zero, with only a negligible number of abortions attributed to parasitic attacks. This was likely a result of abundant rainfall during the trial year. In contrast, in 2024, no flowers were formed on the mother plants during the flowering period, probably due to the absence of rainfall from October 2023 to May 2024.

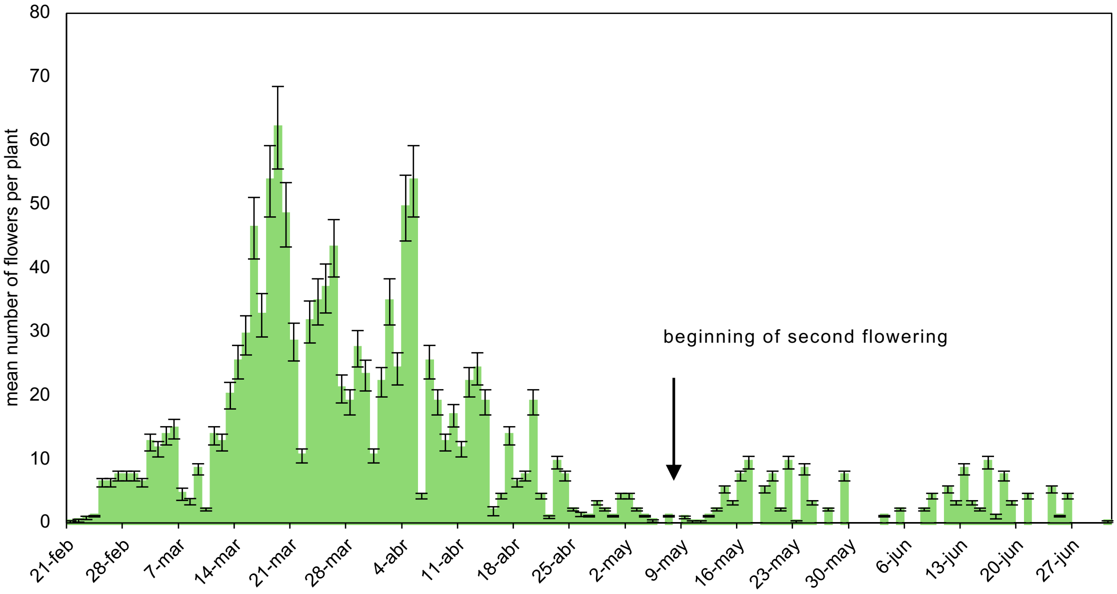


Figure 3-4 Average daily number of flowers per mother plant. The onset of the second flowering phase, involving lateral shoots, is visible at the beginning of May (n = 6 ± SD).

Viability tests of seeds from the six mother plants revealed an average rate of 85.2 ± 8.01% for fresh seeds and 75.76 ± 6.23% for one-year-old seeds, with no statistically significant differences between the two groups ($p > 0.05$).

3.3.2.Germination

Figure 3-5 illustrates the different germination pattern, which was heterogeneous, with some seeds germinating as early as the following day (after simulation of wildfires), while one-year-old seeds began germination on the fifth day. On average, during all trials, germination began three days after treatment and hydration.

Seeds exposed to heat germinated significantly faster than those in other treatments, reaching maximum germination on day 15 in the wildfire simulation, while seeds treated with dry heat reached maximum germination on day 34. No significant differences in germination rates were observed until day six throughout all trials. From day seven, the wildfire simulation group demonstrated an exponential increase in germination, with rates exceeding 50% by day 10. In contrast, seeds subjected to dry heat required twice as long to achieve 50% germination, reaching this maximum on day 20, following an exponential trajectory until day 14, after which the germination rate plateaued. Although seed weight increased significantly between seeds hydrated for 12 hours and those hydrated for 24 hours, no significant differences were observed in germination rates. The wildfire simulation resulted in a final germination rate of 72.6 ± 4.61%. However, the dry heat treatment ultimately yielded a higher germination rate of 80.7 ± 4.03% (Table 3-2).

Table 3-2 Summary of results for all trials: number of seeds, seed biomass per capsule, average weight per seed, weight gain after hydration, and total germination rate after 50 days based on treatment received. Data are presented as mean ± SE, with n = 6; * denotes n = 1 (value calculated for the sample as a whole). The data were analysed via one-way ANOVA with Tukey's HSD post hoc test. Means in the same column followed by different letters are significantly different (*p* < 0.05). No statistically significant differences were observed between hydration times and germination rates, except for one-year-old seeds where 24-hour hydration significantly (*p* < 0.05) increased germination.

treatment	**seeds /capsule**	**mean seed weight /capsule (mg)**	**mean weight /single seed (mg)**	**∆ mean seed weight after treatment and hydration (%)**		**germination rate (%)**	
				12 h	24 h	12 h	24 h
dry heat	81.5 ± 8.6 ^{a}	99.5 ± 10.4 ^{a}	1.22 ± 0.02 ^{a}	28.7 ± 2.6 ^{a}	44.9 ± 8.9 ^{a}	80.7 ± 4.03 ^{a}	77.6 ± 4.04 ^{a}
wild fire	77.5 ± 8.1 ^{a}	94 ± 10.5 ^{a}	1.21 ± 0.03 ^{a}	31.8 ± 7.4 ^{a}	---	72.6 ± 4.61 ^{a}	---
manual scarification	84.8 ± 9.0 ^{ab}	97.2 ± 9.9 ^{a}	1.17 ± 0.04 ^{ab}	114.7 ± 16.7 ^{b}	167.5 ± 33.5 ^{b}	73.9 ± 8.50 ^{a}	79.2 ± 5.04 ^{a}
runoff scarification	97.3 ± 4.1 ^{b}	112.8 ± 4.5 ^{a}	1.13 ± 0.01 ^{b}	98.1 ± 0* ^{b}	---	78.4 ± 0* ^{a}	---
old seeds	83.8 ± 8.8 ^{a}	101.5 ± 10.2 ^{a}	1.22 ± 0.01 ^{a}	22.73± 2.71 ^{c}	42.74 ± 3.05 ^{a}	4.3 ± 0.53 ^{b}	16.4 ± 1.55 ^{b}

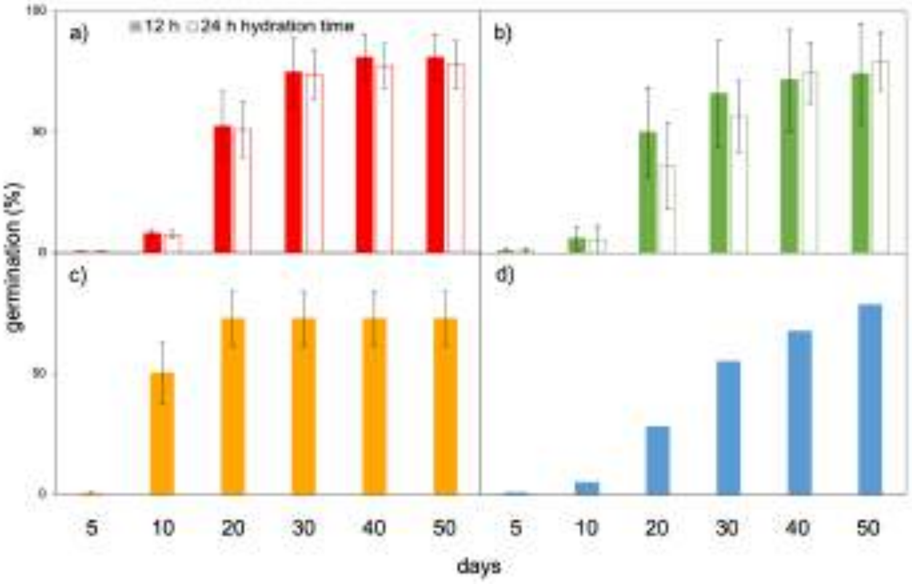


Figure 3-5 Results of germination for 5, 10, 20, 30, 40, and 50 days according to the different treatments and hydration applied: (a) dry heat, (b) controlled scarification, (c) wildfire simulation, and (d) runoff simulation. No significant differences were found in the total germination rate after 50 days between 12 and 24 hours of hydration of dry heat and controlled scarification treatment (*p* > 0.05).

Regarding runoff scarification, the irregular polyhedral shape of the untreated seeds (Figure 3-6a) facilitated the detachment of the hard seed coat along the edges, due to friction with the sharp edged gravel particles in the water. Scarification of the seeds through agitation in the gravel-water mixture resulted in more than 50% of the seed coats being at least partially scarified (visual observation; Figure 3-6d). After 12 hours of exposure to water, seeds that absorbed water were visually distinguished by their larger size and lighter colour (Figure 3-6d). Germination began on the third day, reaching a total germination rate of 78.4% on day 50, despite a lower observed scarification rate. This result may be attributed to the gradual absorption of water by slightly damaged seed coats, which continued to absorb water even later in the Petri dish.

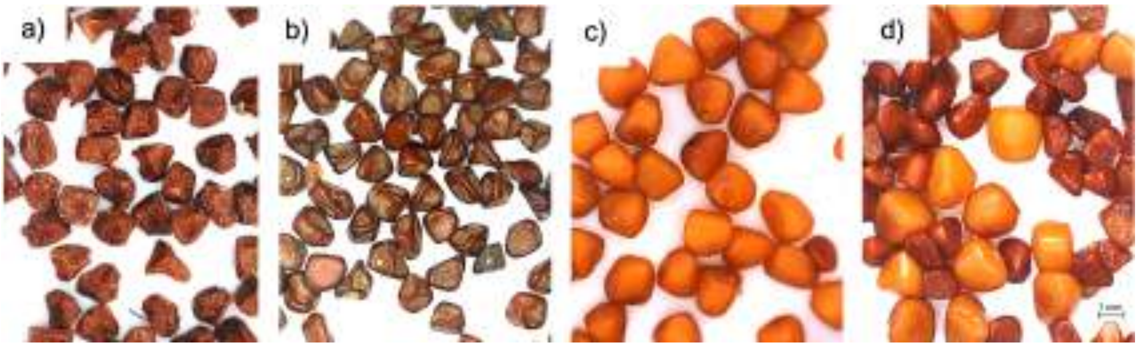


Figure 3-6 Seed stages: (a) Fresh, untreated seeds with intact seed coat; (b) seeds after manual scarification; (c) seeds after manual scarification followed by 12 hours of hydration; (d) seeds after runoff scarification simulation followed by 12 hours of hydration.

In controlled scarification treatment (Figure 3-6c), an average germination rate of 73.9% was achieved after 50 days for seeds hydrated for 12 hours, while seeds hydrated for 24 hours reached a germination rate of 79.2% during the same period. However, the difference between these rates was not statistically significant.

In the case of the one-year-old seeds, hydration facilitated easy detachment from the outer cover (Figure 3-7). However, only 21.2% of these seeds absorbed water and swelled. The germination rate was considerably lower compared to previous trials, with only 4.3% and 16.4% germination observed after 12 and 24 hours of hydration, respectively (Figure 3-8). In particular, unlike fresh seeds, a significant difference ($p < 0.05$) was observed based on the duration of exposure to water, with the germination success rate increasing fourfold as the soaking time extended.

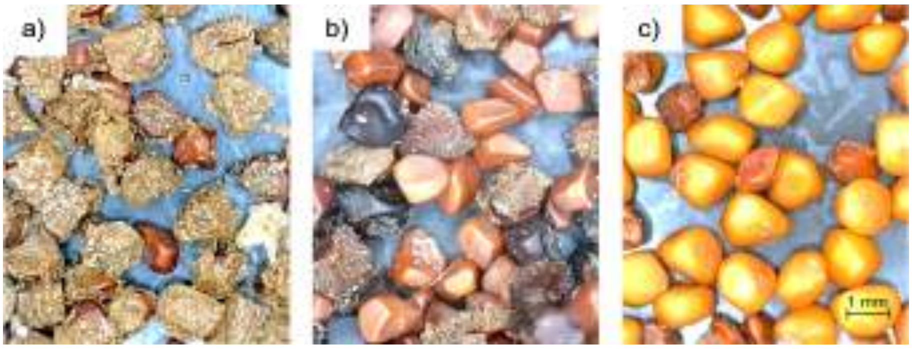


Figure 3-7 One-year-old seeds: (a) Observation of seed coat detachment in untreated seeds; (b) seeds after 12 hours of hydration; (c) seeds after 24 hours of hydration.

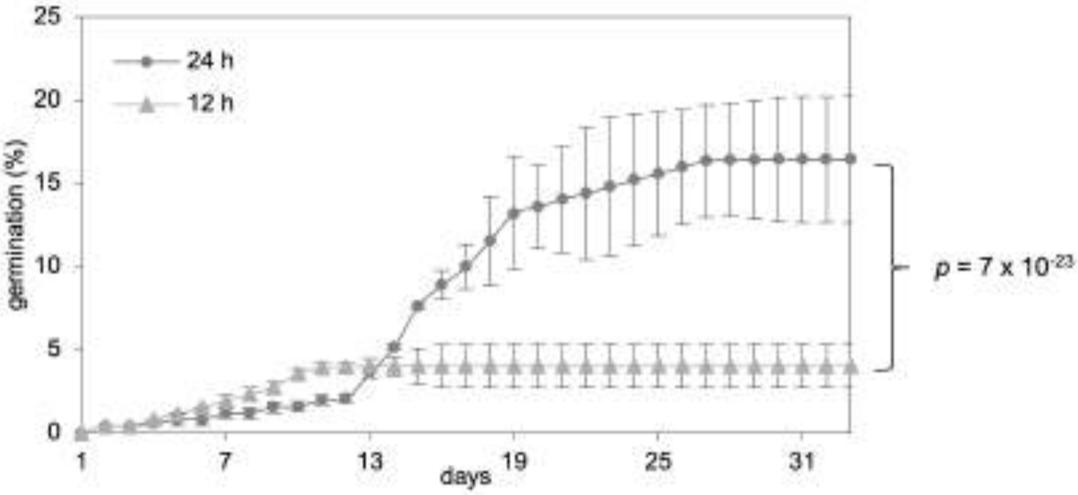


Figure 3-8 Comparison of the germination results of one-year-old seeds with subsequent hydration for 12 and 24 hours, respectively (data are mean values for n = 6 ± SD).

3.3.3. Correlation analysis

In general, only a few significant correlations were identified between the measured parameters. For example, only the relationship between seed weight and germination rate of all seeds (n = 2,986) showed a slight but significant positive correlation ($r_S = 0.601$, $p = 6.263 \times 10^{-6}$; Figure 3-9). When the correlations for the seed weights separated by the individual treatment groups were determined, no significant values were observed.

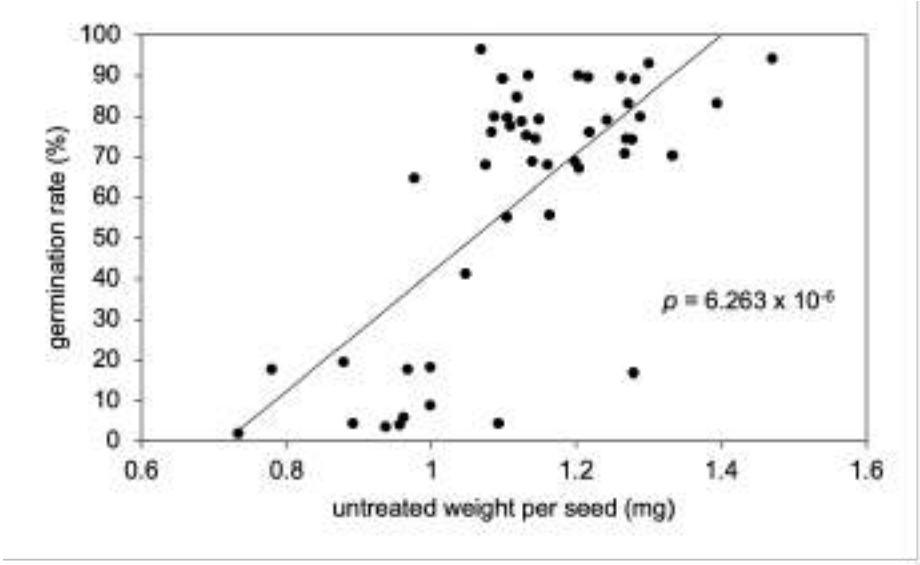


Figure 3-9 Spearman’s rank correlation (rs) between the germination rate (%) and the weight of the seed from the combined results of all seeds before treatments (n = 2986 seeds).

We also observed a weak significant positive correlation ($r_S = 0.314$, $p = 0.031$) between seed weight gain after treatment and hydration and the total germination rate after 50 days. Figure 3-10 presents the individual correlations between the daily germination rate and the weight gain after hydration of one-year-old seeds for each day. Except for the tenth day, significant correlations were observed between the daily germination rate and the total weight gain of the seeds after hydration. This analysis was based on the results of 24 trials that included a total of 317 seeds.

Although significant correlations were not observed on all days, the values indicate a general two-phase trend. Initially, there was an almost linear decline in the correlation strength from medium positive to strongly negative, with the strongest negative correlation observed on day 13 ($r_S = -0.618$, $p = 0.0065$). From day 15 onward, a significant increase in correlation strength was recorded, shifting from strongly negative to strongly positive values. After 31 days, the correlation remained stable at a significant medium strong positive value ($r_S = 0.694$, $p = 0.0178$). For the other treatments analyzed, only nonsignificant correlations were found.

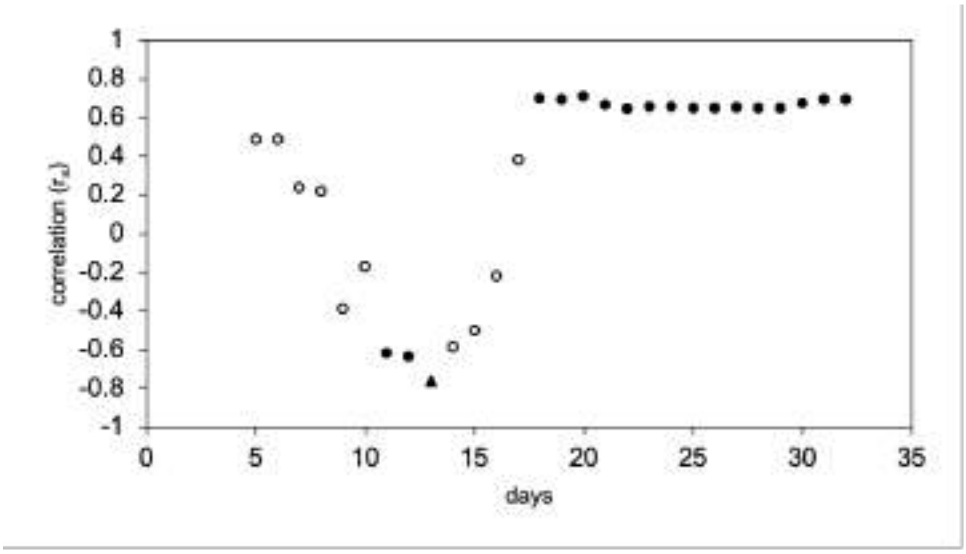


Figure 3-10 Spearman's rank correlation (rs) between germination rate per day (%) and total weight gain of seeds (%) after hydration of one-year-old seeds for each germination day; statistically significance is represented by ● for 0.001 < p ≤ 0.01, ▲ for 0.01 < p ≤ 0.05, and ○ for not significant.

3.4. DISCUSSION

The germination rate of the *C. albidus* seeds was high in all trials, with no significant differences between treatments, except for the one-year-old seeds which had a lower germination rate of 10.4%. Manual scarification resulted in a germination rate of 76.6%, runoff simulation 78.4%, wildfire simulation 72.6%, and dry heat treatment 79.3%. Hydration time (12 h vs 24 h) does not significantly affect fresh seed germination. However, in one-year-old seeds, longer hydration (24 h) significantly improved germination. These results highlight that one-year-old seeds require more water to break dormancy, which may reflect changes in the seed coat's permeability as they age.

A significant positive correlation between seed weight and germination rate suggests that heavier seeds are more likely to germinate successfully, which aligns with previous findings (Müller et al., 2014). Heavier seeds likely contain more resources to support early seedling development, improving their chances of survival. However, no significant correlation was found between seed weight and germination rate within the individual treatment groups, suggesting that this relationship becomes apparent only with a sufficiently large sample size.

One-year-old seeds that remained on plants for more than one reproductive cycle showed reduced germination without scarification. Natural processes such as seed coat aging and cracking can gradually make seeds more permeable to water, facilitating delayed germination under unfavorable conditions (Hamilton & Carpenter, 1975; Hidayati et al., 2001). The gradual opening of the capsules and staggered seed release may represent a survival strategy enabling *C. albidus* to adapt to fluctuating environmental conditions (Bastida & Talavera, 2002). Retaining seeds under unfavorable conditions helps maintain a seed bank on the plant, ensuring species survival in varying environments (Hernandez et al., 2020).

For one-year-old seeds, 24-hour hydration nearly quadrupled germination compared to 12-hour hydration, suggesting that biochemical changes in the seed coat are crucial for breaking dormancy (Liu et al., 2022; Wu et al., 2023). However, no significant differences were observed between germination rates of fresh seeds exposed to 12 or 24 h of hydration.

The correlation analysis provided additional information. A significant positive correlation between total weight gain after hydration and total germination rate ($r_s = 0.314$, $p = 0.031$) highlights the critical role of water absorption in initiating germination (Lechowska et al., 2019). A biphasic correlation for one-year-old seeds indicates complex interactions between seed age, dormancy, and hydration dynamics. Initially, seeds that absorb more water germinated earlier, while seeds with lower initial uptake eventually caught up (Gimenez et al., 2017). This delayed germination in one-year-old seeds may reflect the need for prolonged hydration or cumulative environmental cues to release dormancy (Fenner & Thompson, 2005).

The wildfire simulation demonstrated the importance of heat in accelerating germination, with seeds exposed to fire conditions germinating faster than those subjected to controlled scarification or dry heat alone. This underscores the role of fire in breaking seed dormancy by rupturing the seed coat, a process difficult to fully replicate under controlled conditions (Tavşanoğlu & Çatav, 2012). Heat may also trigger enzymatic changes, accelerating germination (Bouchardet et al., 2015; Lamont et al., 2022). Although dry heat was effective, the natural conditions of a wildfire, including heat, smoke, and soil moisture, provided an optimal environment for germination (Krasuska et al., 2015; Zirondi et al., 2019). Soil moisture during wildfire simulation likely played a role in preventing seeds from drying out, allowing rapid hydration and faster post-fire germination (Ruprecht et al., 2016; Tangney et al., 2019).

Wildfires are influenced by several factors, including plant and soil moisture, plant size, and wind conditions, all of which affect combustion conditions and seed germination (Snyman, 2015). In our simulations, seeds under a thin soil layer (~2 mm) experienced temperatures sufficient to break the seed coat without damaging the seeds, while surface seeds can be destroyed by fire. At a depth of 5 cm, temperatures were not sufficient to break dormancy in the seeds of *C. albidus.*

In hard-seeded species such as *C. albidus*, dormancy is typically broken when the seed coat ruptures. The heat of fire induces this rupture, allowing water to penetrate and initiate germination. The intensity of the fire is crucial: Low-intensity fires may not generate enough heat to break seed dormancy (Auld, 1986; Moreira & Pausas, 2012), while excessively high temperatures at the soil surface can cause seed mortality. Additionally, post-fire moisture is necessary for seed germination and establishment (Morbidoni et al., 2008), but in Mediterranean climates, fire seasons often do not coincide with rainfall, reducing the likelihood of successful post-fire germination. Seeds exposed to fire may lose viability without germinating, as the protective seed coat is lost, making them vulnerable to degradation (Bebawi & Campbell, 2000).

Fires also do not aid in seed dispersal, as seeds remain in place near the mother plant (Bastida & Talavera, 2002), limiting the spatial spread of *C. albidus*. Thus, while fire can break seed dormancy, it does not create favorable conditions for seedling establishment or aid in dispersal. Instead, hydrochory remains the sole dispersal mechanism for *C. albidus*, as the species lacks alternative means of seed dispersal.

Additionally, *C. albidus* relies primarily on water for seed scarification, with runoff serving as a natural process to overcome seed coat dormancy. The seeds of *C. albidus* exhibit typical traits of riparian species, including small size, high quantity, water-impermeable coats, and angular shapes, all of which make them well-suited for dispersal by water (Catford & Jansson, 2014; Kubitzki & Ziburski, 1994). As a result, the seed coat is scarified by abrasion from particles suspended in the water and contact with the streambed. The fact that *C. albidus* can also germinate after a fire may further support the hypothesis that this species could be considered primary a riparian plant, since the tegument of several riparian plants is more strongly developed (Catford & Jansson, 2014) which may help to resist even a wildfire. However, water runoff conditions are more conducive to seed scarification and dispersal, as well as access to moisture for germination than those during wildfire.

It has also been shown that *C. albidus* is less inflammable than the typical Maquis vegetation (Juhren, 1966), which may indicate that this species depend on higher soil moisture. It was shown that *C. albidus* exhibited less resistance to drought stress than its relative *C. clusii*, largely due to a less efficient water conservation strategy (Munné-Bosch et al., 2003). This difference underscores its affinity for more moisture-rich environments. This is supported by morphological traits, such as a deep root system, which is characteristic of species adapted to temporary watercourses (Karrenberg et al., 2002). This trait enables access to groundwater, enhancing drought resilience. In our study area, nearly all *C. albidus* plants had succumbed to water deficiency by the end of October 2024, with soil moisture at a depth of 25 cm dropping below 3% by September (Figure A2), while other species on the plot showed recovery following the October rains. However, *C. albidus* individuals located in a lower-lying *barranco* (a temporary watercourse) displayed complete survival, where soil moisture at the depth of 25 cm remained above 10%. This highlights the ecological adaptations and habitat-specific vulnerabilities of this species, especially regarding moisture dependency, in contrast to other species in the same environment, supporting its riparian affinity. Nevertheless, these observations warrant further investigation.

Taken together, the primary germination and dispersal mechanisms of *C. albidus* rely on hydrochory. Therefore, this species cannot be considered a pyrophyte by definition, but is better classified as a riparian species with opportunistic pioneer characteristics.

Considering these facts, climate change and human activities pose significant threats to *C. albidus*. Infrastructure developments disrupting watercourses can lead to isolated populations that over-age and fail to disperse (Lorente, Zugasti, Ortuño, et al., 2021; Robles et al., 1999). Extreme droughts further stress already weakened plants, leading to die-offs, as observed in several *C. albidus* stands in Valle y Carrascoy regional park during 2024. Over time, this could threaten the survival of the species, as seen in the endangered *C. heterophyllus* subsp. *carthaginensis* (Cardona & Capó, 2023). Effective fuel management practices such as controlled fires under optimal conditions can help mitigate these risks and rejuvenate over-aged stands. However, these practices are only useful if sufficient soil moisture is ensured after the fire (Luna et al., 2023). Our experiments also showed that seedling survival after germination in summer was low, with only 4.8% surviving after 60 days, even with optimal watering, conditions that are unlikely to occur naturally in Mediterranean climates. Summer germination is typically restricted by high temperatures, seed dormancy, and resource competition (Gonsamo et al., 2019). Thus, successful germination and survival after fires in summer are negligible under real conditions.

The adaptation of *C. albidus* to both fire and hydrological processes may be part of a larger survival mechanism within the Cistaceae family. Similar germination strategies have been observed in other species of the genus *C.* such as *C. monspeliensis*, *C. clusii,* and *C. salviifolius*, which also germinate after fires but show greater dispersal in areas of high water availability (Roy & Sonie, 1992; Tilki, 2008; Trabaud & Oustric, 1989). These species also benefit from mechanical conditioning by runoff water, which breaks the seed *coat* and facilitates germination (Trabaud & Renard, 1999). The parallel adaptations observed among these related species indicate that hydrological disturbances in Mediterranean ecosystems exert a greater influence on plant germination and dispersal dynamics than fire. However, the resilience to wildfire observed in these species suggests a potential evolutionary response to shifting climatic conditions, possibly facilitating a transition from riparian specialization to the development of pyrophytic traits (Reynolds & Shafroth, 2017; Stromberg et al., 2010). These dual germination strategies are not exclusive to Cistaceae but have also been observed in other Mediterranean plant families, such as Asteraceae. For example, *Anthemis* spp. exhibit a dual germination strategy, where differences in dormancy depth influence germination under varying conditions (Blandino et al., 2022), suggesting that exploiting different disturbance regimes is an adaptive strategy to survive in the variable environmental conditions of the Mediterranean region.

For effective conservation and restoration, *C. albidus* should be prioritized in microhabitats with high water availability, such as temporary watercourses, where runoff facilitates natural scarification and promotes germination. Moreover, integrated land management practices that align prescribed burns with periods of water availability could help mitigate the mismatch between fire events and subsequent rainfall, supporting successful post-fire seedling establishment. Reforestation efforts focused on these areas are likely to enhance the long-term establishment of *C. albidus* and contribute to stabilizing degraded landscapes. These findings highlight the importance of adapting fire and water management policies to address the increasing challenges posed by a rapidly changing climate.

3.5. CONCLUSIONS

The dual strategy of *C. albidus* to rely on both fire- and water-mediated scarification demonstrates its adaptive flexibility in Mediterranean environments. While wildfires may accelerate germination, hydrological processes provide better conditions for seed dispersal and establishment, challenging the traditional view that *C. albidus* is a pyrophyte by definition.

The findings of this study underscores the importance of hydrological processes in the life cycle of *C. albidus*. This suggests that the species may rely more strongly on water-related disturbances for successful colonization, particularly in fire-free environments, thus broadening the understanding of its ecological strategies beyond pyrophytism. This highlights the importance of integrating water availability considerations into fire management practices. Prescribed burns may only produce positive effects on *C. albidus* regeneration when adequate post-fire soil moisture is present. Lack of moisture after fires can severely limit seedling survival, indicating that fire alone is insufficient to ensure successful regeneration of this species in Mediterranean ecosystems.

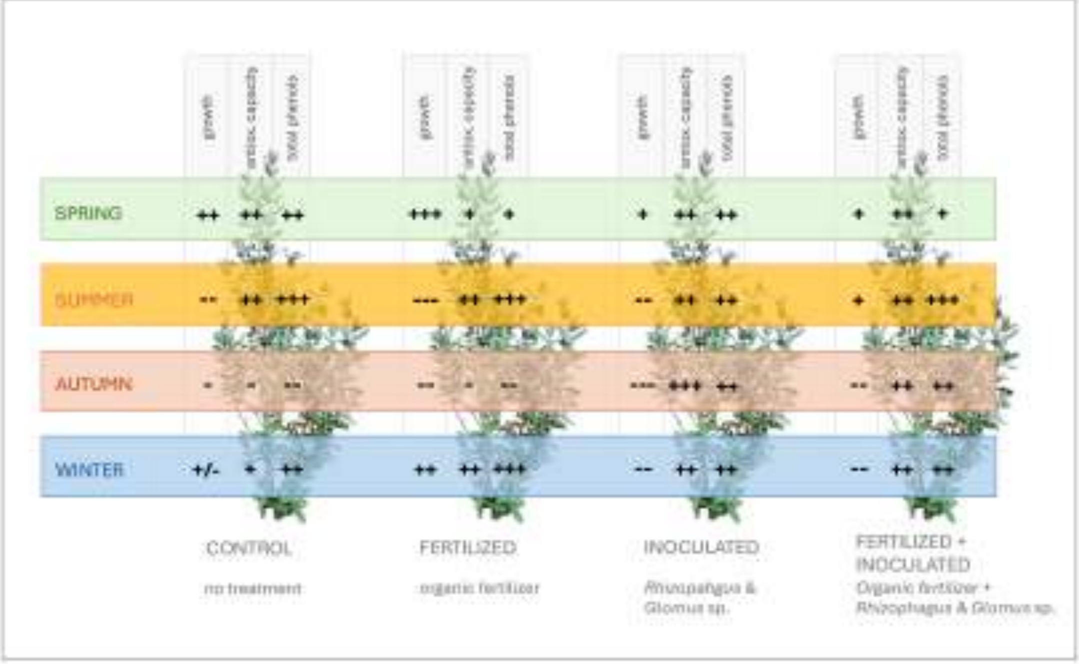
This study contributes to a broader ecological understanding of how Mediterranean plant species balance multiple environmental stressors, such as fire and hydrological events. Our findings may also inform conservation strategies for other species in fire-prone and water-scarce ecosystems facing similar environmental pressures.

Chapter 4

Relationships between Agronomic Factors and Phytochemical Profile

Phytochemical and Growth Patterns in *Cistus albidus* L.: Seasonal Impacts of Inoculation and Fertilization

4. RELATIONSHIP BETWEEN AGRONOMIC FACTORS AND PHYTOCHEMICAL PROFILE



Graphical Abstract 3 In *C. albidus*, arbuscular mycorrhizal inoculation with *Rhizophagus* and *Glomus* species does not enhance growth but significantly increases phenolic content and antioxidant capacity—especially in autumn—highlighting its potential for stress-resilient, pharmacologically optimised cultivation.

Abstract

This study investigated the effects of organic fertilization and arbuscular mycorrhizal fungus (AMF) inoculation with a mixture of *Rhizophagus* and *Glomus* species on the growth parameters, total phenolic content (TPC), and antioxidant capacity of *C. albidus* L., a medicinal Mediterranean plant known for its wide range of pharmacologically active substances. Over one vegetative cycle, 400 uniformly growing plants were randomly divided into four groups of 100 plants each, which received one of four different treatments: control, fertilization, inoculation, or combined fertilization + inoculation. This study monitored the leaf area, fresh and dry weights, leaf index (LI), specific leaf area (SLA), flowering, and other growth parameters. Phytochemical analyses included UHPLC-MS analysis and TPC and antioxidant capacity measurements.

The results indicated that fertilization significantly increased the leaf area and fresh weight, whereas inoculation generally reduced these parameters but increased the SLA. The combined treatment had intermediate effects. Fertilization advanced flowering onset and reduced variability in floral yield. Inoculation alone negatively impacted the cumulative floral yield but significantly improved the antioxidant capacity and TPC, particularly in autumn. Notable correlations were observed between certain polyphenols and plant survival rates, indicating potential markers for stress tolerance.

The results indicate that inoculation with *Rhizophagus* and *Glomus* species either alone or in combination with fertilization does not affect the growth parameters of *C. albidus* and may not establish a beneficial mycorrhizal symbiosis with these fungal genera. This result contrasts with the positive effects observed on other plant species. However, inoculation significantly increases the phenolic compound content and antioxidant capacity, particularly in autumn, enhancing the medicinal properties of this plant.

This study provides insights into optimizing cultivation practices for this species, aiming to maximize its pharmacological potential while understanding the underlying mechanisms of stress tolerance. These findings support the sustainable cultivation of *C. albidus* as a valuable medicinal plant in the face of environmental stressors.

Key words

Antioxidant capacity, AMF inoculation, *Cistus albidus*, Organic fertilization, Phytochemical profile, Total phenol content,

4.1. INTRODUCTION

Phenolic compounds, which are ubiquitous in plants, are essential secondary metabolites known for their diverse biological functions and therapeutic potential, including antioxidant, anti-inflammatory, and antimicrobial activities (Rana et al., 2022). These compounds typically accumulate in the central vacuoles of various plant cells. Environmental stresses can significantly impact plant metabolism, either by inhibiting or promoting the production of secondary metabolites (Xiao et al., 2019). The effects of various climate change components—such as high temperatures, elevated carbon dioxide levels, drought stress, and enhanced ultraviolet-B radiation—on secondary metabolites, especially phenolic compounds, are under continuous investigation, with evidence steadily increasing (Qaderi et al., 2023). Understanding these effects is crucial, as secondary metabolites play significant roles in the adaptability and success of certain plants. Furthermore, optimizing the biosynthesis of phenolic compounds in medicinal plants is of significant interest for enhancing their therapeutic efficacy.

C. albidus L., commonly known as white rockrose, is a Mediterranean shrub with a long history of traditional use. It is valued for its medicinal properties, including antimicrobial and anti-inflammatory activities and potential effects on the central nervous system (Raus de Baviera et al., 2023). The main constituents of this species are terpenes and polyphenols, with more than 200 identified compounds (Raus de Baviera et al., 2023). The increasing interest in *C. albidus*, which is obtained mainly from wild collection, makes it necessary to consider its cultivation.

C. albidus is known for its ability to withstand severe stress situations. Recent research has focused on understanding the mechanisms underlying its tolerance of such situations (Casadesús et al., 2021, 2022; Müller et al., 2014; Munné-Bosch et al., 2003; Pérez-Llorca, Casadesús, Munné-Bosch, et al., 2019). Research indicates that polyphenols, among various other compounds, significantly contribute to stress regulation.

Numerous strategies have been documented to increase secondary metabolism, particularly phenolic compound synthesis. These strategies include abiotic and biotic stress induction (Ahlawat et al., 2023; Tariq & Ahmed, 2024), as well as mycorrhizal inoculation (Avio et al., 2017; Zhang et al., 2013). However, conflicting hypotheses exist regarding the benefits of AMF inoculation. While most studies report increased plant growth and stress tolerance through improved nutrient uptake (Chandrasekaran, 2020), others suggest that such inoculation might act as a stressor, potentially reducing growth but increasing secondary metabolite production in nonmycorrhizal plants (Cosme et al., 2018; Veiga et al., 2013).

C. species have been reported to form both ectomycorrhizal (ECM) and AMF associations (Lorente, Zugasti, Sánchez-Blanco, et al., 2021; Ortuño et al., 2018), whereas another study reported evidence of ECM symbiosis only (Comandini et al., 2006). This study aims to elucidate these complex interactions within the specific context of *C. albidus* cultivation.

The present study explored the effects of organic fertilization and AMF inoculation on the growth parameters, total phenolic content (TPC), and antioxidant capacity of *C. albidus* and their seasonal influences. The effects of these treatments were monitored over one vegetative cycle. The primary aim was to identify cultivation practices that maximize the medicinal value of this species by enhancing the properties of pharmacological interest and, at the same time, contribute to a better understanding of the mechanisms of stress tolerance.

4.2. MATERIALS AND METHODS

4.2.1. Plant material

The plant material was obtained from an experimental culture located in Murcia, Spain (37° 36' 21.64" N; 1° 47' 36.13" W). For this experiment, 400 two-year-old *C. albidus* plants with uniform growth trends were selected. The plants were grown in a southwest orientation 475 m above sea level in polyethylene culture bags that contained substrate (Mediterranean Rambla soil) without any previous treatment. This soil has the same characteristics as the soil of the mother plants from which the seeds of the experimental culture originated (Table A2).

Once the culture was established, it was divided randomly into four groups of 100 plants each to provide different treatments and evaluate the effects of different culture conditions: control plants (CONT), fertilized plants (FERT), inoculated plants (INOC) as well as inoculated plants that received additional fertilization (FERT+INOC) (Table 4-1). Fertilization was performed using organic fertilizer (Table A3) at least 14 days before each harvest. The plants in the last two groups (INOC and FERT+INOC) were inoculated with a mixture of different arbuscular fungi of the genera *Rhizophagus* and *Glomus* to determine the responses of the experimental plants to biotic stimuli. The mixture contained *R. irregularis, G. aggregatum, G. mosseae* and *G. etunicatum* in equal proportions. These fungi belong to the Glomeromycetes class, with the total administration of spores and mycelia divided into two applications of 0.2 mg per plant eight weeks before the first harvest to ensure the establishment of mycorrhizal structures in the roots (Hart & Reader, 2002). Since the CONT plants should serve as a control, they were completely untreated and thus grown under conditions similar to those in the wild.

Throughout the duration of this study, all the plants were provided sufficient water by maintaining the soil moisture content constant at 35.0 ± 0.7%.

Table 4-1 Experimental treatments of the four groups (CONT, FERT, INOC, and FERT+INOC) with n = 100 *C. albidus* plants each.

Sample	**Treatment**	**Concentration per individual plant**
Control (CONT)	No treatment	–
Fertilization (FERT)	Organic fertilization	0.3 mL
Inoculation (INOC)	Fungus inoculation (spores, mycelia)	0.1 mg
Combination (FERT+INOC)	Organic fertilization + fungus inoculation (spores, mycelia)	0.3 mL (FERT) + 0.1 mg (INOC)

Flowering was determined based on a daily count from February to July of both years, 2021 and 2022.

Leaves were collected from healthy plants during one cultivation cycle in spring (May 2021), summer (July 2021), autumn (November 2021) and late winter (March 2022). Leaves were always collected in the early morning before sunrise to ensure the maximum content of flavonoids, as shown in a previous study by Gori et al. (Gori et al., 2020). Three to six healthy and completely developed leaves were selected from the same position (2nd–4th node levels of leaves down from the apices) of fully developed branches (with 5 or more leaf nodes) per plant and cleaned with pressurized air. Leaves with visible malformations, damage or abnormal coloration were discarded. A total of 200 leaves were harvested from each treatment group and in each season. Half of the leaves were assigned to the growth analysis, with 90 uniformly growing leaves selected per treatment group. Leaves destined for the growth analysis were measured using ImageJ software (version 2.3.0/1.53q) to obtain a leaf profile and area after being scanned at 600 dpi resolution using a flatbed scanner (TS 5100 series; Canon, Tokyo, Japan). An electric balance (ML 204; Mettler Toledo Company, Greifensee, Switzerland; measurement accuracy 0.0001 g) was used to obtain the fresh weight and dry weight of the samples after they were dried in an oven at 70 °C to a constant mass.

The plant heights were measured in July 2021 and 2022. The mean growth of the lateral and principal shoots was measured between the shoot apical meristem and first leaf node of three representative shoots per plant of five plants per treatment group during the growth season between December 2021 and the end of May 2022.

4.2.2. Extraction procedures

The plant material used for the phytochemical analysis, consisting of 100 fresh leaves per treatment group, was ground using a mechanical mill to a maximum size of 2 mm for further processing.

C. albidus aqueous extracts were produced using distilled water at a temperature of 50 °C. The preparations were gently agitated for approximately 4 h at a plant-to-solvent ratio of 1:5. The filtered extract (using a Büchner device) was then centrifuged to remove insoluble solid components, and only the supernatant was used. The extracts were concentrated by rotary evaporation and stored at -80 °C until one day before use, at which time the temperature was increased to 4 °C. Three independent extracts were prepared for each condition.

4.2.3. Extract characterization

4.2.3.1. Total phenol content and UHPLC analysis

The TPC of the *C. albidus* extracts was determined spectrophotometrically using the Folin–Ciocalteu assay as described by Álvarez-Martínez et al. (Álvarez-Martínez et al., 2021). The molecular composition of the extracts was analysed via an ultrahigh-pressure liquid chromatography system (UHPLC) with a Nexera UHPLC system (Shimadzu Scientific Instruments, Inc., Tokyo, Japan) composed of a DGU-405 degasser, an LC-40D × 3 binary pump, a SIL-40C autosampler, a CTO-40C column oven and a CBM-40 controller. The UHPLC system was coupled to an LCMS-8050 triple quadrupole mass spectrometer from Shimadzu equipped with electrospray ionization (ESI) mode (Shimadzu Scientific Instruments, Inc., Tokyo, Japan). Chromatographic separation was performed with a Poroshell 120 SB-C18 column (4.6 × 150 mm, 2.7 µm) (Agilent Technologies, Inc., Palo Alto, CA, USA), as described by Barrajón-Catalán et al. (Barrajón-Catalán et al., 2011).

For the identification of the main compounds, a homemade library of polyphenolic compounds was used. Therefore, the retention times and MS/MS data of the peaks in the samples were compared with those of authentic standards or data reported in the literature (Barrajón-Catalán et al., 2011; Fernández-Arroyo et al., 2010; Lukas, Bragagna, et al., 2021). The interpretation of the spectra and identification of the main compounds were conducted using LabSolutions software (v. 5.109) from Shimadzu.

4.2.3.2. Trolox equivalent antioxidant capacity assay

In the Trolox equivalent antioxidant capacity (TEAC) assay, the antioxidant capacity was determined by evaluating the effects of the extracts on the free radical $ABTS^{\cdot+}$ (2,2′-azino-bis (3-

ethyl-benzothiazoline-6-sulfonic acid)). This assay was performed as described by Barrajón-Catalán et al. (Barrajón-Catalán et al., 2011).

4.2.4. Statistical analysis

Plants with average growth and no abnormalities were selected to determine all growth parameters, the antioxidant capacity, and concentrations of phenolic compounds. The statistical analysis was performed using the Python SciPy library. Analysis of variance was performed, and Duncan's multiple range test was conducted to compare the means. Bartlett tests were performed to assess differences between the treatment groups and determine the homogeneity of variance.

The Shapiro–Wilk test was used to assess the normality of the data. Where appropriate, depending on the independent variables, either one-way or two-way ANOVA was performed. In addition, Tukey's honestly significant difference (HSD) post hoc test with a 0.05 significance level was conducted (Hsu, 1996). Since neither the normal distribution nor the homogeneity of the variances were given, a Kruskal–Wallis test was used to assess differences between groups. If statistical significance was observed, the Mann–Whitney U test was performed for each pairwise comparison of the data with the subsequent Bonferroni correction.

Pearson's correlation analysis was performed with interaction terms, considering the correlations with other variables to assess the linear relationships between the treatments and the various vegetative parameters. The significance of the correlation was evaluated using a two-tailed *p* value with a significance level set at 0.05. The results are reported as the correlation coefficients (r) along with the corresponding *p* values.

The results are presented as the means ± standard errors (SEs). The results of the statistical analysis are provided in tables in the Supplementary Information.

4.3. RESULTS

4.3.1. Leaves

The temporal progression of seasons exerts a critical influence on the phenotypic development of leaf characteristics, as shown in Table 4-2, manifesting distinct patterns across various experimental groups.

In the spring season, peak leaf development was observed across all the treatment groups, with the leaves of the fertilized group displaying the largest mean leaf area (8.55 ± 0.23 cm^2). The significant differences among all the groups suggested an effect of the treatment on leaf development, with a marked increase in leaf expansion due to fertilization. The control group presented a mean leaf area of 7.42 ± 0.15 cm^2, followed by the inoculated (5.77 ± 0.17 cm^2) and fertilized + inoculated groups (5.24 ± 0.09 cm^2), with the latter two exhibiting a significant reduction in the mean leaf area. The maximum leaf area for all the treatment groups was recorded in spring, with a subsequent decline observed as the seasons transitioned into summer and autumn. The lowest leaf surface areas were noted during the summer for FERT and CONT, whereas FERT+INOC presented the greatest value (5.68 ± 0.09 cm^2), followed by INOC. Conversely, the inoculated groups experienced minimal growth in autumn. The mean values observed in autumn were generally lower than those observed in spring and winter across groups, whereas the winter leaves showed a slight increase, indicating the commencement of a new growth cycle in late winter, as this species exhibits continuous growth throughout the year with slowing growth in summer and winter.

Table 4-2 Results for leaf parameters measured over one vegetative cycle: leaf area (cm^2), perimeter (cm) and fresh weight per leaf (mg) from leaves harvested in four seasons (data are presented as the means ± SEs of n = 90 plants). The data were analysed via one-way ANOVA with Tukey's HSD post hoc test. Means in the same column followed by different letters are significantly different ($p < 0.05$).

	SPRING	SUMMER	AUTUMN	WINTER
		Leaf area (cm^2)		
CONT	7.42 ± 0.15 ^{a}	3.51 ± 0.06 ^{a}	4.28 ± 0.10 ^{a}	4.57 ± 0.10 ^{a}
FERT	8.55 ± 0.23 ^{b}	3.22 ± 0.06 ^{b}	3.53 ± 0.06 ^{b}	4.74 ± 0.09 ^{b}
INOC	5.77 ± 0.17 ^{c}	4.16 ± 0.08 ^{c}	2.62 ± 0.06 ^{c}	3.27 ± 0.06 ^{c}
FERT+INOC	5.24 ± 0.09 ^{d}	5.68 ± 0.09 ^{d}	2.83 ± 0.06 ^{c}	2.87 ± 0.07 ^{d}
		Leaf perimeter (cm)		
CONT	11.66 ± 0.10 ^{a}	8.55 ± 0.14 ^{a}	8.58 ± 0.13 ^{a}	9.16 ± 0.09 ^{bc}
FERT	11.35 ± 0.13 ^{a}	8.15 ± 0.15 ^{a}	8.81 ± 0.12 ^{a}	10.28 ± 0.12 ^{ab}
INOC	10.69 ± 0.16 ^{a}	8.91 ± 0.17 ^{a}	7.83 ± 0.10 ^{a}	8.1 ± 0.09 ^{bc}
FERT+INOC	10.1 ± 0.10 ^{a}	5.68 ± 0.12 ^{a}	7.97 ± 0.11 ^{a}	7.63 ± 0.09 ^{c}
		Fresh weight per leaf (mg)		
CONT	157.19 ± 3.14 ^{a}	115.33 ± 4.23 ^{a}	133.33 ± 1.01 ^{a}	153.00 ± 5.77 ^{a}
FERT	153.72 ± 3.60 ^{a}	142.31 ± 3.09 ^{b}	153.17 ± 2.74 ^{b}	150.31 ± 2.96 ^{b}
INOC	80.67 ± 1.54 ^{b}	73.69 ± 3.94 ^{c}	64.92 ± 2.93 ^{c}	124.58 ± 2.57 ^{c}
FERT+INOC	65.07 ± 1.62 ^{c}	93.81 ± 4.00 ^{d}	87.2 ± 2.57 ^{d}	96.77 ± 3.26 ^{d}

As shown in Figure 4-1, significant differences in leaf area were detected between all groups in spring and summer, whereas no differences between INOC and FERT+INOC were observed in autumn and winter, and in winter, no differences were detected between CONT and FERT. Observations conducted in winter revealed no significant differences between the control and fertilized treatment groups. Conversely, significant differences were noted for FERT+INOC and INOC compared with CONT and FERT, underscoring the significant effect of inoculation (with or without fertilization) on the leaf area in winter. Across harvest times, only FERT was significantly different from all other groups in spring. However, the fertilized plants presented significant differences at all harvest times, indicating a distinct effect of fertilization, depending on the season. Interestingly, no differences were detected between FERT in summer and FERT+INOC and INOC in autumn and winter. During summer, FERT+INOC had the most pronounced positive effect on leaf area, with significant differences observed in comparison to all other treatments, except for INOC in spring. However, both the combined treatment and inoculation alone significantly influenced the leaf area compared with that of untreated or solely fertilized plants at each harvest time.

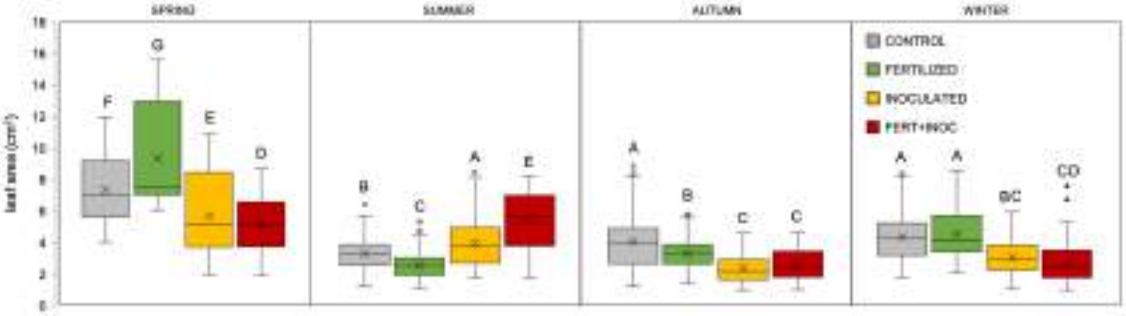


Figure 4-1 Boxplots of the leaf areas according to the treatment group. The data are presented as the means ± SE of n = 90 leaves per group. The data were analysed by two-way ANOVA with Tukey's HSD post hoc test. The letters above the whiskers are used to show the significance of the difference between any two measurements. Combinations with the same letter are not significantly different ($p < 0.05$).

In terms of leaf perimeter, although no statistically significant differences were observed among the treatment groups during spring, summer and autumn, the results indicated that both the different treatments and the various harvest times had significant effects on the leaf perimeter of the plants in winter. In particular, the combined treatment of inoculation and fertilization resulted in a significant ($p = 0.035$) difference from fertilization alone in winter, indicating seasonal influences on plant growth.

When the mean leaf fresh weights were compared across seasons (data not shown), FERT presented higher values (149.9 ± 5.26 mg × leaf^{-1}) than CONT (147.6 ± 29.96 mg × leaf^{-1}). In contrast, INOC and FERT+INOC resulted in significantly reduced weights (85.9 ± 26.54 and 85.7 ± 14.33 mg × leaf^{-1}, respectively). As shown in Figure 4-2, compared with CONT, fertilization was associated with more uniform leaf development, as evidenced by the reduced variance in fresh weight. Inoculation, either alone or in combination with fertilization, tended to produce lighter leaves. The combination of inoculation and fertilization did not result in significant differences in leaf fresh weight compared with that of inoculated plants, which indicated that the predominant effect was caused by inoculation.

Significant differences in the mean values of dry weight (mg) of leaves were observed between the CONT and FERT groups and the inoculated groups (Figure 4-2) confirming the significant influence of inoculation. No significant difference was noted between FERT+INOC and INOC.

The interannual average drying ratio remained constant at 0.61 ± 0.01 across all the groups and was unaffected by the treatments but varied with the harvest timing. The highest drying ratios were measured in autumn (0.71 ± 0.01 for CONT and FERT; 0.70 ± 0.01 for INOC and FERT+INOC), with the lowest values recorded in winter for CONT and FERT and in summer for INOC and FERT+INOC (ranging from 0.52 ± 0.01 to 0.55 ± 0.03).

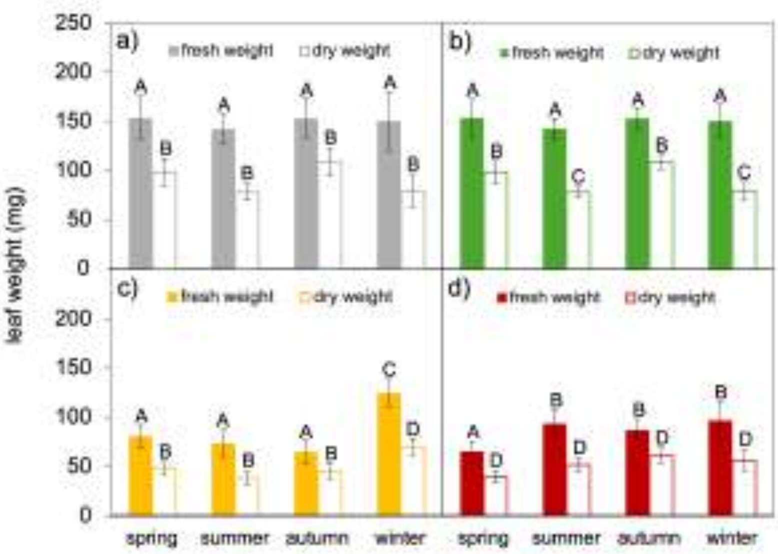


Figure 4-2 Fresh and dry weights over one growth cycle: control (a), fertilized (b), inoculated (c) and fertilized + inoculated (d). The data are presented as the means ± SEs of n = 90 leaves per group. The data were analysed by two-way ANOVA with Tukey's HSD post hoc test. Homogeneity of variance was analysed by Bartlett's test, and normality was analysed by the Shapiro–Wilk test. The same letters indicate no significant differences between the results ($p \leq 0.05$) within each treatment group.

The leaf area-to-perimeter ratio, or the leaf index (LI) shown in Figure 4-3, serves as a measure of leaf shape and efficiency. FERT and CONT presented interannual average LIs of 0.51 ± 0.1 and 0.51 ± 0.11, respectively, in contrast to INOC (0.44 ± 0.11) and FERT+INOC (0.45 ± 0.08). The broadest leaves were formed in spring by FERT (0.81 ± 0.30) and CONT (0.64 ± 0.10), which then significantly narrowed, reaching their minimum in summer. The narrowest leaves were observed in autumn for both inoculated groups, with similar values (0.33 ± 0.07 for INOC and 0.34 ± 0.07 for FERT+INOC). A pattern of narrowing from spring to autumn, followed by a significant widening in late winter, was observed across all groups, with summer leaves tending toward smaller sizes in all groups except for FERT+INOC, which presented the highest ratio (0.54 ± 0.086) in this season.

The specific leaf area (SLA), a critical measure of leaf efficiency indicating the surface area of a leaf relative to its mass, as represented in Figure 4-3, consistently presented the highest values in all groups in spring. INOC and FERT+INOC displayed mean interannual SLAs of 10.70 ± 1.87 and 9.28 ± 1.59 m^2/kg, respectively, which were higher than those of FERT (6.96 ± 1.12 m^2/kg) and CONT (6.83 ± 0.74 m^2/kg), indicating thinner leaves with a greater surface area relative to their mass. The interannual fluctuation in the SLA was pronounced within the groups, except for the control group, which showed a nearly linear decrease from spring (8.75 ± 0.70 m^2/kg) to winter (5.12 ± 0.84 m^2/kg). This pattern partly resembled the pattern of the LI. When the different samples were compared, INOC presented a similar SLA trajectory to that of the control group, with a nearly linear decrease in SLAs over the year. The two inoculated groups achieved the highest SLAs (16.37 ± 4.16 m²/kg for INOC and 16.32 ± 2.61 m²/kg for FERT+INOC), with the lowest values measured in winter for INOC and CONT and in autumn for FER+INOC, whereas FERT presented the lowest value in summer (4.78 ± 2.17 m²/kg). The SLA development of FERT paralleled that of FERT+INOC, with maximum values in spring (11.01 ± 2.71 m²/kg) and minimum values in summer and autumn (4.78 ± 1.25 m²/kg and 4.87 ± 1.73 m²/kg, respectively), indicating the influence of fertilization on the leaf pattern.

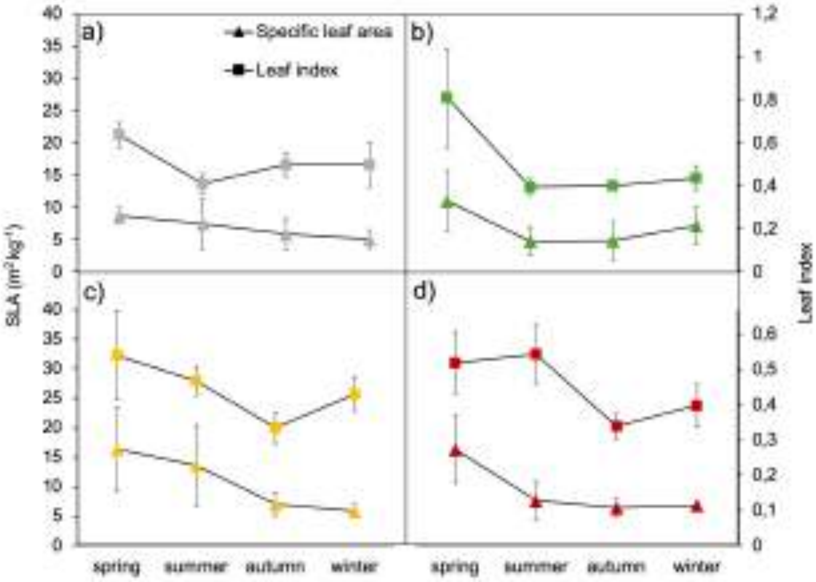


Figure 4-3 Comparison of the specific leaf area (SLA) and leaf index (leaf area/leaf perimeter ratio): control (a), fertilized (b), inoculated (c) and fertilized + inoculated (d). The data are presented as the means ± SEs of n = 90 leaves per group.

Since the SLA data were not normally distributed except for those in the control group, the Kruskal–Wallis test was used to test for significant differences between the treatment groups. Afterward, the Mann–Whitney U test was performed for each pairwise comparison, and the *p* values were adjusted using the Bonferroni method. A statistically significant difference was observed in the SLAs between CONT and INOC, as well as between FERT and INOC, before applying the Bonferroni correction. However, no significant differences were detected between the groups after correction. The results of the Mann–Whitney U test for each pairwise comparison of the harvest times and the adjusted p values suggested that the harvest time had a significant effect on the specific leaf area, especially when the spring data was compared with the data from later seasons.

4.3.2. Flowering

In the first year of cultivation within the controlled pot environment, the experimental plants presented a mean floral yield of less than two inflorescences per individual. In contrast, the subsequent year experienced substantial increases, with the mean floral yield approaching nearly twelve inflorescences per plant.

The initial flowering phase was observed uniformly across all treatment groups around mid-March, irrespective of the experimental conditions imposed. The peak daily floral yield was observed in the temporal window extending from early to mid-April (Figure 4-4). Despite the homogeneity in daily floral patterns across the various groups, a discernible variance in the aggregate floral yield was substantiated after the application of the Mann–Whitney U test, which was further adjusted by the Bonferroni correction. CONT had the greatest floral yield, with 2.84 ± 0.41 inflorescences per plant, followed by INOC, with a yield of 2.12 ± 0.409 inflorescences. FERT and FERT+INOC presented comparable yields, with yields of 1.24 ± 0.25 and 1.34 ± 0.28 inflorescences per plant, respectively. The interval spanning from early May to late June was characterized by a residual floral yield, a period typically associated with the blooming of lateral shoots. Owing to the small size of the specimens, only a marginal fraction of the lateral shoots attained the blooming phase.

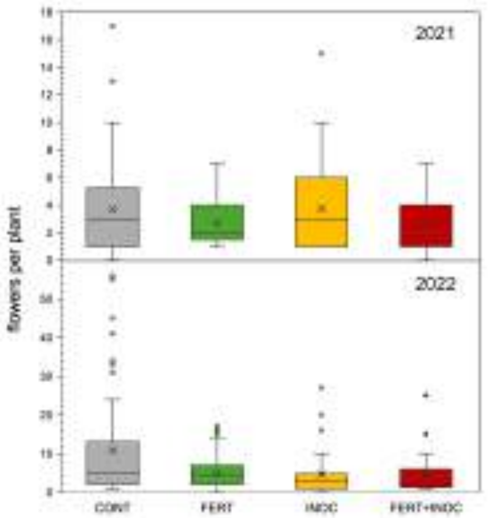


Figure 4-4 Boxplots of cumulative flowering per treatment group for the first (2021) and second (2022) years. Since the homogeneity of the variances was not given, the Kruskal–Wallis test was used to assess differences between treatment groups. The Mann–Whitney U test was subsequently performed for each pairwise comparison of the flowering data with the subsequent Bonferroni correction. All the treatment groups differed significantly from each other. In the first flowering stage (2021), all the treatment groups even presented significant differences after the Bonferroni correction; however, in the second year, only FERT and CONT differed significantly from each other and from the other groups according to the corrected Mann–Whitney U test.

In the second year of pot cultivation, the onset of flowering in the groups subjected to fertilization (FERT and FERT-INOC) advanced by an average of three weeks compared with that in the first year. Conversely, CONT and INOC exhibited an onset of flowering that was only marginally earlier, by less than a week, than it was in the inaugural year, as delineated by the corresponding date of the previous year. An analysis of the cumulative floral yield also revealed statistically significant differences across treatment groups. Nonetheless, subsequent to the application of the Bonferroni correction, these differences were predominantly attributed to inoculation. CONT resulted in the highest mean floral yield per specimen (flowers/single plant), with a value of 16.53 ± 1.96, followed by FERT, with 14.08 ± 0.45. FERT+INOC and INOC resulted in significantly lower mean floral yields, with values of 9.21 ± 0.64 and 7.58 ± 1.05, respectively. FERT was observed to exert a regulatory effect on vegetative development, as evidenced by the reduced variability in floral yield among the fertilized specimens relative to CONT. Conversely, the daily floral yield did not differ significantly, although the blooming of lateral shoots was more pronounced in the second year.

Correlation analyses revealed a significant negative correlation between fertilization in the first year and both the cumulative and daily floral yields, whereas inoculation was negatively correlated solely with the cumulative floral yield. The floral yield data for the second year indicated that inoculation was negatively correlated with both the cumulative and daily floral yields, with a more pronounced correlation observed with the cumulative floral yield. Fertilization did not significantly correlate with the cumulative floral yield; however, a weak negative correlation, which was statistically significant, was observed with the daily floral yield.

4.3.3. Growth parameters

The investigation of plant growth dynamics under various conditions revealed significant disparities in growth uniformity. The observed hierarchy in terms of homogeneity was as follows: FERT > FERT+INOC > INOC > CONT. Specifically, FERT presented the most consistent growth patterns, characterized by elongated shoots (represented in Figure 4-5) devoid of lateral branching throughout the researched phase of cultivation. These plants also presented a compact yet expansive morphology. Conversely, CONT displayed a broad spectrum of growth forms and heights, with a marked proliferation of lateral branches.

Figure 4-5 Simplified schematic representation of a typical branch of the control group with individual secondary shoots as it appears in mid-May, with secondary shoots surpassing principal shoots. The development of the shoots on average begins in September after the first major rainfall, as typically occurs in the Mediterranean, and ends with the onset of drought and heat in late June to early July.

Both INOC and FERT+INOC presented growth patterns akin to that of CONT, characterized by robust lateral shoot development. However, FERT+INOC exhibited marginally greater homogeneity than did INOC.

An aspect pertinent to the stress response was the quantification of nodes (leaf levels on a branch), with a lower stress level correlating with a greater leaf support capacity. The annual mean node count was highest in FERT and CONT, at 8.33 ± 2.02 and 8.14 ± 1.79, respectively. In contrast, INOC and FERT+INOC manifested significantly reduced node counts of 6.1 ± 1.29 and 5.76 ± 1.23, respectively.

No statistically significant differences were observed in maximum height growth (the tallest shoots of n = 33 individuals per treatment group with regular growth, Figure 4-6a). CONT exhibited relatively uniform height growth, with an average plant height of 43.4 cm and extremities between 35 and 48 cm. FERT attained an average height of 46.0 cm, ranging from 35 to 53 cm. The INOC plants were marginally shorter than the CONT plants were, achieving an average height of 38.8 cm, with a maximum height of 46 cm and a minimum height of 32 cm. FERT+INOC displayed an average height of 39.3 cm, with a maximum height of 45 cm and a minimum height of 33 cm.

During the initial year, trunk perimeter measurements did not differ significantly across treatment groups (Figure 4-6b). However, in the second year, both fertilized groups presented a markedly larger trunk perimeter, with fertilized plants achieving the greatest circumference of 32.57 ± 0.21 cm, resulting in the least variation among individuals. No significant differences in trunk perimeter were noted between the control and both inoculated groups.

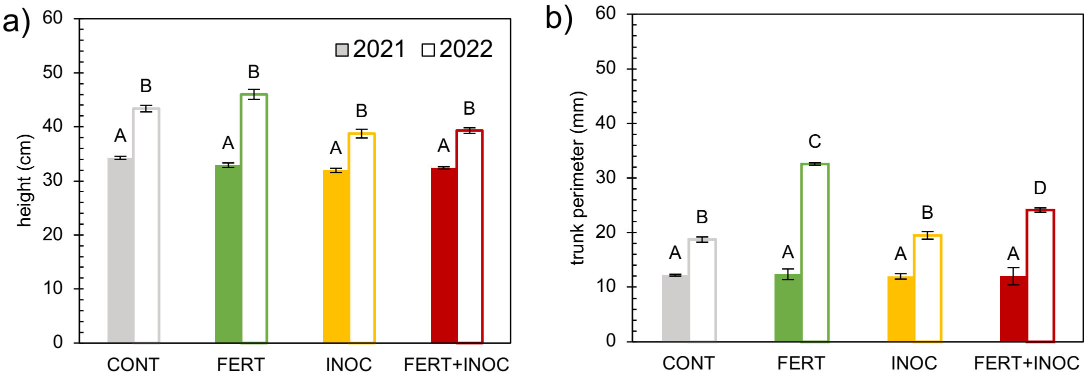


Figure 4-6 Mean height of plants in the first and second years of growth in pots (a) and trunk perimeter at the base (b). The data are presented as the means ± SEs of n = 33 individuals per treatment group. The data were analysed by two-way ANOVA with Tukey's HSD post hoc test. Homogeneity of variance was analysed by Bartlett's test, and normality was analysed by the Shapiro–Wilk test. The same letters indicate no significant differences between the results (*p* > 0.05).

Distinct variations in branch growth among the treatment groups were evident, with INOC impeding the growth of both the main and lateral branches, whereas FERT positively impacted plant height and growth velocity. FERT+INOC yielded intermediate results in terms of shoot growth and development pace. No significant differences were noted in lateral shoot growth between CONT and FERT, although the main shoots of fertilized plants exhibited significantly faster growth (Figure 4-7).

Interestingly, the maximum height of the plants was not significantly affected by the different growth conditions of the shoots. This result is mainly because the inoculated plants developed their side shoots close to the terminal umbelliform cyme of the main shoot, whereas those of CONT and FERT developed their side shoots further down.

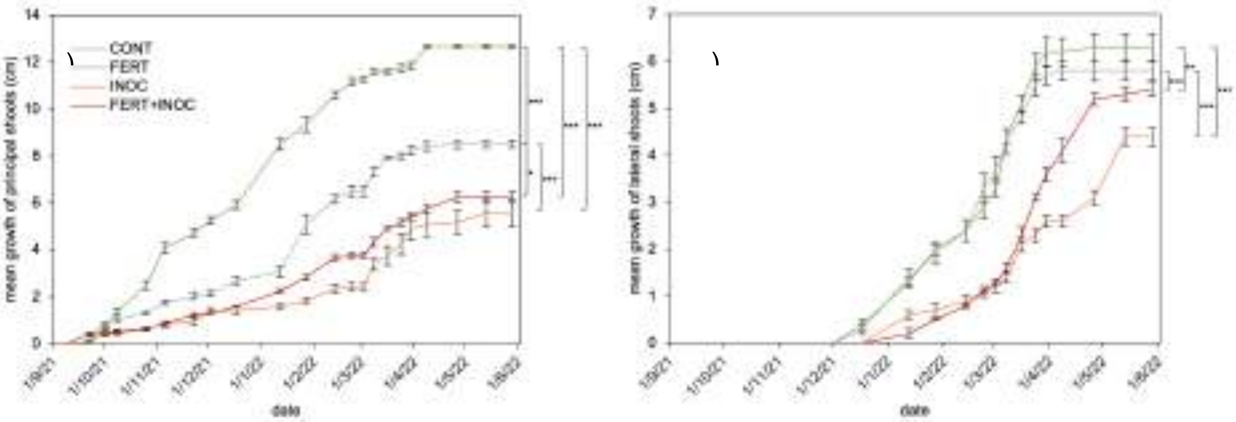


Figure 4-7 Mean growth of the principal shoots (a) and lateral shoots (b) measured between the shoot apical meristem and first leaf node during the main growth season (n = 15 shoots per treatment group ± SE). The data were analysed by one-way ANOVA with Tukey's HSD post hoc test. Statistical significance is represented by *** for $p \leq 0.001$, ** for $0.001 < p \leq 0.01$, and * for $0.01 < p \leq 0.05$.

Plant mortality rates, as presented in Figure 4-8, highlighted seasonal inflection points, suggesting the influence of environmental or external factors across all treatment groups. No plant deaths were recorded in spring, and no deaths were observed among the INOC and FERT+INOC groups during summer. However, mortality rates of 9% and 5% were observed for CONT and FERT, respectively, at the end of summer, with the majority of deaths occurring in autumn and winter. In the summer of the second year, FERT and CONT presented the highest survival rates, with values of 60% and 52%, respectively. In contrast, the survival rates of the INOC and FERT+INOC groups were only 28% and 40%, respectively.

Deceased plants were characterized by having 3 or fewer leaf nodes with living leaves, equating to a total of 6 or fewer leaves on each of all the shoots. Plants exhibiting signs of illness survived if they retained leaves on more than 3 leaf nodes.

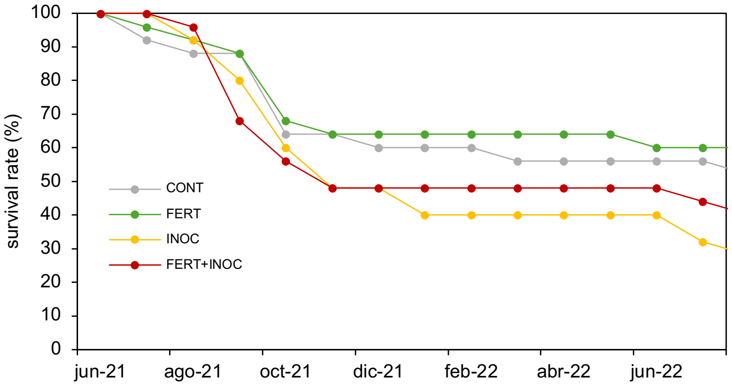


Figure 4-8 Survival rates of all the treatment groups during pot culture from December 2020 to July 2022.

The correlation analysis did not reveal a significant relationship between plant mortality and the total phenol content or antioxidant capacity. However, moderately to strongly significant correlations, both positive and negative, were observed with several of the analysed polyphenols. Notably, dehydrated tergallic C-glucoside, prodelphinidin B2-3'O-gallate and myricetin hexoside demonstrated strong and very significant correlations with plant survival rates. On the other hand, quercetin glucoside and ellagic acid 7-xiloside were significantly strongly correlated with plant death (Figure 4-9).

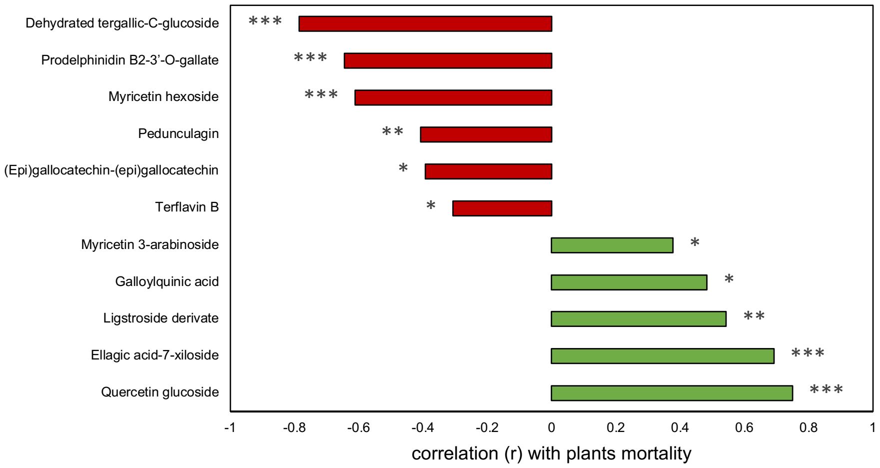


Figure 4-9 Pearson's correlation coefficients (r) between plant mortality and the analysed polyphenols during one vegetative cycle. Only statistically significant ($p < 0.05$) correlations are presented: *** for $p \leq 0.001$, ** for $0.001 < p \leq 0.01$, * for $0.01 < p \leq 0.05$. Positive values indicate that a measured polyphenol correlates with plant death; negative values correlate with the survival of the plants.

4.3.4. Total phenolic content

The quantification of the TPC, as shown in Table 4-3 and Figure A6 was conducted using the Folin–Ciocalteu assay. This analysis revealed a variation in the TPC across extracts, ranging from 3.72 to 38.85 mg GAE/g extract, with an aggregate mean value of 18.48 mg GAE/g extract observed in CONT. FERT presented phenolic concentrations ranging from 3.97 to 36.73 mg GAE/g extract, resulting in a mean value of 18.45 mg GAE/g extract. INOC presented phenolic concentrations ranging from 17.86 to 35.21 mg GAE/g extract, with a calculated mean of 26.94 mg GAE/g extract. FERT+INOC presented phenolic levels ranging from 12.75 to 36.32 mg GAE/g extract, with an overall mean of 23.45 mg GAE/g extract. Notably, the peak phenolic concentration was identified in CONT during summer, whereas the lowest value was also observed in CONT but in autumn, at 3.72 mg GAE/g extract.

Table 4-3 Results for the total phenolic content of *C. albidus* aqueous extracts from leaves harvested in four seasons determined using the Folin–Ciocalteu assay and presented in gallic acid equivalents (GAEs) per gram of plant extract (data are presented as the means ± SEs of n = 3 samples). The data were analysed by one-way ANOVA with Tukey's HSD post hoc test. Means in the same column followed by different letters are significantly different ($p < 0.05$).

	SPRING	SUMMER	AUTUMN	WINTER
CONT	8.89 ± 0.61 ^{a,b}	38.85 ± 0.31 ^{a}	3.72 ± 1.41 ^{a}	22.46 ± 1.95 ^{a}
FERT	4.87 ± 1.7 ^{a}	28.21 ± 4.45 ^{a}	3.97 ± 1.32 ^{a}	36.73 ± 1.73 ^{b}
INOC	21.10 ± 1.07 ^{a,b}	33.59 ± 2.24 ^{a}	17.86 ± 1.78 ^{b}	35.21 ± 0.94 ^{b}
FERT+INOC	13.34 ± 1.41 ^{b}	36.32 ± 4.58 ^{a}	12.75 ± 2.62 ^{b}	31.4 ± 1.29 ^{b}

In general, all the treatments consistently yielded the highest TPC, particularly in the summer and, to a lesser extent, in the winter, which confirms the strong influence of high and low temperatures on polyphenol biosynthesis, as observed in other studies (Balasooriya et al., 2019; Sharma et al., 2019; Zhou et al., 2018). A comparative analysis across the four treatment groups revealed a descending order of average interannual TPC as follows: INOC > FERT+INOC > CONT > FERT, with CONT and FERT showing nearly equal concentrations.

The statistical analysis revealed significant differences in spring, autumn and winter among several different treatment groups. The most significant differences were found in autumn between the inoculated plants (INOC and FERT+INOC) and the other treatment groups. In the summer, no differences were detected between any of the groups, whereas in the winter, the differences were limited to CONT and the remaining plants. Interestingly, for all seasons, no significant differences were observed between INOC and FERT+INOC. Furthermore, no significant correlations with TPC were observed for any of the treatments.

4.3.5. Antioxidant capacity

A TEAC assay was employed to evaluate the antioxidant potential of *C. albidus*, as described in Table 4-4 and shown in Figure A5, with a focus on the reactional variability across the various treatment groups throughout the designated harvest periods.

The total antioxidant activity exhibited variability across the treatment groups. For CONT, the activity ranged from 3.93 to 9.92 mmol TE/100 g extract, with an interannual mean of 5.21 mmol TE/100 g extract. FERT displayed antioxidant activity ranging from 4.05 to 8.44 mmol TE/100 g extract, yielding an overall mean of 6.67 mmol TE/100 g extract. INOC manifested a total antioxidant capacity ranging from 6.90 to 15.74 mmol TE/100 g extract, with a mean value of 9.82 mmol TE/100 g extract. Furthermore, FERT+INOC exhibited antioxidant capacities between 7.63 and 11.8 mmol TE/100 g extract, with a mean value closely paralleling that of INOC at 9.87 mmol TE/100 g extract.

Table 4-4 Results of the TEAC assay of *C. albidus* extracts from leaves harvested in four seasons, presented as mmol equivalent Trolox/100 g extract (data are presented as the means ± SEs of n = 3 extracts). The data were analysed via one-way ANOVA with Tukey's HSD post hoc test. Means in the same column followed by different letters are significantly different (p < 0.05).

	SPRING	SUMMER	AUTUMN	WINTER
CONT	9.92 ± 0.23 ^{a}	8.42 ± 0.8 ^{a}	3.93 ± 0.72 ^{a}	7.09 ± 0.16 ^{a}
FERT	6.34 ± 1.16 ^{b}	8.44 ± 0.08 ^{a}	4.05 ± 0.54 ^{b}	7.84 ± 0.05 ^{a}
INOC	8.4 ± 0.94 ^{ab}	8.24 ± 0.6 ^{a}	15.74 ± 0.43 ^{c}	6.9 ± 0.67 ^{a}
FERT+INOC	10.27 ± 0.15 ^{a}	9.78 ± 0.95 ^{a}	11.8 ± 0.9 ^{d}	7.63 ± 0.21 ^{a}

In general, the inoculated treatment groups, irrespective of the fertilization status, consistently yielded the highest TEAC values, particularly in autumn, indicating a temporal increase in antioxidant capacity attributed to inoculation toward winter. A comparative analysis of the interannual average antioxidant capacities revealed a descending order of mean antioxidant capacity as follows: FERT+INOC > INOC > CONT > FERT. FERT+INOC and INOC showed almost the same results, 39.48 and 39.28 mmol TE/100 g extract, respectively. INOC demonstrated a markedly superior antioxidant capacity in autumn, approximately quadrupling that of CONT. These results were significantly different from each other, with inoculation having the most significant effect on the antioxidant capacity ($p = 6.83 \times 10^{-5}$) and fertilization in combination with inoculation enhanced this effect (p = 0.015). However, significant differences were observed only in spring and autumn when the combined results of the same harvest times across all the treatment groups were considered. In contrast, no such differences were found between summer and winter or between individual treatment groups during those seasons. The most significant differences were observed in autumn between the inoculated plants (INOC and FERT+INOC) and those in the other treatment groups. Further analysis confirmed these observations, with the antioxidant capacity correlated with INOC (r = 0.501, p = 0.0003) and FERT+INOC (r = 0.306, p

= 0.03). In spring, the differences were less pronounced and could be found only between FERT and FERT+INOC and between FERT and CONT.

4.3.6. Correlation between the antioxidant capacity and TPC

The correlation between the TPC and the antioxidant capacity was examined to gain a deeper understanding of the relationship between these two parameters in different extracts. The correlations between the TPC and antioxidant capacity were generally not significant across the harvest times. However, in spring, FERT+INOC showed a very strong correlation (r = 0.99, p = 0.018). With respect to the treatments only, a significant positive correlation was observed between the antioxidant capacity and TPC for FERT (r = 0.663, p = 0.026). When individual compounds were examined, predominantly weak and statistically nonsignificant correlations with antioxidant capacity were found (Figure A7 to Figure A8).

4.3.7. Extract composition

The chemical composition of the extracts was evaluated by UHPLC–MS as described in the Methods section. Overall, depending on the harvest time, 30 major peaks were observed, representing 92% to 100% of the total UHPLC peak area. Among these peaks, which corresponded up to 16 compounds divided into several isomers, five flavonols (myrecitin 3-O-(2″-O-galloyl)-hexoside, myricetin hexoside, myricetin 3-arabinoside, quercetin glucoside, kaempferol diglycoside), two flavanols ((-)-(epi)gallocatechin-(epi)gallocatechin dimer, prodelphinidin B2-3’-O-gallate), five ellagitannins (dehydrated tergallic-C-glucoside, punicalagin, pedunculagin, terflavin B, ellagic acid-7-xiloside), three phenolic acids (coumaroylquinic acid, galloylquinic acid, caffeoyl hexose), and one secoiridoid glycoside (ligstroside derivate) were identified (Table 4-5).

Extracts from all the treatment groups had an annual average of 21 peaks. Most peaks were observed in the extracts obtained in spring from FERT, with 30 detected compounds, followed by CONT, with 29. The fewest peaks were found in winter for INOC, with only 17 identified compounds. The relative areas of the peaks identified as isomers were summarized with the corresponding main compounds and are not shown individually.

4.3.7.1. Phytochemicals

The results of the relative distribution of the studied polyphenols obtained via UHPLC–MS are shown in Table 4-5. The compounds organized by substance class were significantly influenced by the harvest time, with the exception of ellagitannins. With respect to the treatments, among the substance classes analysed, significant differences between the treatment groups were observed only for ellagitannins (p = 0.0082).

For all the individual compounds, significant differences in concentration related to harvest time were observed, with the exception of myricetin 3-arabinoside (Table 4-5). With the exception of caffeoyl hexose and pedunculagin, the treatments resulted in no significant differences in the measured concentrations. A comparison of single compounds between treatments applied over the vegetative cycle using the Kruskal–Wallis test with the subsequent Bonferroni correction revealed no statistically significant differences.

Below, the concentrations of the compounds were analysed as the average of all treatment groups for each season and as the average of all harvest times for each individual treatment group (Table 4-5) to examine the treatments and harvest times in detail. Boxplots of the cumulative concentrations of the total compounds studied during the vegetative cycle depending on the treatment are shown in Figure A9 to Figure A13 in the appendix section.

Table 4-5 Effects of the treatment (CONT, FERT, INOC, and FERT+INOC) and harvest time (spring, summer, autumn, and winter) on the composition of *C. albidus* aqueous extracts. UHPLC–MS retention times (Rt) of the 16 evaluated peaks, mass data (base ions in both positive and negative mode [M−H]+ and [M−H]−), main fragment ions (MS/MS), peak identification and relevance of compounds (range of relative area percentages at 280 nm). The relative area is represented by the mean value ± standard deviation of three replicates. The data were analysed by one-way ANOVA with Tukey's HSD post hoc test. Statistical significance is shown separately for each treatment group and harvest time. The same letters within each observation (treatment, harvest time) are not significantly different ($p \leq 0.05$).

Peak	Proposed Compound	[M-H] −(m/z)	MS/MS (m/z)	RT (min)	Literature	Relative area depending on treatment (%)				Relative area depending on harvest time (%)			
						CONT	FERT	INOC	FERT+INOC	SPRING	SUMMER	AUTUMN	WINTER
1	Pedunculagin	783	275, 301, 451, 481	10.1	[512]	2.98 ± 2.14 ^{a}	2.65 ± 1.77 ^{bc}	3.32 ± 2.57 ^{ab}	3.59 ± 2.49 ^{c}	2.79 ± 1.83 ^{a}	5.23 ± 1.40 ^{b}	2.02 ± 1.05 ^{a}	2.22 ± 2.43 ^{a}
2	(-)-(Epi)gallocatechin-(epi)gallocatechin dimer	609	423, 441	10.6	[131,513]	2.69 ± 1.75 ^{a}	3.06 ± 2.53	5.04 ± 4.40 ^{a}	3.26 ± 1.57 ^{a}	1.75 ± 1.97 ^{a}	5.99 ± 2.18 ^{b}	3.08 ± 0.53 ^{a}	1.68 ± 1.47 ^{a}
3	Prodelphinidin B2-3'-O-gallate	761	423, 609	10,6	[514]	5.94 ± 8.0 ^{a}	6.31 ± 5.74 ^{a}	3.57 ± 2.35 ^{a}	6.44 ± 8.80 ^{a}	13.67 ± 5.17 ^{a}	4.68 ± 3.75 ^{b}	1.37 ± 0.35 ^{bc}	1.71 ± 0.76 ^{bc}
4	Coumaroylquinic acid	337	161	10,7	[515]	11.71 ± 7.56 ^{a}	10.51 ± 5.52 ^{a}	11.53 ± 10.03 ^{a}	8.37 ± 3.92 ^{a}	8.13 ± 2.15 ^{a}	6.33 ± 4.38 ^{ab}	17.92 ± 6.40 ^{c}	5.59 ± 2.21 ^{ab}
5	Terflavin B	783	451, 631	11,7	[516,517]	1.77 ± 1.27 ^{a}	2.11 ± 1.94 ^{a}	2.32 ± 2.01 ^{a}	3.57 ± 3.15 ^{a}	3.63 ± 2.73 ^{a}	1.16 ± 2.11 ^{b}	1.94 ± 0.45 ^{ab}	1.72 ± 0.71 ^{ab}
6	Punicalagin	1083	301, 601, 781	14.2	[131,518–520]	2.66 ± 2.64 ^{a}	2.56 ± 2.19 ^{a}	3.13 ± 2.91 ^{a}	0.85 ± 0.61 ^{a}	4.38 ± 2.78 ^{a}	0.00 ± 0.00 ^{b}	1.01 ± 0.80 ^{b}	1.39 ± 0.44 ^{b}
7	Galloylquinic acid	343	151, 169, 191	14,5	[521]	3.65 ± 3.24 ^{a}	6.44 ± 3.01 ^{a}	7.34 ± 4.62 ^{a}	6.29 ± 3.87 ^{a}	3.07 ± 2.02 ^{a}	1.83 ± 1.96 ^{ab}	11.65 ± 9.16 ^{c}	7.46 ± 2.81 ^{ac}
8	Cafeoyl-hexose	341	179	14,6	[522]	6.39 ± 2.82 ^{a}	6.09 ± 2.92 ^{ab}	8.24 ± 3.53 ^{b}	6.92 ± 3.25 ^{ab}	7.91 ± 2.26 ^{abc}	6.03 ± 2.26 ^{b}	10.40 ± 3.71 ^{c}	6.14 ±3.09 ^{abd}
9	Ligstroside derivate	453	151, 169, 313	14,9	[523]	5.39 ± 2.49 ^{a}	6.42 ± 1.52 ^{a}	5.13 ± 3.21 ^{a}	6.01 ± 2.17 ^{a}	5.70 ± 2.02 ^{a}	3.51 ± 2.19 ^{a}	6.23 ± 1.63 ^{ab}	9.22 ± 4.32 ^{b}
10	Putative Myricetin 3-O-(2″-O-galloyl)-hexoside or myricetin-galactoside-gallate	631	317, 479	17,1	[524,525]	3.22 ± 0.62 ^{a}	4.41 ± 2.36 ^{a}	3.25 ± 1.83 ^{a}	3.46 ± 2.37 ^{a}	2.70 ± 3.37 ^{a}	4.42 ± 0.95 ^{b}	2.82 ± 0.93 ^{c}	3.20 ± 1.71 ^{d}
11	Myricetin hexoside	479	179, 271, 316	17,7	[522]	11.28 ± 6.79 ^{a}	9.39 ± 6.03 ^{a}	10.21 ± 3.90 ^{a}	8.44 ± 3.60 ^{a}	11.16 ± 2.13^{a}	15.91 ± 3.74 ^{b}	8.83 ± 4.84 ^{ac}	5.85 ± 3.25 ^{c}
12	Dehydrated tergallic-C-glucoside	615	301	18,3	[526]	4.52 ± 3.96 ^{a}	5.14 ± 2.46 ^{a}	4.38 ± 3.21 ^{a}	6.12 ± 4.00 ^{a}	7.19 ± 1.97 ^{a}	8.46 ± 1.60 ^{a}	3.82 ± 2.88 ^{b}	2.88 ± 0.90 ^{b}
13	Myricetin 3-arabinoside	449	179, 271, 316	19.2	[514]	7.77 ± 1.48 ^{a}	10.03 ± 5.90 ^{a}	9.53 ± 2.93 ^{a}	11.87 ± 3.25 ^{a}	8.03 ± 2.76 ^{a}	9.26 ± 2.39 ^{a}	10.48 ± 5.46 ^{a}	13.26 ± 7.76 ^{a}
14	Quercetin glucoside	463	151, 301	21,4	[514]	8.79 ± 7.22 ^{a}	14.39 ± 11.86 ^{a}	12.49 ± 7.39 ^{a}	15.15 ± 9.02 ^{a}	5.55 ± 3.61 ^{a}	8.59 ± 5.59 ^{a}	8.97 ± 2.63 ^{a}	22.49 ± 6.72 ^{b}
15	Ellagic acid-7-xiloside	433	301	26.	[527]	12.81 ± 6.66	9.69 ± 3.63 ^{a}	14.81 ± 8.99 ^{a}	12.23 ± 3.98 ^{a}	7.07 ± 2.11 ^{a}	9.33 ± 1.72 ^{a}	14.89 ± 5.83 ^{b}	18.23 ± 7.02 ^{b}
16	Kaempferol diglycoside	593	285, 447	37,1	[514]	6.94 ± 2.83 ^{a}	6.45 ± 3.34 ^{a}	8.27 ± 3.09 ^{a}	6.79 ± 1.05 ^{a}	7.29 ± 2.47 ^{a}	9.26 ± 1.46 ^{ab}	4.65 ± 1.75 ^{c}	7.13 ± 3.46 ^{ac}

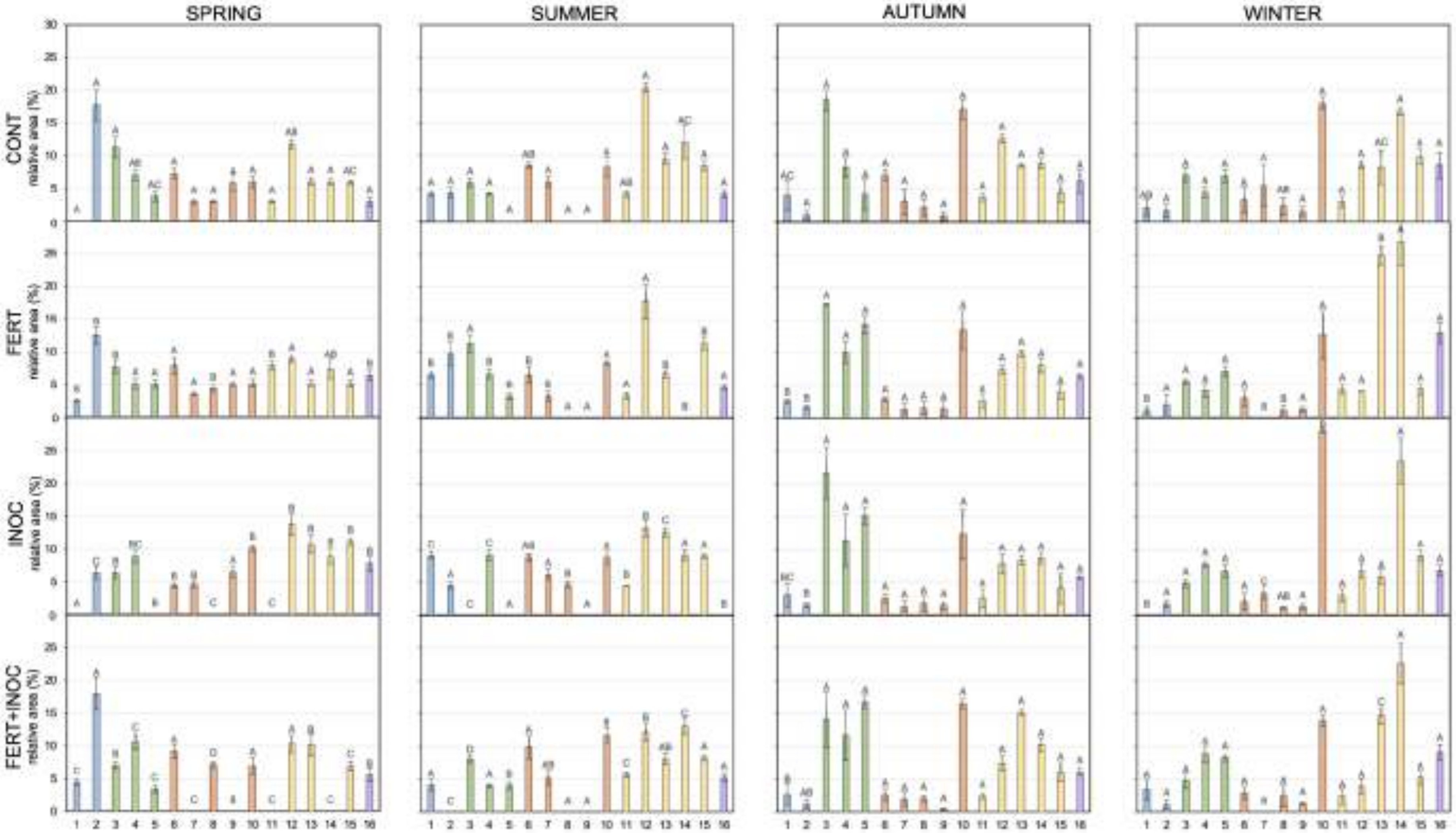


Figure 4-10 Seasonal profiles of the relative distributions of the studied polyphenols extracted with water according to the relative area of each UHPLC–MS profile. Blue: flavan-3-ols; green: phenolic acids; brown: ellagitannins; yellow: flavonols; purple: secoiridoids. Compounds: 1. (-)-(epi)gallocatechin-(epi)gallocatechin dimer, 2. prodelphinidin B2-3’-O-gallate, 3. coumaroylquinic acid, 4. caffeoyl hexose, 5. galloylquinic acid, 6. dehydrated tergallic-C-glucoside, 7. pedunculagin, 8. terflavin B, 9. punicalagin, 10. ellagic acid-7-xiloside, 11. myrecitin-3-O-(2″-O-galloyl)-hexoside, 12. myricetin hexoside, 13. myricetin 3-arabinoside, 14. quercetin glucoside, 15. kaempferol diglycoside, 16. ligstroside derivative. The relative area is represented by the mean value ± standard deviation of three replicates. The data were analysed by one-way ANOVA with Tukey’s HSD post hoc test. Statistical significance is shown between the same compounds for each harvest time. The same letters within each observation (subplot) are not significantly different ($p \leq 0.05$).

Flavan-3-ols

The seasonal average concentrations of flavan-3-ols (represented by blue bars in Figure 4-10) in all the treatment groups were highest in spring. Specifically, prodelphinidin B2-3’-O-gallate showed a significant peak in spring, whereas (-)-(epi)gallocatechin-(epi)gallocatechin was either present at low or undetectable concentrations during this time but reached its peak in summer (peak 2). By summer, the concentration of prodelphinidin B2-3’-O-gallate decreased significantly, continuing to decrease through autumn, with a slight increase observed in winter. In contrast, (-)-(epi)gallocatechin-(epi)gallocatechin displayed less variation throughout the year, peaking in summer, slightly decreasing in autumn, and maintaining similar concentrations in both spring and winter.

The highest average concentrations of prodelphinidin B2-3’-O-gallate across all harvest periods were observed under fertilized conditions (FERT and FERT+INOC), with comparable values for both treatment groups, while the lowest levels were observed for the INOC treatment group. For (-)-(epi)gallocatechin-(epi)gallocatechin, the highest average concentration was observed for INOC, and the lowest was observed for CONT. However, none of these differences were statistically significant.

Interestingly, significant ($p < 0.05$) differences were observed between individual treatments and harvest periods for flavan-3-ols. For example, no (-)-(epi)gallocatechin-(epi)gallocatechin was detected in the CONT and INOC treatment groups in spring, and it was also absent from the INOC treatment group in winter, whereas prodelphinidin B2-3’-O-gallate was absent in the FERT+INOC treatment group during summer.

Throughout the year, the correlation between the concentrations of the two flavan-3-ols was negligible. However, a strong negative correlation was observed between the harvest period and the concentration of prodelphinidin B2-3'-O-gallate ($r = -0.990$, $p = 1.28 \times 10^{-3}$). As the year progressed from spring to winter, the concentration of this compound decreased significantly, regardless of the treatment applied.

Phenolic acids

With the exception of caffeoyl hexose (peak 8), the analysed set of phenolic acids (green bars in Figure 4-10) showed significant ($p < 0.0001$) seasonal fluctuations, with a pronounced peak in autumn and the significantly lowest values observed in winter.

When all the treatment groups were averaged across seasons, the analyzed phenolic acids exhibited several notable patterns. For coumaroylquinic acid (peak 4), no clear yearly trend emerged. Its concentration decreased slightly from spring to summer, increased significantly from summer to autumn, and then decreased sharply to its lowest average concentration in winter. The concentration of galloylquinic acid (peak 7) decreased during the seasons with longer daylight (spring to summer) but increased significantly in the seasons with shorter daylight, peaking in autumn before decreasing again in late winter. Caffeoyl hexose concentrations were more stable throughout the year, with a significant peak in autumn.

The harvest time was strongly positively correlated with the concentrations of coumaroylquinic acid (r = 0.898, *p* = 0.038) and galloylquinic acid (r = 0.988, *p* = 1.58 × 10^{-3}) but strongly negatively correlated with the concentration of dehydrated tergallic C-glucoside (r = -0.949, *p* = 0.013).

When the average concentration measured in all harvest periods for each treatment group was considered, only caffeoyl hexose was significantly different (*p* = 0.01) between the INOC treatment and CONT groups. However, no significant differences were observed between INOC and FERT+INOC or between INOC and FERT. The concentrations of other phenolic acids did not differ significantly across the treatment groups.

Significant differences were observed between the treatments and harvest periods for the concentrations of some phenolic acids. Compared with the other treatments, coumaroylquinic acid presented significantly higher concentrations in CONT in spring, although the differences in other seasons were not significant, except for INOC in summer, where coumaroylquinic acid was not detected. The concentration of caffeoyl hexose was significantly different between the treatment groups in spring and summer but not in autumn and winter, with both the INOC and FERT+INOC treatment groups presenting increased concentrations of this compound, except for FERT+INOC in summer.

Correlation analyses between individual phenolic acids revealed a significant positive relationship between the concentrations of caffeoyl hexose and coumaroylquinic acid (r = 0.459, *p* = 2.89 × 10^{-3}). While FERT and FERT+INOC showed no significant correlations with substance concentrations (with all correlations being either close to zero or weakly negative), a significant positive correlation was observed between INOC and the caffeoyl hexose concentration (r = 0.397, *p* = 0.0084).

Ellagitannins

In general, the concentrations of ellagitannins (brown bars in Figure 4-10) increased over the course of the vegetative cycle. The average concentrations in all treatment groups per season reached their maximum values in late winter, primarily due to an increase in the ellagic acid-7-xyloside concentration (peak 15). In contrast, the lowest values were observed in summer, mainly because terflavin B (peak 5) was not detected in all the treatment groups except for INOC. The level of dehydrated tergallic-C-glucoside (peak 12) exhibited an increasing trend through spring and summer but decreased significantly in autumn, reaching its lowest concentration in winter. The concentration of pedunculagin (peak 1) fluctuated throughout the year, with no consistent trend, although higher concentrations were generally observed during the warmer seasons, peaking significantly in summer. Its lowest concentrations appeared sporadically, especially in autumn. The concentrations of punicalagin (peak 6) exhibited pronounced seasonal fluctuations, with its highest levels typically observed in spring. Its concentrations decreased significantly through autumn and winter and were not detected during summer, indicating a clear seasonal pattern in its biosynthesis. Terflavin B presented a developmental pattern similar to that of punicalagin, with peak concentrations in spring that significantly decreased in summer, suggesting a strong response to environmental or physiological changes. The concentration of ellagic acid-7-xyloside increased steadily throughout the year, with higher concentrations detected during the colder seasons. The lowest levels were generally observed in spring, gradually increased through summer, peaked significantly in autumn, and reached the highest values in winter.

In terms of treatment, significant differences were found in the seasonal accumulation of ellagitannins. However, these differences were primarily due to pedunculagin, which responded significantly to fertilization at relatively low concentrations. The highest values were recorded in INOC, followed by CONT. The concentrations of other ellagitannins did not differ significantly among the treatment groups (Table 4-5).

Significant differences between individual treatment groups and harvest times were also observed for the concentrations of ellagitannins. Pedunculagin was not detected in FERT+INOC during spring and winter or in FERT during winter. Terflavin B was absent from INOC in spring but present in summer across all the treatment groups except INOC. Punicalagin was not detected in FERT+INOC in spring or in any treatment group during summer. Ellagic acid-7-xyloside was present across all the treatment groups, with the highest concentration recorded in INOC during winter, which was five times greater than the value measured in FERT during spring.

All the measured ellagitannins exhibited significant, strong correlations with the harvest time. The correlations were strongly negative for dehydrated tergallic C-glucoside, pedunculagin, punicalagin, and terflavin B, with very significant values approaching 1. However, ellagic acid-7-xyloside was positively correlated with the harvest time.

Moderate positive correlations were detected between terflavin B and punicalagin concentrations ($r = 0.697$, $p = 2.18 \times 10^{-4}$) and between punicalagin and pedunculagin concentrations ($r = 0.603$, $p = 6.23 \times 10^{-3}$) during the vegetative cycle. Negative correlations were observed between ellagic acid-7-xyloside and punicalagin concentrations ($r = -0.599$, $p = 2.8518 \times 10^{-4}$), as well as between ellagic acid-7-xyloside and terflavin B concentrations ($r = -0.598$, $p = 6.15 \times 10^{-4}$), indicating a moderate inverse relationship. No significant correlations were observed for the other compounds.

Flavonols

For the measured flavonols (yellow bars in Figure 4-10), significant seasonal differences were generally observed, with peak levels occurring in summer and, to a lesser extent, in winter. However, quercetin glucoside (peak 14) and myricetin arabinoside (peak 13) were present at the highest concentrations in winter. The concentrations of most of the compounds did not differ significantly between spring and autumn.

The concentration of myricetin-3-O-(2″-O-galloyl)-hexoside (peak 10) displayed a relatively stable pattern, starting with a lower level in spring and gradually decreasing throughout the year. The concentration of myricetin hexoside (peak 11) exhibited significant fluctuations, with concentrations increasing during the warmer months and peaking in summer, followed by the lowest level in winter. The concentration of myricetin 3-arabinoside (peak 13) also varied, with an increasing trend toward the end of the year, the lowest concentration occurring in spring and the maximum concentration occurring in winter. Similarly, quercetin glucoside concentrations displayed pronounced fluctuations, with the highest concentration occurring in winter and the lowest occurring in spring. Kaempferol diglycoside concentrations (peak 16) were initially relatively low in spring, increased to a peak in early summer, and then declined until autumn. This decline stabilized somewhat as winter approached, with a slight increase in concentration.

In terms of the seasonal averages of the individual treatment groups, the highest flavonol concentrations were observed in FERT+INOC, followed by INOC, with lower levels detected in FERT and CONT, with the latter presenting the lowest levels. However, no statistically significant differences were observed between the treatment groups for any of the individual flavonols analysed.

The analysis of individual treatment groups within each season revealed statistically significant differences in the concentrations of all flavonols in spring and summer, whereas in winter, such differences were only significant for myricetin arabinoside.

Among all flavonols examined, statistically significant differences across harvest times were observed only for myricetin 3-arabinoside, which was strongly positively correlated ($r = 0.909$, $p = 0.03$), and for myricetin-3-O-(2″-O-galloyl)-hexoside, which was significantly negatively correlated ($r = -0.964$, $p = 8.19 \times 10^{-3}$). The other flavonols showed no significant correlation with harvest time, suggesting that their concentrations may not be directly influenced by seasonal factors or that other factors may play a more significant role in determining their levels.

Additionally, the concentrations of most flavonols showed weak or nonsignificant correlations with each other, except for myricetin hexoside, which was positively correlated with kaempferol diglycoside ($r = 0.517$, $p = 2.31 \times 10^{-4}$) and negatively correlated with quercetin glucoside ($r = -0.440$, $p = 3.51 \times 10^{-3}$) and myricetin arabinoside ($r = -0.306$, $p = 0.04$). These correlations suggest that these compounds may be involved in compensatory biosynthetic pathways.

Secoiridoid glycosides

The only secoiridoid glycoside studied (purple bars in Figure 4-10) was a ligstroside derivative (peak 9). The analysis of ligstroside derivative levels revealed distinct seasonal patterns, with a general increasing trend throughout the year and a peak in winter. Significant differences were observed in winter compared with spring and summer.

Compared with CONT, fertilization and inoculation (FERT, INOC, and FERT+INOC) resulted in significantly higher average levels of the ligstroside derivative in spring. However, no significant differences were observed between treatment groups in the other seasons, except for INOC in summer, where the ligstroside derivative was not detected.

4.3.8. Effects of the treatments and harvest timing

The Bartlett tests for homogeneity of variance revealed significant results, indicating unequal variance between treatment groups. This result suggests that certain treatments may affect some compounds in ways that cannot be identified through comparisons of mean values alone but may instead be due to individual plant responses or specific conditions. Consequently, treatment effects cannot be fully understood without considering seasonal influences.

Box plots (Figure A9 to Figure **A13** in the appendix section) illustrate the distribution of substance concentrations across treatment groups. Some overlap between the groups was evident, with the INOC group showing higher medians and a broader interquartile range, indicating both higher concentrations and greater variability. FERT had a distribution similar to that of CONT, with a slight tendency toward higher concentrations, although the variability between these groups appeared similar. Compared with CONT, INOC presented a greater mean and standard error. The means for the fertilized and nonfertilized groups were comparable, with a slight increase in the standard error for FERT.

Overall, fertilization seems to have a minimal effect on both the growth parameters and the phytochemical composition of the leaves. Significant differences between treatment groups throughout the vegetative cycle were observed only for pedunculagin and caffeoyl hexose concentrations (Table 4-3). All other compounds exhibited only minor deviations in annual average concentrations. Inoculation led to greater fluctuations in the values, although these fluctuations were not statistically significant, with the exception of the caffeoyl hexose concentrations.

Most compounds presented significant differences in variance between treatment groups at specific harvest times (Figure 4-10). Some compounds were more sensitive to particular treatments at certain times of the year, as indicated by greater variability in their concentrations. Significant differences were most apparent in spring and summer, whereas differences in autumn and winter were less pronounced or absent. For example, the concentrations of flavan-3-ols (-)-(epi)gallocatechin-(epi)gallocatechin and prodelphinidin B2-3’O-gallate differed significantly across all the treatment groups within each season, with only (-)-(epi)gallocatechin-(epi)gallocatechin significantly influenced by inoculation throughout the entire vegetative cycle. Terflavin B and myricetin 3-O (2’’-O-galloyl)-hexoside concentrations followed a similar pattern, with inoculation significantly affecting the concentrations of these compounds in spring and summer. In contrast, ellagic acid 7-xyloside and myricetin 3-arabinoside concentrations were significantly affected by fertilization throughout the vegetative cycle, except in autumn.

In general, the harvest timing had the most substantial effect on phytochemical parameters (Table 4-3). Strong, significant correlations were identified for 10 of the 16 analysed phytochemicals. The contents of six compounds decreased throughout the vegetative cycle, whereas the contents of myricetin arabinoside, galloylquinic acid, coumaroylquinic acid, and ellagic acid 7-xyloside increased significantly over this period (Figure 4-11).

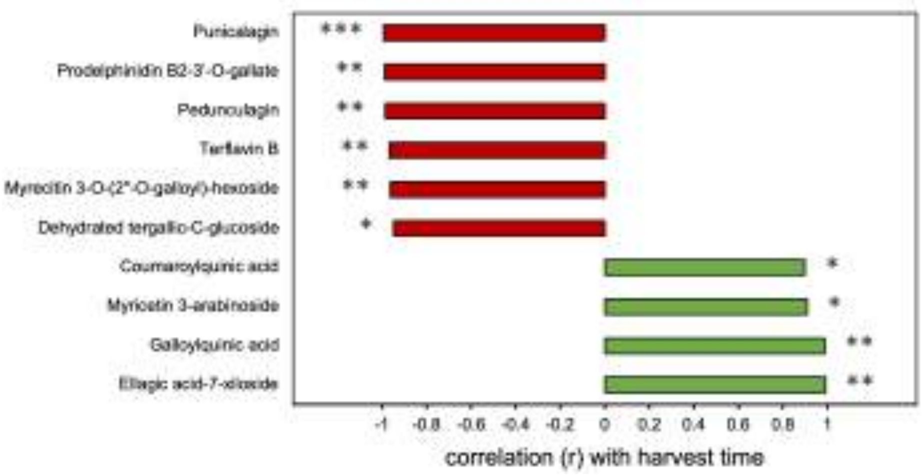


Figure 4-11 Pearson's correlation coefficients (r) between single compounds and the harvest time during one vegetative cycle. Only statistically significant ($p < 0.05$) correlations are presented: *** for $p \leq 0.001$, ** for $0.001 < p \leq 0.01$, * for $0.01 < p \leq 0.05$. Positive values indicate that the concentration of a measured polyphenol correlates with the end of the vegetative cycle; negative values correlate with earlier harvest times.

However, no significant correlation was found between the harvest timing and total phenol content or antioxidant capacity, possibly because of opposing trends in the concentrations of individual compounds.

The potential harvest dates were assessed by evaluating three key variables: the mean leaf dry weight and the biochemical components TEAC and TPC (Table 4-6). Significant differences in harvest timing, independent of treatment, were observed only for leaf dry weight in summer and TPC between all seasons, except spring and autumn and summer and winter, whereas TEAC did not show significant differences. These findings suggest that the harvest timing could significantly impact production quality and yield.

Given the significant peak in TPC and the lack of variation in annual TEAC values, late winter appears to be the optimal harvest time, which is further supported by the high mean leaf dry weight during this period.

Table 4-6 Parameters evaluated for determining the harvest time included the mean leaf dry weight (mg per leaf), antioxidant capacity (TROLOX equivalents per 100 g extract, TEAC) and total phenol content (gallic acid equivalent per gram extract (TPC)) independently of the treatment from leaves harvested in four seasons. The data were analysed by one-way ANOVA with Tukey's HSD post hoc test. Within each observation, the letters indicate a significant difference ($p < 0.05$) compared with spring, summer, autumn and winter (data are presented as the means ± SEs of n = 90 leaves for leaf dry weight and n = 100 each for TEAC and TPC analyses).

	Mean leaf dry weight (mg)	**TEAC (mmol equivalent Trolox/100 g extract)**	**TPC (gallic acid equivalent/g)**
Spring	71.4 ± 8.68 ^{a}	8.73 ± 0.57 ^{a}	8.52 ± 1.36 ^{ac}
Summer	58.2 ± 4.83 ^{b}	8.72 ± 0.35 ^{a}	27.09 ± 4.84 ^{b}
Autumn	77.5 ± 8.00 ^{a}	8.88 ± 1.56 ^{a}	9.58 ± 1.98 ^{c}
Winter	76.8 ± 5.74 ^{a}	7.18 ± 0.24 ^{a}	31.45 ±1.79 ^{bd}

4.4. DISCUSSION

4.4.1. Vegetative observations

Climate change poses a significant threat to global crop production. Rising temperatures, altered precipitation patterns, and the increased frequency and severity of extreme weather events, such as droughts, have profound impacts on agricultural systems. Droughts, in particular, typically increase the abscisic acid (ABA) content, leading to stomatal closure, which helps *C. albidus* tolerate this stress (Pérez-Llorca et al., 2021). However, in this study, sufficient water was available, and thus the stomata likely remained open, allowing for better temperature regulation through transpiration and more efficient photosynthesis. However, the plants still presented signs of stress, indicating other influencing factors. This study details the effects of the season on plant physiological parameters, especially the leaf characteristics of *C. albidus*. Spring facilitated maximal growth across all the treatment groups, with seasonal variations significantly influencing the leaf area, LI and SLA, independent of water availability and treatment. This result highlights the complex interplay between the effects of environmental factors and treatments on plant growth observed for other *Cistus* species (Catoni et al., 2012).

Compared with the control treatment, organic fertilization generally increased physiological parameters, although not significantly. The increased leaf area and fresh weight indicate that nutrient availability is crucial for growth, but the lack of significant differences suggests that genetic and environmental factors might also play significant roles, as has been shown for *Brassica* sp. (Karamat et al., 2021).

Inoculation, either alone or combined with fertilization, reduced the leaf size and weight, indicating a potential stress response and complex interactions between plants and inoculants. Initially, inoculation was expected to increase growth by improving nutrient uptake or protecting against pathogens but had an inhibitory effect, reducing leaf size and weight. This result suggests potential antagonistic interactions between inoculated agents and plants, resulting in a stress-like response. The generally reduced leaf size and weight in the inoculated groups could be due to the specific experimental conditions. The limited substrate volume and potential competition for nutrients such as nitrogen and phosphorus between AMF and plants might explain the observed stress responses, as well as the incompatibility of microbial strains with the host plant. However, Glomeromycota inoculation has been reported to successfully establish associations within the roots of *Cistus* species, especially between *C. albidus* and *G. iranicum*, and enhance plant growth and stress tolerance by improving nutrient uptake or inducing systemic resistance to pathogens within a relatively short time (Ortuño et al., 2018). However, this specific fungal species was not included in the mixture used in the present study, suggesting that the inoculation results may depend on the specific plant–fungi pairing. Additionally, maintaining the soil moisture content at the field capacity level may have influenced the outcome of plant–inoculant interactions, as studies have reported an improved inoculation response in arid climates under water stress conditions (Chandra et al., 2019; Rubin et al., 2017), although Glomeromycota are able to form symbioses under flooded conditions (Xu et al., 2021).

Flowering onset was uniform across treatment groups and triggered by environmental cues such as the photoperiod and temperature rather than specific treatments. This observation aligns with the literature, which confirms that plants may rely on specific environmental signals to initiate flowering (Amasino, 2010; Y. He et al., 2020). The low initial flowering yield likely resulted from plants allocating energy to root and vegetative growth rather than reproduction. A significant increase in flowering in the second year, particularly in the fertilized groups, demonstrated the successful environmental adaptation and positive effects of fertilization on reproductive production.

However, differences in total flowering yield among the treatment groups highlight the distinct impacts of fertilization and inoculation on reproductive output and suggest that inoculated plants might allocate more energy toward root growth because of improved nutrient uptake. However, this change should have led to more robust flowering, as healthier root systems and improved overall plant vigor contribute indirectly to better flowering performance. However, in the initial stages of mycorrhizal plant development, which was the stage of the experimental plants, growth is predominantly directed toward the roots and less toward reproductive development (Begum et al., 2019; Liu et al., 2024). This finding could indirectly confirm the formation of a symbiosis with the inoculum. On the other hand, fertilized plants presented consistent growth patterns, highlighting the influence of nutrient availability. The control plants presented more lateral branching, whereas the fertilized plants presented elongated shoots, reflecting a trade-off between vertical and horizontal growth strategies. This phenomenon is consistent with optimal partitioning theory, which assumes that plants optimize their growth patterns based on resource availability, allocating more resources to root or shoot growth depending on the limiting factor (Kobe et al., 2010). No significant differences in height were observed between treatments, which may indicate a complex interplay between genetic and environmental factors.

Survival rates and correlations among plant mortality rates and leaf node counts revealed critical thresholds for *C. albidus* survival under the experimental conditions. Mortality peaked between late winter and early spring and was more pronounced between late summer and autumn, which is consistent with seasonal changes in the ABA concentration. This finding is consistent with observations from López-Carbonell et al., where leaf samples from winter plants presented low ABA concentrations, which increased in spring and summer (López-Carbonell et al., 2009). The higher survival rates in the treated groups despite the stress responses highlight the benefits of fertilization and inoculation.

A theory suggests that aging is caused by oxidative stress from reactive oxygen and nitrogen species (ROS/RNS), which damage cellular components despite antioxidant defences (Harman, 1956). Studies indicate that plant-based antioxidants, especially polyphenols, counteract biotic or abiotic stresses by mitigating oxidative stress (Šamec et al., 2021; A. Sharma et al., 2019). However, a direct relationship between phenol concentrations and the survival rate of stressed plants was not established. The concentrations of phenolic compounds such as ellagic acid, 7-xiloside and galloylquinic acid, which are associated with stress responses, were positively correlated with plant mortality, indicating significant stress conditions. Ellagic acid is regarded as one of the primary antioxidant molecules due to its phytochemical characteristics (Khan et al., 2017). As the ellagic acid 7-xiloside exerts a protective effect on oxidative stress by increasing the levels of antioxidant components (Abu El-Soud et al., 2013; Khan et al., 2017), this compound may serve as a marker of stress. Additionally, galloylquinic derivatives are highly efficient free radical scavengers (Baratto et al., 2003). However, the derivatization of the hydroxyl groups of phenolic compounds significantly reduces the antioxidant activity of their derivatives, as was shown for quercetin glucoside (Lesjak et al., 2018). Nonetheless, high levels of these phenolics might indicate that plants were experiencing significant stress, potentially due to high temperatures, UV radiation or other factors, in addition to water stress. These conditions may accelerate the production of phenolic compounds as part of the plant's defensive strategy. While the production of these phenolics is a response to stress and may be related to plant health, excessive or prolonged stress leading to high phenolic concentrations might be correlated with reduced survival rates. These findings suggest that while these compounds are part of the plant's defence mechanisms, they may also indicate limits to how much stress the plant can endure before mortality rates increase.

Conversely, the concentrations of compounds such as dehydrated tergallic-C-glucoside and prodelphinidin B2 3’-O-gallate exhibited strong negative correlations with plant death, suggesting healthier plants or less overall stress. Heat stress can disrupt cellular homeostasis, but some plants acclimate by upregulating heat shock proteins and antioxidants (Hasanuzzaman et al., 2013). Among the compounds analysed in this study, delphinidin B2 3'-O-gallate is likely to have the strongest antioxidant capacity because its multiple hydroxyl groups can donate hydrogen atoms. The survival rates measured in the experiment reflect the ability of fertilized plants to tolerate elevated temperatures, resulting in lower mortality than that of inoculated plants, possibly due to enhanced stress tolerance mechanisms. We suggest that fertilization together with sufficient available water supported the production of various polyphenols. In particular, the fertilized plants contained significantly more flavan-3-ols, mainly prodelphinidin B2 3'O-gallate, than did the plants in the other groups. This result could mean that increasing the biosynthesis of such compounds through breeding or agronomic practices might improve plant resilience.

4.4.2. Phenolics and antioxidant capacity

The antioxidant capacity of *C. albidus* extracts, as assessed through the $ABTS^{\bullet +}$ radical scavenging assay, exhibited a clear pattern of seasonal adaptation driven by the plant's need to cope with environmental stress (Jubany-Mari et al., 2008). Agricultural treatments such as inoculation and fertilization also influenced the antioxidant capacity, with the combination of both resulting in the highest mean antioxidant capacity. Seasonal variations affected antioxidant capacity, with inoculated groups showing the highest values toward the end of the year, particularly in autumn.

In the absence of temperature decreases or water stress in the experiment, the increased antioxidant capacity in the inoculated groups compared with that in the control groups suggested that AMF inoculation significantly increased antioxidant levels in autumn. Other plant species have also shown increased secondary metabolite production, including that of antioxidants, when subjected to combined microbial and nutrient treatments, which is attributed to improved plant health and nutrient status (Parada et al., 2019).

In addition to reactive ROS, secondary metabolites in plants play a role in signal transduction under stress conditions as a natural defensive mechanism (Bekheet, 2011). The lower antioxidant capacity in the control group of plants in our experiment compared to wild-growing *C. albidus* plants reported by Lukas et al. (Lukas, Bragagna, et al., 2021) could be due to the sufficient water supply that prevented stress-induced antioxidant defence mechanisms. Our results suggest that water stress may play a subordinate role in modulating the antioxidant capacity of *C. albidus*. This finding may be confirmed indirectly by the observations of Moreira et al., who reported that reduced rainfall had no effect on the phenolic content (Moreira et al., 2020).

However, other compounds may influence the antioxidant capacity of *C. albidus* extracts. Jubany-Mari et al. demonstrated that H_2O_2 and ascorbic acid played leading roles in the measured antioxidant capacity of *C. albidus* (Jubany-Mari et al., 2008). This finding may be confirmed by the absence of significant differences in the TPC between spring and autumn, despite the significant variations in the antioxidant capacity. Generally, the antioxidant capacity depends on the phenolic content, either through enzymatic pathways or by directly scavenging radicals, mitigating the detrimental effects of ROS generated in cells due to abiotic stresses (Sakihama et al., 2002). However, in *C. albidus*, the antioxidant capacity may be influenced by multifactorial interactions within plant tissues and extraction conditions. Interactions among different phenolic compounds or with other constituents in the plant matrix can enhance or inhibit the overall antioxidant effect (Freeman et al., 2010; Giordano & Lionetto, 2023). Furthermore, variations in environmental conditions such as sunlight, temperature, and soil nutrition during the growth of plants can affect the biosynthesis of compounds involved in the antioxidant capacity. This result could also explain why a significant positive correlation was observed between the total phenolic content and the antioxidant capacity only in the fertilized group. These results highlight the diverse effects of individual phenolic compounds on the antioxidant capacity, as the properties of the chemical functional groups of a given phenolic compound may change depending on its concentration.

The significant differences in the total phenol content at different harvest times underscore the influences of environmental and developmental factors on phenolic biosynthesis. These compounds play crucial roles in plant defence mechanisms and stress responses, which can vary seasonally or with the developmental stage. This result aligns with studies reporting the effects of agricultural practices and environmental conditions on secondary metabolite production in plants (Ahanger et al., 2014; Hashem et al., 2018). These seasonal changes affect both the vegetation and reproductive organs of plants, indicating an adaptation to the climatic rhythms of the respective environment (Marchioretto et al., 2007; Semenyutina et al., 2022). Studies of *Paeonia lactiflora* Pall. have shown that phenolic levels increase during the growing season and reach their maxima during the seed formation phase before decreasing again toward the end of the growing season (Oyungerel et al., 2017).

The correlation analysis revealed that the positive correlation between antioxidant capacity and total phenol content was significant only for FERT, suggesting that fertilization increases phenolic synthesis or accumulation (Azaizeh et al., 2005; Onofrei et al., 2017). This finding further suggests the presence of nonphenolic antioxidants such as ABA, tocopherols, and carotenes in the extract (Casadesús et al., 2021; Maruta et al., 2016; Wongsa et al., 2012). The lack of correlation in the combined treatment group might indicate that an antagonistic effect altered the balance or availability of effective antioxidant compounds. However, changes in the TPC are not always followed by variations in the antioxidant capacity, indicating a complex relationship between the TPC and antioxidant activity. This apparently complex relationship between fertilization, the TPC, and antioxidant activity was also observed in rapeseed (Amarowicz et al., 2024).

4.4.3. Phytochemicals

The treatments did not affect all the polyphenols uniformly. Flavan-3-ols and flavonols responded selectively to microbial inoculation, increasing their biosynthesis in response to stress, whereas phenolic acids and ellagitannins showed minimal changes, indicating that their biosynthetic pathways were not influenced by this treatment (Mueller-Harvey, 2001). Published findings concerning the effects of fertilization on polyphenol production are inconclusive (Sałata et al., 2022), and several studies suggest that polyphenol concentrations are influenced primarily by genetic and environmental factors rather than by agronomic treatments. Plants often possess redundant pathways for synthesizing certain compounds, which can buffer them against changes induced by treatments, thereby stabilizing the concentrations of these compounds across different conditions. This redundancy, as discussed by Dixon and Paiva (Dixon & Paiva, 1995), may also be linked to the inherent genetic composition of *C. albidus*, which plays a crucial role in determining compound biosynthesis (McClure et al., 2019). Genetic factors can overpower the effects of external treatments, resulting in uniform compound levels across different treatment groups. Some plants have genetically determined set points for specific metabolites that are not easily altered by external factors unless a modification in gene expression occurs (Treutter, 2010). This finding aligns with previous research indicating that pathways, particularly those involved in flavonoid biosynthesis, are tightly regulated and respond more to genetic and environmental factors than to direct agricultural inputs (Fini et al., 2012; Holopainen & Gershenzon, 2010).

Furthermore, plants maintain a certain level of homeostasis for critical compounds, e.g., flavonols, which are involved in UV protection and antioxidant functions (Nichols & Katiyar, 2010). Treatments that do not drastically alter the stress level or the physiological balance of the plant may not significantly change the flavonol levels. This result is supported by findings from Close and McArthur (Close & McArthur, 2002), indicating that homeostatic mechanisms can maintain consistent levels of certain metabolites despite various treatments.

The responses of compounds grouped according to their phytochemical class to various treatments varied. Flavan-3-ols and flavonols responded selectively to microbial inoculation, whereas phenolic acids and ellagitannins showed minimal changes. The season and treatment interactions produced specific patterns, with the combined FERT+INOC treatment resulting in the highest concentrations of flavonols and flavan-3-ols in certain seasons. The concentrations of ellagitannins exhibited marked changes across different harvest times, reflecting environmental influences on their biosynthesis.

Individual compounds also presented differential responses to the treatments. The concentrations of flavonols, which are involved in UV protection and antioxidant functions, were significantly affected by the harvest time, with compounds such as quercetin glucoside being influenced by inoculation. Seasonal variations, especially in summer, in peak flavonol concentrations align with their UV protection function (Nichols & Katiyar, 2010; Treutter, 2005). The concentrations of quercetin glucoside and myricetin derivatives fluctuated significantly with the treatment and harvest period, reflecting complex metabolic interactions and environmental adaptations. For example, the content of myricetin hexoside decreased over time, whereas that of quercetin glucoside increased under combined fertilization and inoculation, corroborating the hypothesis that nutritional and biological treatments can synergistically enhance specific flavonol synthesis pathways (Omidiji & Ehimidu, 1990; Qi et al., 2023). On the other hand, the decrease in the concentration of myricetin hexoside deviates from studies suggesting the accumulation of myricetin derivatives as defensive compounds in plants under stress (Cheynier et al., 2013). This discrepancy may be attributed to plant age or specific environmental conditions during the experiments, which could have influenced the expected stress response.

The phenolic acid contents significantly fluctuated across harvest times, indicating dynamic responses to environmental conditions and developmental stages. Inoculation notably affected caffeoyl hexose concentrations, suggesting that biotic stress-induced biosynthesis is part of the plant's defence mechanism (Cheynier et al., 2013). However, the concentrations of other phenolic acids remained largely unaffected, indicating selective adaptation.

The concentrations of ellagitannins such as dehydrated tergallic-C-glucoside, pedunculagin, terflavin B, punicalagin, and ellagic acid-7-xiloside changed significantly across harvest times, reflecting strong temporal influences on the biosynthesis of these compounds (Buer et al., 2010). Terflavin B and punicalagin concentrations decreased over time, whereas ellagic acid-7-xiloside accumulated, suggesting that differential biosynthetic and degradation rates are influenced by plant development or environmental pressures. The correlations between the concentrations of different ellagitannins suggest complex biosynthetic and regulatory pathways.

The concentrations of flavan-3-ols were also associated with treatment and seasonal influences. Prodelphinidin B2-3'-O-gallate concentrations decreased over time, suggesting a shift from the growth stage to the reproductive stage. Fertilization increased its concentration, whereas inoculation influenced the concentration of (-)-(epi)gallocatechin-(epi)gallocatechin, highlighting nuanced stress response mechanisms as signalling molecules in plant defence pathways (War et al., 2012).

Secoiridoid glycosides, which are recognized for their antioxidant and potential health-promoting properties (Xue & Yang, 2016), serve as markers of plant responses to environmental stressors and developmental cues (Fons et al., 1999). The concentrations of the ligstroside derivative, the only analysed secoiridoid glycoside, was affected by the harvest time, suggesting dynamic regulation. The treatments did not significantly alter the concentrations of this molecule, indicating that its stable biosynthesis pathways are less influenced by external factors.

4.4.4. Primary and secondary metabolism

The carbon/nitrogen balance (CNB) hypothesis suggests that under nitrogen limitation, plants may increase the synthesis of carbon-based secondary metabolites due to excess fixed carbon (Bryant et al., 1983). This theory might explain why the highest polyphenolic compound concentrations were detected in the control and inoculated groups, where nitrogen was a limiting factor. Increased CO_2 levels can enhance the mycorrhizal colonization of plant roots, improving nutrient absorption (Asha et al., 2017; Zhu et al., 2016), although this process does not always correspond to improved nutrient transfer to the host plants (Smith & Read, 2008).

The protein competition model (PCM) posits that the availability of phenylalanine, which is essential for both protein and phenolic synthesis, dictates the allocation between these metabolic pathways and is influenced by growth demands and environmental cues (Jones &

Hartley, 1999). This theory supports the idea that secondary metabolite production results from the interplay between environmental and genetic factors (Fini et al., 2012). Since secondary metabolism is linked to primary metabolism, diverting substrates from primary to secondary biosynthetic pathways significantly influences it (Kołton et al., 2022). Consequently, in the resource-limited groups (CONT and INOC), carbon partitioning to secondary metabolism increased, increasing compound concentrations compared with those of FERT and FERT+INOC. This finding supports previous research indicating that while fertilization can impact overall plant growth and primary metabolism, its effects on secondary metabolite pathways, particularly those involved in stress responses, are less predictable (Treutter, 2005).

4.4.5. Mycorrhization or stress response

The evidence suggests that inoculation can potentially lead to a mycorrhizal response in *C. albidus*. Mycorrhizal associations, particularly with fungi from the Glomeromycota phylum, have been reported to establish symbiotic relationships within the roots of *C.* species, including *C. albidus*, increasing nutrient uptake and improving stress tolerance (Lorente, Zugasti, Sánchez-Blanco, et al., 2021; Ortuño et al., 2018).

The experimental findings of this study indicate that inoculated plants often exhibit increased concentrations of phenolic compounds and greater antioxidant capacity, which can indicate enhanced defence mechanisms typically associated with mycorrhizal symbiosis. These compounds play crucial roles in plant defences against various stressors, including biotic and abiotic factors, suggesting a possible increase in the plants' innate stress response systems due to mycorrhizal associations (Qaderi et al., 2023).

The results indicate that inoculation triggers a stress-like response in plants, as evidenced by several key observations. Inoculated plants presented significantly smaller leaf areas and weights, along with greater variability in leaf area, suggesting differing individual responses to inoculants. Additionally, these plants presented relatively high SLA values, suggesting an adaptive mechanism to maximize photosynthesis under stress conditions. Inoculation also led to less uniform growth, reduced node counts, and lower flower production in the second year, which are all typical signs of stress.

Furthermore, the inoculated plants presented relatively high concentrations and high variability of phytochemicals. This result could indicate that the plants responded to inoculation via a stress response. Plants often produce increased levels of secondary metabolites such as flavonoids and phenols as a defence mechanism against biotic and abiotic stress (Ahlawat et al., 2023; Tariq & Ahmed, 2024). The observation that the concentrations of certain phytochemicals, such as (-)-(epi)gallocatechin-(epi)gallocatechin and terflavin B, were significantly affected by inoculation throughout the vegetative cycle suggests that inoculation acts as a consistent stressor. This continuous response could be a sign of an ongoing stress response.

The statistical analysis revealed significant differences in the antioxidant capacity and TPC between the treatment groups, with inoculation having the greatest impact. Significant differences in these parameters were most pronounced in spring and autumn, indicating a stronger stress response during periods of increased plant activity under non-stressful environmental conditions.

Finally, the significant correlations between the concentrations of certain polyphenols and plant survival rates further support the occurrence of a stress response. These findings collectively suggest that AMF inoculation induced a stress response in this study, leading to various physiological and biochemical changes aimed at mitigating stress.

However, the presence of multiple AMF species in our study may have created complex interactions where the overall benefit to the plant is influenced by factors such as nutrient availability, soil conditions, and plant species, as observed by Liu et al. (Chen et al., 2017; Liu et al., 2021). Although the combination of *Glomus a*nd *Rhizophagus* species might have provided mycorrhizal benefits due to functional complementarity between distantly related AMF, as reported by Crossay et al. (Crossay et al., 2019), these benefits were accompanied by stress responses under the experimental conditions, highlighting the complexity of AMF–plant interactions. These findings suggest that *C. albidus* may be a species that does not establish a functional mycorrhizal symbiosis, as approximately 29% of vascular plant species are not hosts for AM fungi (Van Der Heijden et al., 2015). In plants that cannot form a full AM symbiosis, rudimentary AM structures can arise under certain circumstances. However, these structures are often formed only to a lesser extent and are not always functional (Cosme et al., 2018). In some cases, the presence of AM fungi can even inhibit the growth of nonsymbiotic plants, as the fungi extract resources from the host without providing a corresponding benefit (Lekberg et al., 2015; Ocampo, 1986; Veiga et al., 2013). These findings support the hypothesis that inoculation may have acted as a significant stressor on *C. albidus* as a host, stimulating plants to increase their defences. Therefore, we suggest that *C. albidus* cannot form AMF symbiosis with *Glomus* and *Rhizophagus* spp.

4.5. CONCLUSIONS

In this study, a comprehensive analysis of the effects of fertilization and inoculation on the growth and biochemical properties of *C. albidus* throughout the seasons of one vegetative cycle was conducted. This study highlights how fertilization positively affected growth parameters such as leaf size and biomass, whereas inoculation tended to suppress these parameters, especially under nutrient-deficient conditions.

Key findings indicate that while organic fertilization generally promoted growth, AMF inoculation with fungi from the *Rhizophagus* and *Glomus* genera induced a stress response, reducing leaf size and weight, increasing growth, and increasing the production of defense-related phytochemicals. Nevertheless, inoculation, especially when combined with fertilization, significantly increased the phenolic content and antioxidant capacity, particularly in autumn. Despite potential symbiotic benefits, the complex interaction of AMF species and environmental factors suggests that *C. albidus* may not establish beneficial mycorrhizal symbioses, possibly exacerbating stress responses under the experimental conditions.

The synthesis and accumulation of specific polyphenols in *C. albidus* are intricately linked to environmental conditions, seasonal changes, and developmental stages. The harvest timing is crucial to maximize the yield of specific beneficial compounds, with earlier harvests capturing peak concentrations of flavan-3-ols and flavonols and later harvests resulting in increased ellagitannin concentrations. While treatments such as inoculation and fertilization influence specific compounds, genetic and environmental factors primarily drive polyphenol biosynthesis. These observations suggest that the biosynthetic pathways for phenolic acids and ellagitannins are more stable (less influenced) than those for flavonols and flavan-3-ols. Redundant pathways in plants may buffer against treatment-induced changes, stabilizing the concentrations of these compounds. This finding underscores the importance of strategic harvest timing and understanding the complex interplay between plant metabolism and external factors. Thus, the adaptive mechanisms and natural resilience of *C. albidus* likely play a key role in the limited effects of treatments such as fertilization and inoculation on the phytochemical profile compared with the harvest time.

This study contributes to a broader understanding of how cultivation techniques can be optimized to increase the production of valuable secondary metabolites in medicinal plants without significantly compromising plant biomass. This information is especially relevant for large-scale agricultural practices, where the implementation of inoculation techniques can reduce reliance on synthetic chemical fertilizers, promote better ecological management of natural resources and contribute to soil biodiversity conservation. Furthermore, the strategic use of these practices could increase crop resilience to environmental stressors, which is a critical factor in the context of climate change. In addition, the insights gained from this research have implications for the pharmaceutical, cosmetic and nutraceutical sectors, which can become the final beneficiaries of optimized and more sustainable cultivation methods to produce high-quality natural compound-based ingredients with enhanced biological activities.

Future research should explore the interactions between different types of AMF and their specific effects on the phytochemical profiles of *C. albidus*. Additionally, expanding this study to include other *C.* species could provide a broader understanding of the response of this genus to AMF inoculation and organic fertilization. Investigating the long-term effects of these treatments under varying environmental conditions would also be valuable in determining the sustainability and practical application of these findings in diverse agricultural settings. Understanding these mechanisms could lead to more precise strategies that optimize both the yield and quality of the natural compounds derived from *Cistus* species.

Chapter 5

General Discussion and Conclusions

Key Findings, Recommendations for Future Research and Practical Applications for the Cultivation of *Cistus albidus* L.

5. GENERAL DISCUSSION

5.1. DOMESTICATION AS A STRATEGY FOR SUSTAINABLE PRODUCTION

The domestication of *C. albidus* as a medicinal plant offers a strategic way to harness its large phytochemical profile while alleviating pressure on wild populations. Cultivating this traditionally wild Mediterranean shrub under controlled conditions can ensure a reliable, standardized supply of bioactive compounds (notably polyphenols and terpenoids) for pharmacological use. Importantly, *C. albidus* naturally thrives on marginal, nutrient-poor soils with minimal water availability; this resilience means domestication can be achieved with lower inputs while still maintaining high phytochemical yields. By bringing *C. albidus* into cultivation, not only pharmaceutical demands for consistent medicinal raw material are met but it is also contributed to biodiversity conservation, as wild stands may face threats from overharvesting.

This dissertation extends prior research by experimentally demonstrating that *C. albidus* can be domesticated in a manner that reconciles vegetative yield with the maintenance of valuable secondary metabolites. In particular, the results reveal how strategic combinations of fertilization, AMF inoculation, and seasonal harvest timing can be fine-tuned to enhance both plant biomass and compound content. The overarching goal is to balance pharmacological value with vegetative productivity—to maximize the concentration of therapeutic compounds per unit biomass without significantly compromising plant growth and yield. These findings collectively show that through optimized cultivation practices, which mirror the plant's natural adaptive strategies while incorporating modern agronomy, we can fulfil the dual aims of sustainability and medicinal efficacy.

5.2. INTEGRATION OF THE RESULTS

The integration of the different results, resumed in Table 5-1. obtained in the various experiments on *C. albidus* provides a comprehensive understanding of the interrelationships between phenotypic development, germination strategies, floral production, phytochemical content, and environmental conditions. This synthesis is crucial for contextualizing the domestication and cultivation of this wild species as a medicinal plant, offering insights for optimizing both agronomic management and bioactive compound production.

5.3. AGRONOMIC STRATEGIES FOR THE DOMESTICATION

A key outcome of the research is that *C. albidus* exhibits broad **ecological adaptability**, not requiring specific soil or climate conditions for successful growth. Plants cultivated under different soil qualities showed robust establishment, underscoring that genetic factors may play a dominant role in phytochemical production over edaphic factors (Durán et al., 2024; Grant et al., 2006; Munné-Bosch et al., 2003). In practice, however, the vegetative performance and secondary metabolite profiles of *C. albidus* were significantly influenced by cultivation treatments and seasonal timing.

Table 5-1 Summary of the most important results related to the cultivation of *C. albidus* as a medicinal plant with reference to vegetative and pharmacological parameters.

Category	Subcategory	Result	Optimal Season and/or Treatment
Vegetative Traits	Leaf Area	8.55 ± 0.23 cm²	Spring / FERT
	Leaf Perimeter	11.35 ± 0.13 cm	Spring / FERT
	Fresh Weight per Leaf	153.72 ± 3.60 mg	Spring / FERT
	Dry Weight per Leaf	109.14 ± 2.56 mg	Autum / FERT, CONT
	Specific Leaf Area (SLA)	10.70 ± 1.87 m²/kg	Spring / INOC
Floral Traits	Flower Production Year 1	2.84 ± 0.41 inflorescences/plant	CONT, FERT
	Flower Production Year 2	16.53 ± 1.96 inflorescences/plant	CONT
	Flowering Onset Year 2	Earlier onset by 3 weeks	FERT
Germination	Germination under Wildfire Simulation	72.6 ± 4.61% germination rate	Wildfire simulation
	Germination under Dry Heat	80.7 ± 4.03% germination rate	Dry heat treatment
	Germination (Old Seeds)	4.3% (12 h hydration) 16.4% (24 h hydration)	Old seeds respond to longer hydration
	Scarification by Water Flow	78.4% germination rate	Water flow scarification simulation
Phytochemical Compounds	Ellagitannins	Ellagic acid-7-xyloside peak	Autumn, Late Winter
	Flavonols	Quercetin glucoside peak	Late Winter
	Phenolic Acids	Galloylquinic acid peak	Autumn
	Secoiridoid Glycosides	Ligstroside derivative peak	Late Winter
Pharmacological Activity	Antioxidant Activity	Peak in antioxidant capacity	Autumn, Late Winter / INOC, FERT+INOC
	Anti-inflammatory Potential	Peak in key phytochemicals	Autumn, Late Winter

Organic fertilization emerged as a beneficial agronomic factor, significantly improving plant survival, biomass accumulation, and uniformity of growth. Fertilized plants grew taller with greater dry weight and even flowered earlier than unfertilized controls, while also displaying more uniform plant height and flowering output across the species. Such uniformity and vigour are desirable traits in domestication, as they translate to predictably high yields of raw material in cultivation. Moreover, fertilization did not reduce the production of bioactive compounds; rather, it provided a strong vegetative platform on which secondary metabolism could still operate, especially when combined with other practices.

With regard to the individual compounds, fertilization alone generally had a positive effect on the number of detected substances. In fact, all researched compounds were measured in this group—except during the summer, when terflavin B, punicalagin, and quercetin glucoside were absent. Notably, terflavin B and punicalagin were also missing in the other groups, with the exception of the inoculated group, where terflavin B was detected. Therefore, the only compound whose absence in summer appeared to be specifically associated with fertilization was quercetin glucoside, suggesting an overall positive effect of fertilization on the compound profile. This aligns with observations made for other Mediterranean medicinal plants, such as *Ocimum basilicum* and *Cynara scolymus* under fertilization (Nguyen & Niemeyer, 2008; Sałata et al., 2022).

A particularly intriguing aspect of this study is the observed response to AMF inoculation. Contrary to expectations, the tested AMF strains did not enhance biomass but significantly upregulated several secondary metabolites. This suggests that in *C. albidus*, certain symbiotic interactions function less as nutrient sources and more as elicitor signals. Several studies with other plant species confirm that AMF, particularly *Rhizophagus* and *Glomus* spp., may not enhance biomass but modulate secondary metabolite synthesis (Iakab et al., 2022; Kaur & Suseela, 2020; Ran et al., 2022; Wu et al., 2021; Zhao et al., 2022). The exclusive increase in antioxidant capacity during autumn observed in inoculated *C. albidus* suggests that mycorrhizal symbiosis triggers specific physiological or hormonal responses not activated in fertilized or untreated plants. As observed for this species, these responses may involve jasmonate-mediated pathways that promote vitamin E biosynthesis, enhancing the plant's preparedness for winter stress (Casadesús et al., 2021). In contrast, nutrient-rich conditions from fertilization may suppress such defence-related metabolic pathways in favour of growth. Additionally, biotic stress caused by the inoculum may have activated plant defence pathways, channelling resources toward protective compounds at the expense of growth (Tariq & Ahmed, 2024; Tuladhar et al., 2021; Zagoskina et al., 2023).

The observed **trade-off between** growth and secondary metabolite production aligns with established ecological paradigms: plants have finite resources and often allocate them either to growth/reproduction or to defence compounds, depending on environmental pressures. Similar patterns have been observed in other medicinal plants, where stress conditions such as nutrient limitation, drought, or pathogen challenges result in higher concentrations of phenolics, alkaloids, or terpenes while reducing vegetative growth (Bot et al., 2009; Chen et al., 2024; Fernandez et al., 2016; Garrido et al., 2022; Ramakrishna & Ravishankar, 2011).

Interestingly, under favourable conditions (adequate fertilization and absence of microbial challenge), plants generally exhibited lower TPC, except for leaves harvested in late winter. In contrast, inoculated plants displayed a less complex phenolic profile than both control and fertilized groups. Thus, the hypothesis of this dissertation that controlled cultivation enhances phytochemical profiles, particularly through AMF inoculation, is only partially supported. While fertilization significantly improved vegetative parameters and influenced phytochemical composition, AMF inoculation produced mixed results: it increased TPC and antioxidant capacity but significantly reduced vegetative growth. Therefore, AMF inoculation did not yield the anticipated biomass benefits.

Beyond controlled interventions, the seasonal increase in phenolics mirrors patterns in other Mediterranean shrubs, where harsher seasons correlate with higher polyphenol levels (Gori et al., 2020; Morais et al., 2022). Environmental pressures such as episodic droughts, intense solar radiation, nutrient-poor soils, and periodic wildfires tend to favour genotypes that can survive and even thrive under chronic stress. In such habitats, natural selection often promotes the development of robust secondary metabolite pathways, including antioxidants, UV-protective flavonols, and antifungal tannins. Many of these compounds derive from the **phenylpropanoid pathway**, which plays a central role in plant defence against **abiotic stress** (Ahmad et al., 2019; Francini et al., 2019; Reine et al., 2021). Nonetheless, it remains possible that these biochemical responses represent a strategy of stress avoidance rather than genuine physiological tolerance, as described for Sinapis arvensis (Stanton et al., 2000).

However, **seasonal environmental factors** emerged as the most **critical determinant** of both biomass and phytochemical yield in *C. albidus*. The plant's phenological cycle with naturally occurring periods of growth and stress that can be leveraged in cultivation. During spring and early summer, when temperatures are warm and photoperiod is longer, *C. albidus* allocates most of its resources to vegetative growth: leaves expanded to larger surface areas and accumulated biomass, and flowering was prolific. By contrast, in autumn and winter, as conditions became cooler and harsher (with lower light intensity and shorter days), the plants showed a marked increase in secondary metabolite accumulation. Leaves harvested in late winter contained the highest concentrations of key bioactive compounds, such as ellagic acid derivatives and quercetin glycosides, whereas leaves collected in the peak growing season had greater biomass and were better suited for processes like essential oil distillation due to higher yields (Chandel et al., 2024; Malaka et al., 2022).

From an agronomic perspective, these insights can be directly applied by adjusting harvest times based on **three key variables**: mean leaf biomass, TEAC, and TPC. Significant seasonal differences in harvest timing, independent of treatment, were observed only for leaf dry weight in summer and for TPC across all seasons except between spring and autumn and summer and winter. Although no significant differences were found for TEAC, these findings indicate, in general, that harvest timing significantly influence both yield and phytochemical composition.

Given the pronounced peak in TPC and the relatively stable TEAC values throughout the vegetative cycle, **late winter** appears to be the **optimal harvest period**. This conclusion is reinforced by the high mean leaf dry weight during this season.

When considering treatments, fertilization during this season maximized TPC and ranked second for TEAC (with no significant difference from the highest values recorded in summer). Although no statistically significant difference in these parameters were observed between fertilized and the inoculated groups, fertilization led to significantly higher TPC compared to the control, which exhibited the lowest TPC values.

Thus, it can be concluded that for agronomic-pharmacological purposes, the most effective treatment strategy is fertilization combined with harvesting between late winter and early spring, if high TPC and antioxidant capacity values are targeted while simultaneously achieving the greatest possible yield of leaf biomass.

However, the **highest antioxidant capacity** is achieved in **autumn** by both inoculated groups being this an additional viable harvest-time, as for Mediterranean species several possible harvest-times were reported (Gori et al., 2020). In contrast, the control and fertilized groups exhibited significantly lower antioxidant capacity during this season and compared to the other seasons. Although the total phenolic content in the inoculated groups does not differ significantly from spring levels, their antioxidant capacity is markedly higher, particularly in the inoculated only group (INOC). However, since vegetative growth is at its lowest in autumn for INOC and only slightly higher for FERT+INOC, a clear stress response can be inferred, raising concerns about yield and, consequently, the economic viability of harvesting during this period.

The extensive phytochemical profile of *C. albidus* reflects its ability to adapt to diverse environmental conditions, balancing metabolic investment between growth and defence in response to fluctuating stressors. This trait is particularly characteristic of **riparian plants** that rely on **hydrochorous dispersal**, as they must withstand alternating floods and droughts to survive (Isah, 2019). Such environmental variability exerts strong selective pressure for biochemical versatility, promoting the production of a broad spectrum of secondary metabolites that enhance resilience under extreme conditions.

This aligns with the findings of this study, which demonstrate that *C. albidus* modulates both its growth rates and bioactive compound production in response to varying environmental stimuli being an indication of its degree of adaptability. Especially the extensive phytochemical profile observed for this species suggests a high degree of **ecophysiological plasticity** (Grant & Incoll, 2005), as described for other species (Diethelm et al., 2022; Fernández-Marín et al., 2017).

Moreover, the germination experiments of this dissertation indicate that while *C. albidus* responds to fire cues reflecting known fire-following strategies within the Cistaceae (Trabaud & Oustric, 1989), its seeds exhibit an even stronger response to water-mediated scarification, suggesting a primary reliance on hydrochorous dispersal rather than strict pyrophytic recruitment challenging previous assumptions about fire being the dominant driver of its reproductive strategy. These traits, associated with riparian specialization, inherently may confer characteristics that facilitate fire resilience since the tegument of several riparian plants is more strongly developed (Catford & Jansson, 2014) which may help to resist even wildfires. This flexible survival strategy has likely facilitated its persistence and expansion across fire-prone landscapes, allowing it to colonize disturbed habitats while maintaining its phytochemical adaptability as a key resilience factor.

The ability of hydrochorous plants to cope with extreme hydrological fluctuations by developing broad phytochemical defences further explains the extensive metabolite diversity observed in *C. albidus*. Similar adaptations are well-documented in riparian species such as *Salix* spp. and *Sambucus nigra* (Sánchez-Hernández et al., 2023; Tawfeek et al., 2021), which also exhibit significant bioactivity that enhances their resilience in adverse climates.

The hydrochorous dispersal origin of this species may also be reflected in the etymological origins of its common name. For instance, the Spanish term “Jaguarzo”, referring to *Cistus* species, may originate from a pre-Romanic language such as Iberian or Basque. A possible derivation suggests a combination of the Basque terms “Igar” or “Igaro” (run, pass through [in the context of water flow]) and “Zuhaitz” or “Zuhaixka” (shrub, tree), implying that the plant may have historically been related to water runoff. This linguistic evidence aligns with the physiological observations presented in this study, reinforcing the idea that *C. albidus* was originally adapted to riparian environments.

Thus, these findings confirm the that *C. albidus* –originally adapted to hydrochorous dispersal and the stressors of riparian environments– exhibits pyrophytic traits due to the riparian requirements. While this evolutionary flexibility has enabled its success in dynamic landscapes, it also raises questions about the potential constraints imposed by genetic diversity on its long-term adaptability. If *C. albidus* exhibits reduced genetic variability due to its previous adaptation strategy, this could impair its ability to cope with new challenges (e.g. climate change).

This aspect becomes particularly relevant when considering that *C. albidus* studied by Lukas et al. exhibited significantly lower genetic diversity compared to *C. creticus*, suggesting a reduced ecophysiological plasticity and a potentially higher susceptibility to biotic and abiotic stress (Lukas, Jovanovic, et al., 2021). This observed genetic homogeneity may have arisen through natural selection in stable habitats, but it could also be linked to **historical human use** or selective cultivation, possibly driven by its medicinal and aromatic properties, since *C. albidus* is generally described as genetically very heterogeneous (Grant et al., 2006; Grant & Incoll, 2005). Historical accounts documenting the psychoactive properties of this species (Raus de Baviera et al., unpublished; Mulet Pascual, 1991) and its traditional use through smoking and oral ingestion (Ledesma, 2004; Maccioni et al., 2007; Raus de Baviera et al., 2023; Segarra i Durà, 2008) support its past cultivation. Cultivation efforts have historically aimed to enhance these properties, reflecting their perceived significance in traditional practices (Gootenberg, 2022; Merlin, 2003). Furthermore, isolated stands of *C. albidus* were identified in the Parque Regional Valle y Carrascoy (Murcia, Spain), exhibiting an extended flowering period from mid-December to mid-July. Given that wild populations of *C. albidus* typically flower between February and June (Müller et al., 2014), this deviation may serve as additional evidence of historical cultivation and selective breeding of this species. Such an **extended flowering period** is characteristic of cultivated plants, which often display prolonged phenophases compared to their wild counterparts (Gaudinier & Blackman, 2020).

A potential consequence of a limited genetic basis may lead to restrict the species' ability to respond to climatic shifts or emerging pathogens, thereby posing a risk to its long-term survival as observed in *C. heterophyllus* (Cardona & Capó, 2023). To mitigate these risks, conservation strategies aimed at enhancing genetic diversity—such as controlled crossings with genetically diverse populations—are essential.

The genetic and ecological factors shaping these responses also have implications for domestication efforts. Different wild populations may exhibit variations in compound profiles or stress tolerance—key factors for selecting resilient cultivation lines. Maintaining genetic variability in cultivation, such as by sourcing seeds from multiple regions or integrating agroforestry systems, helps prevent genetic bottlenecks (Ivetić et al., 2016; Lengkeek et al., 2005). Furthermore, screening wild populations for chemotypic diversity could uncover lines with superior stress resilience or enhanced compound yields (Jm et al., 2022; Wilkinson et al., 2024). These strategies could not only support the conservation of *C. albidus* but also optimize its potential for sustainable use in pharmacological and ecological applications.

5.4. THERAPEUTICAL RELEVANCE

Several bioactive compounds, including derivatives of myricetin, ligstroside, ellagic acid, quercetin, as well as galloylquinic acid, accumulate progressively in *C. albidus* throughout the year, exhibiting a clear relationship with enhanced plant survival under biotic and abiotic stress. Several of these metabolites have been associated with the pharmacological effects of *C. albidus*, including neuroprotective, neurosedative, analgesic, and anti-inflammatory properties (Raus de Baviera et al., 2023).

The ecological adaptation of *C. albidus* as a hydrochorous riparian plant subjected to extreme environmental challenges likely promoted the evolution of its diverse phytochemical composition. This biochemical diversity allows the plant to maintain internal **homeostasis** despite severe stresses, such as drought, UV radiation, pathogens, and flooding disturbances as observed for other riparian species (Sánchez-Hernández et al., 2023; Tawfeek et al., 2021). This suggests that the plant's stress-induced metabolic shifts may play a direct role in shaping its therapeutic potential, as medicinal plants exhibiting a broad spectrum of therapeutic applications, such as *C. albidus*, inherently rely on a rich and diverse phytochemical composition consisting of numerous secondary metabolites as known for *Cannabis sativa* (Pattnaik et al., 2022).

The therapeutic efficacy of *C. albidus*, as well as its inherent capacity to maintain biochemical homeostasis under challenging environmental conditions, may be additionally attributed to synergistic interactions among the diverse array of bioactive compounds present within the plant matrix (Riaz et al., 2023; Vieira et al., 2025; Zhou et al., 2016). Instead of individual constituents acting in isolation, these phytochemicals jointly modulate multiple interconnected biological pathways simultaneously. Such multi-targeted modulation allows for more comprehensive therapeutic effects and reduces the likelihood of side effects and toxicity, as lower concentrations of each active compound are required for efficacy (Chaachouay et al., 2022; Donkor et al., 2023). Notably, this synergistic behaviour is supported by the **functional plasticity of polyphenols**, which enables context-dependent modulation of signalling pathways involved in inflammation, oxidative stress, and cell proliferation. This adaptive biochemical versatility has been highlighted as a key advantage of complex natural extracts over single-compound therapies in the treatment of multifactorial diseases such as cancer and neurodegenerative disorders (Herranz-López et al., 2018).

Plants characterized by an expansive phytochemical repertoire, exemplified by *C. albidus*, inherently should possess greater therapeutic versatility and broader clinical applicability compared to plants with more limited compound spectra, as they may modulate simultaneously multiple biological pathways, such as oxidative stress management, inflammatory signalling, neurotransmitter dynamics, and metabolic regulation (Dehghanian et al., 2024; Liu et al., 2024; Paul et al., 2024). This perspective highlights the importance of whole-plant preparations and suggests that therapeutic applications based on phytochemical synergy could provide more effective and balanced modulation of biological networks compared to single-compound interventions (Fisher et al., 2022; W. Xia et al., 2024; Tomás-Menor et al., 2015).

The evolutionary conservation of biochemical pathways between plants and humans suggests that phytochemicals evolved to enhance stress resilience in *C. albidus* may similarly support homeostatic mechanisms in humans (Akula & Mukherjee, 2020; Dehghanian et al., 2024; Hong et al., 2024; Su et al., 2024). This is consistent with the concept of **xenohormesis**, which suggests that phytochemicals synthesized under plant stress can act as evolutionary signals, promoting adaptive stress responses in other species, including humans (Howitz & Sinclair, 2008). In this view, bioactive compounds synthesized by *C. albidus* under abiotic stress conditions may act as evolutionary signals that trigger adaptive cellular responses in humans, enhancing resilience to stress mechanisms. Such xenohormetic interactions provide a compelling rationale for the clinical effectiveness of whole-plant extracts rich in stress-responsive metabolites (Menendez et al., 2013). *C. albidus* thus exemplifies a species whose bioactive repertoire may convey cross-kingdom stress adaptations with therapeutic relevance.

Therefore, and based on the presented ecological, biochemical, and pharmacological evidence of this dissertation, *C. albidus* can be classified as an **adaptogenic** plant by definition (Brekhman & Dardymov, 1969). Its ability to synthesize and accumulate bioactive compounds in response to environmental stress, coupled with the evolutionary conservation of stress-response pathways across species, provides a strong conceptual basis for its adaptogenic properties (Panossian et al., 2021). This biochemical and evolutionary alignment underpins the extensive therapeutic potential of this species and justifies further research as a promising treatment for ADHD-typical symptoms by enabling effective modulation of multiple targets with minimal side effects (Chaachouay et al., 2022; Donkor et al., 2023).

From an applied perspective, these findings confirm that agronomic interventions can be strategically applied to tailor phytochemical profiles, optimizing the plant's medicinal properties for specific therapeutic applications. This is further supported by the observation that pharmacological activity of medicinal plants is modulated by environmental conditions, potentially leading to variations in therapeutic efficacy (Pant et al., 2021).

The ability to modulate cultivation conditions to promote specific bioactive profiles presents a promising avenue for developing targeted medicinal formulations. By refining agricultural strategies, it may be possible to cultivate *C. albidus* under conditions that maximize the presence of desired phytochemicals, creating products with more consistent, personalized, and pharmacologically relevant properties. However, these findings also highlight challenges regarding standardization and reproducibility in plant-based medicinal products. Variability in environmental conditions can lead to fluctuations in phytochemical composition, potentially affecting the consistency and efficacy of pharmaceutical derivatives.

5.5. KEY FINDINGS

1. **Phytochemical Profile Expansion**

   The phytochemical profile of *C. albidus* was expanded by 16 newly identified compounds, including the secoiridoid ligstroside. This is the first time that a secoiridoid, a compound class with strong health benefits, was identified in *C. albidus*.

2. **Best treatment strategy to improve phytochemical and vegetative yield**

   For agronomic-pharmacological purposes, if highest seasonal antioxidant capacity values are desired while simultaneously achieving the greatest possible yield of phenolic substances, the best treatment strategy is fertilization.

3. **Influence of Harvest Timing on Phytochemical Composition**

   Best harvest-time is in late winter to early spring, rendering the highest vegetative yields and TPC values in fertilized, inoculated and fertilized + inoculated plants, while control plants showed significant less TPC values. An additional interesting harvest time was identified in autumn, leading to increased antioxidant capacity of both inoculated groups compared to untreated and only fertilized plants. Summer harvest leads to significant less vegetative yields while TPC and antioxidant capacity were similar to late winter harvesting.

4. **Elicitation Mechanisms in *Cistus albidus***

   Instead of a strictly symbiotic interaction, *Glomus* and *Rhizophagus* spp. were identified as elicitors, influencing the plant's secondary metabolism and vegetative growth through a stress response.

5. **Genetic Regulation and Environmental Influence**

   C. albidus exhibits strong genetic regulation, making it less dependent on external factors such as fertilization and inoculation. However, specific responses to these factors still modulate the production of the measured bioactive compounds.

6. **Identification of Potential Biomarkers for Harvesting purposes**

   Quercetin glucoside is proposed as a potential biomarker to determine the optimal late winter to early spring harvest time, due to its strong association with antioxidant capacity, especially in both fertilized and fertilized + inoculated groups. For autumn, no suitable biomarker could be identified, due to other factors than phenolic compounds being responsible for the higher antioxidant capacity.

7. ***Cistus albidus* a previously cultivated species?**

   C. albidus may have been used within ancient mystery cults, a context in which this species could have been intentionally cultivated, possibly driven by the plant's medicinal and aromatic properties, potentially explaining the observed genetic homogeneity in a study.

8. **Riparian Origin and Wildfire Adaptation**

   Evidence suggests that *C. albidus* exhibits ecological traits characteristic of riparian plants, enhancing its resilience to wildfires. Hydrochorous dispersal may play a crucial role in its long-term survival in natural habitats and could also be a key factor in its successful domestication under Mediterranean climatic conditions.

9. ***Cistus albidus,* an Adaptogen Species**

   Based on the presented evidence, *C. albidus* shows characteristics consistent with adaptogenic plants. The accumulation of bioactive compounds under biotic and abiotic stress, coupled with their neuroprotective, anti-inflammatory, and homeostatic regulatory properties, suggests potential adaptogenic activity.

5.6. LIMITATIONS OF THE STUDY

While the results of this study provide a foundational framework for the potential domestication of *C. albidus* as a medicinal plant, several limitations should be considered:

Specificity of Microbial Treatments

The stress-induced metabolic shifts observed in inoculated plants raise concerns regarding the specificity of microbial treatments. Future research should explore alternative microbial consortia, such as plant growth-promoting rhizobacteria (PGPR) or endophytic fungi, which may provide more balanced interactions without imposing excessive physiological stress for these species.

Controlled Experimental Conditions vs. Agroforestry Complexity

The study primarily focused on controlled experimental conditions, which may not fully capture the complexity of agroforestry environments. The interaction of *C. albidus* with different tree species, microbial communities, and variable climatic conditions remains underexplored and requires long-term field trials.

Influence of Additional Environmental Stressors

The observed phytochemical variations were analysed under specific nutrient and microbial treatments. However, the effects of additional environmental stressors—such as prolonged drought, salinity, or pest interactions—on secondary metabolite synthesis remain unclear. Future studies should investigate how these factors influence the consistency of bioactive compound production in different agroecological settings.

Trade-Offs Between Primary and Secondary Metabolism

The observed trade-offs highlight the necessity of deeper research on agricultural techniques such as controlled nutrient delivery and bio-stimulant applications to optimize both growth and phytochemical production. While mycorrhizal inoculation was found to increase secondary metabolite production, the exact microbial dynamics remain poorly understood. The potential role of endophytic fungi, rhizobacteria, or other plant-associated microorganisms in *C. albidus* cultivation should be further explored to optimize beneficial plant–microbe interaction.

Relative Quantification of Phytochemicals

The UHPLC analyses conducted in this study provide relative, not absolute, quantifications of phytochemical compounds. Future research should employ absolute quantification approaches, to ensure precise measurements of bioactive compounds.

Study Duration

The experiments were relatively short. Since phytochemical production and plant–microbe interactions can shift over multiple growing seasons, long-term studies are necessary to validate the stability of observed patterns and optimize cultivation strategies accordingly.

Soil Type

Experiments were conducted on a specific soil type, which does not represent the full range of soils in which *C. albidus* could be cultivated. Further research should assess the plant's adaptability to different soil textures and nutrient compositions to enhance its agroforestry potential across various environments.

Climatic Range

The climate in which this study was conducted is characteristic of a semi-arid Mediterranean region with mild winters and dry, hot summers. While this provides insights into how *C. albidus* performs under these conditions, its adaptability to other climatic regions remains uncertain. Future studies should examine the plant's cultivation potential alternative environments to determine its broader applicability.

Selectivity of Phytochemical Analysis

This study exclusively focused on the quantification of phenolic compounds, omitting terpenes due to their inherently low concentrations in the analysed plant material. However, given the well-documented pharmacological significance of terpenes, their potential contribution to the bioactivity of *C. albidus* should not be overlooked. Future research should integrate advanced analytical techniques to assess terpene profiles comprehensively, ensuring a more holistic evaluation of the plant's medicinal potential.

5.7. FUTURE DIRECTIONS AND APPLICATIONS

Looking forward, the insights gained point to several avenues for future research to optimize *C. albidus* cultivation and utilization. One priority is refining cultivation strategies to achieve the best possible: high biomass production alongside elevated concentrations of target compounds. This could involve experiments with controlled stress elicitation, such as applying brief drought periods, regulated deficit irrigation, or exposure to increased light/UV at certain growth stages, to intentionally stimulate polyphenol and terpene biosynthesis without causing irreversible harm to the plants. The concept of elicitation is already well-known in medicinal plant agronomy, but determining the ideal intensity and timing of stress for *C. albidus* (perhaps at the onset of autumn, or just before a harvest) will be important to develop protocols that consistently boost phytochemical content.

Similarly, further exploration of plant-microbe interactions is warranted. The current study used a commercially available AMF inoculum. Future trials might test different mycorrhizal species or consortia, possibly native fungal isolates that co-evolved with *C. albidus*, such as the ectomycorrhizal *Tuber melanosporum****,*** *Lactarius tesquorum****,*** *Russula cistoadelpha* and *Hebeloma cistophilum* as they were identified as highly specialized symbionts (Comandini et al., 2006). There is also the possibility of using non-symbiotic endophytic fungi or plant growth-promoting rhizobacteria as biostimulants – these could induce stress-related pathways or enhance nutrient uptake in ways that increase secondary metabolites (Backer et al., 2018; Thomloudi et al., 2021).

Understanding the genetic control of phytochemical pathways in *C. albidus* would also greatly aid domestication. Research could focus on identifying genetic markers or specific enzymes regulating the synthesis of key compounds (like ellagitannins or specific flavonoids) and how their expression is triggered by stress. Such knowledge opens doors to breeding or selection programs: for example, selecting genotypes that naturally produce higher levels of desired compounds or that respond robustly to elicitation.

Since *C. albidus* is still essentially a wild species being brought into cultivation, there may be considerable untapped variation in its populations. Screening wild accessions for chemotypic diversity and stress resilience could allow breeders to combine desirable traits (high yield, high compound content, disease resistance, etc.) into new cultivars optimized for agriculture. Care should be taken, however, to retain broad genetic bases and avoid inbreeding, given the value of diversity noted above.

Another future direction is to optimize sustainable agronomic practices specific to this species. Organic and low-input farming methods should be fine-tuned – for instance, determining the minimal fertilizer needed to boost growth without diluting phytochemicals, or using slow-release organic amendments to mimic the nutrient-poor conditions the plant prefers. Irrigation scheduling that conserves water (since the plant is drought-hardy) will be important in dry regions; capturing seasonal rainfall or using drip irrigation can support the plant’s needs without overwatering (excess water might induce stress signalling). Additionally, implementing *C. albidus* in agroforestry systems or mixed-crop setups could be tested: as a shrubby species it might grow well beneath taller trees or alongside other native medicinal plants, potentially enhancing microclimatic stress in beneficial ways and improving overall farm biodiversity.

From an ecological sustainability perspective, cultivating *C. albidus* could also be synergistic with land restoration efforts. Future studies might examine how cultivating this shrub on degraded land helps rehabilitate soil health and prevents erosion, all while yielding medicinal products – essentially a dual-use approach that aligns with regenerative agriculture principles.

Finally, the demonstrated pharmacological potential of this species suggests that phytochemical optimization in cultivation can directly translate to more effective herbal medicines. Continued pharmacological research will be needed in tandem, to pinpoint which compounds or combinations are most active for specific therapeutic applications (such as the traditional use for ADHD symptoms). This feedback can inform cultivation, as agronomic methods can be tailored to enhance that compound's synthesis (through stress or breeding).

5.8. CONCLUSIONS

This study establishes *C. albidus* as a resilient riparian pioneer with facultative pyrophytic traits, capable of thriving under agronomic control while producing a chemically rich metabolome of medicinal relevance.

Germination assays show that mechanical scarification by torrential runoff reliably breaks dormancy, whereas brief heat pulses accelerate germination only when soil moisture is sufficient. Hydrological processes, rather than fire, thus emerge as the primary drivers of natural establishment, calling for a redefinition of *C. albidus* as a riparian specialist rather than an obligate pyrophyte.

Controlled cultivation markedly influences both vegetative growth and secondary metabolite production. Moderate organic fertilization enhances biomass accumulation without diluting polyphenols, while inoculation with *Rhizophagus* and *Glomus* fungi restricts vegetative expansion but significantly boosts phenolic content and antioxidant capacity. The highest pharmacochemical yield is achieved through combined fertilization and inoculation, with harvesting timed to early shoot elongation.

Seasonally resolved UHPLC–MS profiling reveals strong temporal shifts in chemotype: flavan-3-ols peak in early spring, phenolic acids in autumn, and ellagitannins and flavonols at the end of the vegetative cycle. Soil chemistry has only minor effects, underscoring genotype and harvest timing as dominant determinants of metabolic variance. These chemotypic shifts highlight the importance of cultivation environment and phenology as controllable levers for tailoring the phytochemical profile toward specific pharmacological targets.

Stress-responsive metabolites—prodelphinidin gallates, galloylquinic acids, pedunculagin/terflavin B, and myricetin galloyl glycosides—rise consistently during high-radiation, high-temperature periods, a pattern amplified by mycorrhizal inoculation, highlighting their central role in photo-oxidative buffering rather than drought acclimation.

These findings demonstrate that standardized cultivation of *C. albidus* enables reproducible production of high-quality phytochemicals, overcoming the variability of wild populations and aligning with pharmaceutical demands for consistency. They also position *C. albidus* as an adaptogenic species with broad therapeutic potential, including applications in treating complex disorders such as ADHD.

Future works should refine long-term cultivation protocols, explore synergistic mycorrhizal interactions, and optimize harvest strategies to enhance desired bioactive compounds selectively. Together, these insights lay the groundwork for sustainable, demand-driven phytopharmaceutical production using *Cistus albidus* as a model Mediterranean species.

5.9. CONCLUSIONES

Este estudio consolida a *C. albidus* como una especie pionera ribereña resiliente, dotada de rasgos pirófitos facultativos, capaz de prosperar bajo condiciones de cultivo agronómico controlado, al tiempo que genera un metaboloma complejo y químicamente diversificado de alta relevancia farmacológica.

Los ensayos de germinación evidencian que la escarificación mecánica provocada por escorrentías torrenciales rompe de forma eficaz la latencia seminal, mientras que breves pulsos térmicos aceleran la germinación únicamente bajo condiciones adecuadas de humedad edáfica. Estos resultados indican que los procesos hidrológicos, más que el fuego, constituyen los principales impulsores del establecimiento natural de la especie, lo que justifica una redefinición funcional de *C. albidus* como especialista ribereño, en lugar de considerarla estrictamente como una pirófita obligada.

El cultivo bajo condiciones controladas influye significativamente tanto en el desarrollo vegetativo como en la biosíntesis de metabolitos secundarios. La fertilización orgánica moderada promueve la acumulación de biomasa sin comprometer la concentración de compuestos polifenólicos, mientras que la inoculación con hongos micorrícicos arbusculares del género *Rhizophagus* y *Glomus* limita la expansión vegetativa pero incrementa de manera sustancial la concentración de compuestos fenólicos y la capacidad antioxidante. El mayor rendimiento farmacológico se alcanza mediante una estrategia combinada de fertilización e inoculación, con la cosecha sincronizada con la fase inicial de elongación de los brotes.

El perfil químico estacional, caracterizado mediante espectrometría de masas acoplada a cromatografía líquida de ultra alta resolución, revela variaciones temporales pronunciadas en el quimiotipo de la especie: los flavan-3-oles predominan en primavera temprana, los ácidos fenólicos en otoño, y los elagitaninos y flavonoles al cierre del ciclo vegetativo. La influencia de la química del suelo sobre el perfil metabolómico resulta marginal, lo que subraya el papel determinante del genotipo y del momento de cosecha como factores principales en la modulación de la variabilidad metabólica. Estas oscilaciones quimiotípicas ponen de manifiesto la importancia crítica del entorno de cultivo y de la fenología como variables agronómicas controlables para orientar la producción fitoquímica hacia objetivos farmacológicos específicos.

Los metabolitos asociados a la respuesta adaptativa al estrés—incluidos los galatos de prodelphinidina, los ácidos galloilquínicos, la pedunculagina/terflavina B y los glucósidos galato de miricetina—experimentan un incremento sostenido durante periodos de alta radiación y temperatura, patrón que se ve amplificado por la inoculación micorrícica. Este comportamiento apunta a un papel funcional predominante de estos compuestos en la amortiguación del estrés fotooxidativo, más que en la adaptación a la sequía.

En conjunto, los resultados obtenidos demuestran que la domesticación agronómica estandarizada de *C. albidus* permite una producción reproducible de fitoquímicos de alta calidad, superando la variabilidad intrínseca de las poblaciones silvestres y satisfaciendo los estándares farmacéuticos de consistencia y eficacia. Además, posicionan a *C. albidus* como una especie adaptógena con amplio potencial terapéutico, incluidas aplicaciones prometedoras en el abordaje de trastornos complejos como el trastorno por déficit de atención e hiperactividad (TDAH).

Las futuras líneas de investigación deberán centrarse en la optimización de protocolos de cultivo a largo plazo, en la exploración de sinergias específicas entre simbiontes micorrícicos y en la mejora estratégica de las condiciones de cosecha para potenciar de forma dirigida la acumulación de metabolitos bioactivos. Estos avances sientan las bases para una producción fitofarmacéutica sostenible, eficiente y orientada a la demanda, utilizando a *Cistus albidus* como especie modelo en ecosistemas mediterráneos.

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APPENDIX A

A.1. Additional tables and figures

A.1.1. Experimental plot at Regional Park of Valle y Carrascoy

Table A1 Soil analysis of the experimental plot at Regional Park "Valle y Carrascoy" (Murcia, Spain), detailing key physicochemical properties such as pH, organic matter content, nutrient composition, and soil texture.

sand	**loam**	**clay**	**Clasif,**	**OM**	**pH**	**N (Kjeldahl)**	**P**	**K⁺**
%	%	%	(UDSA)	%		%	mg x $100g^{-1}$	mg kg^{-1}
45	40	15	loam	0.6	7.83	0.1	4.5	101

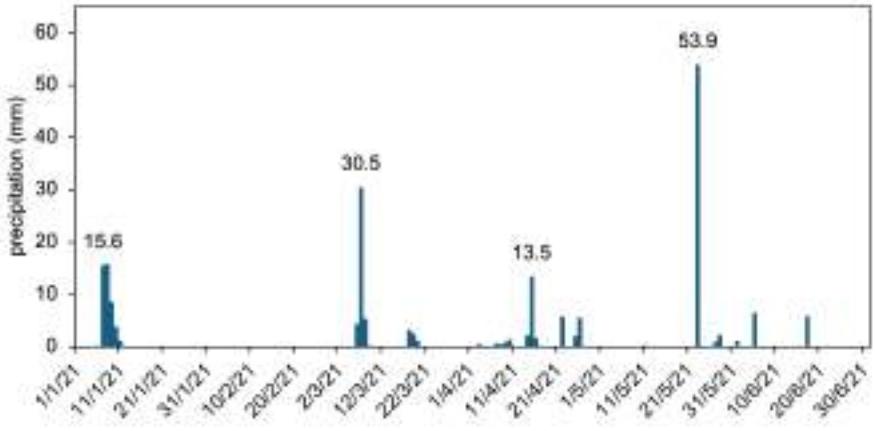

Figure A1 Rainfall (blue bars in mm x m^{-2}). Data measured at the experimental plot of origin of the mother plants from January 1 to June 30, 2021.

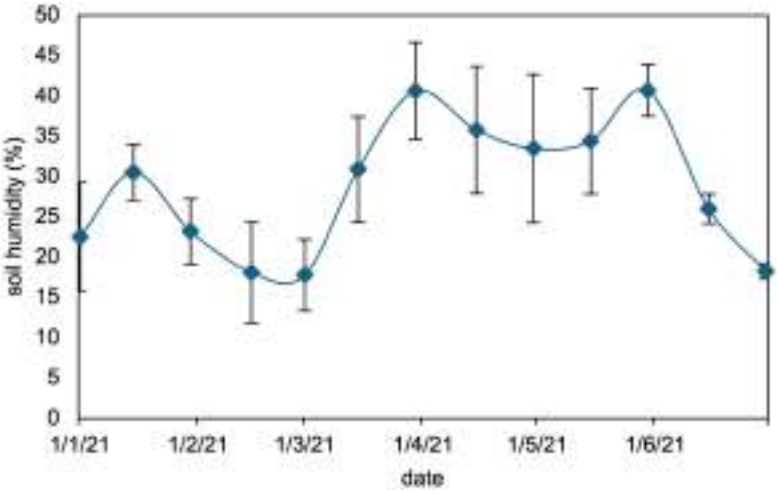

Figure A2 Soil humidity at a depth of 0.25 m (n = 3), measured every 15 days. Data measured at the experimental plot of origin of the mother plants from January 1 to June 30, 2021.

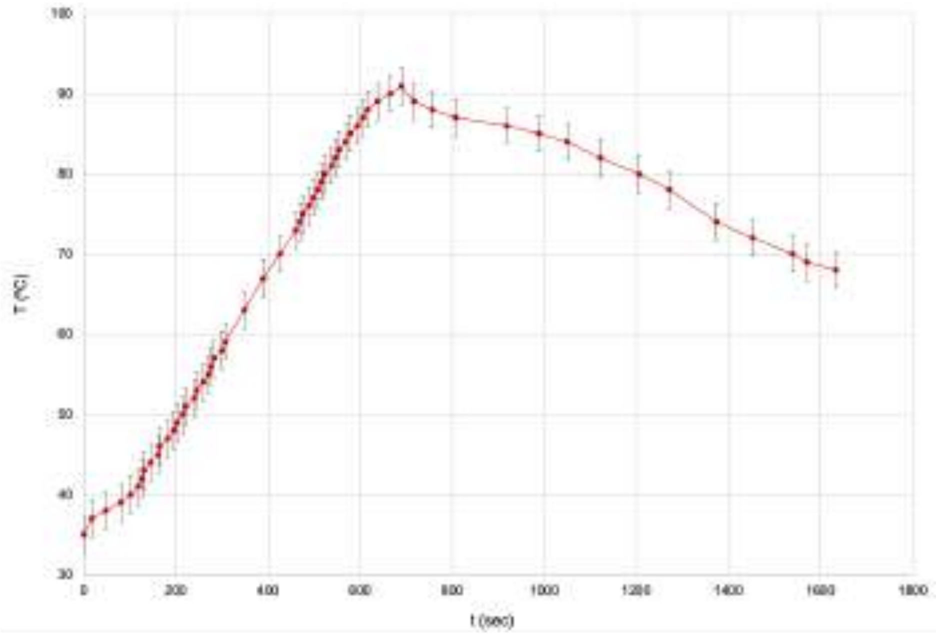

Figure A3 Temperature curve depending on time exposed to the wildfire simulation at a depth of 2 ± 1 mm below the surface (n = 3).

A.1.2. Experimental culture at Peñas de Béjar

Table A2 Soil analysis of the substrate used (rambla soil) for the experimental culture.

Parameter	Result
Sand (%)	45
Silt (%)	40
Clay (%)	15
Texture	Loam
pH	7.83
Electrical Conductivity at 25ºC (µS/cm)	3050
Active Limestone (%)	21
Carbonates (%)	31
Sodium (mg/kg)	519
Potassium (mg/kg)	101
Calcium (mg/kg)	2921
Magnesium (mg/kg)	437
Iron (mg/kg)	1.46
Copper (mg/kg)	1.36
Manganese (mg/kg)	13.17
Zinc (mg/kg)	0.89
Kjeldahl Nitrogen (%)	0.1
Assimilable Phosphorus (mg/100g)	4.5
Oxidizable Organic Matter (%)	0.6

Table A3 Composition of the used organic fertilizer, including its macronutrient and micronutrient content, organic matter percentage, and key physicochemical properties.

N		**K_2O**	**MgO**	**Na**	**S**	**MO**
total	available	total				
%	%	%	%	%	%	%
3	0.13	4	0.3	0.9	0.4	20

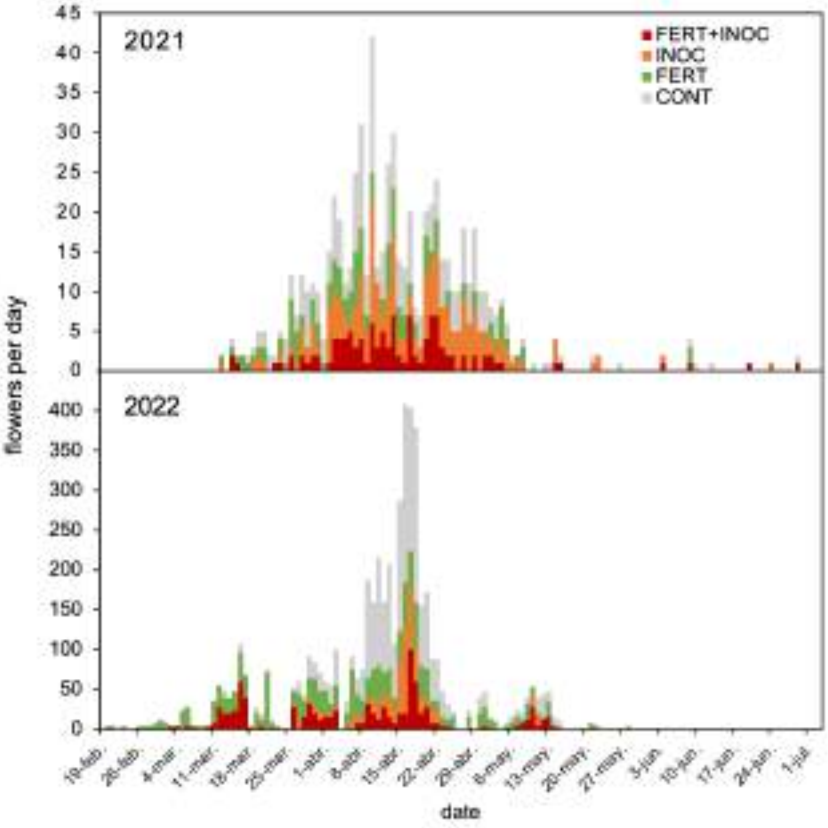

Figure A4 Stacked columns of daily flowering per treatment group during flowering period for the first and the second year. Between treatments no significant differences in flowering pattern were observed (*p*>0.05).

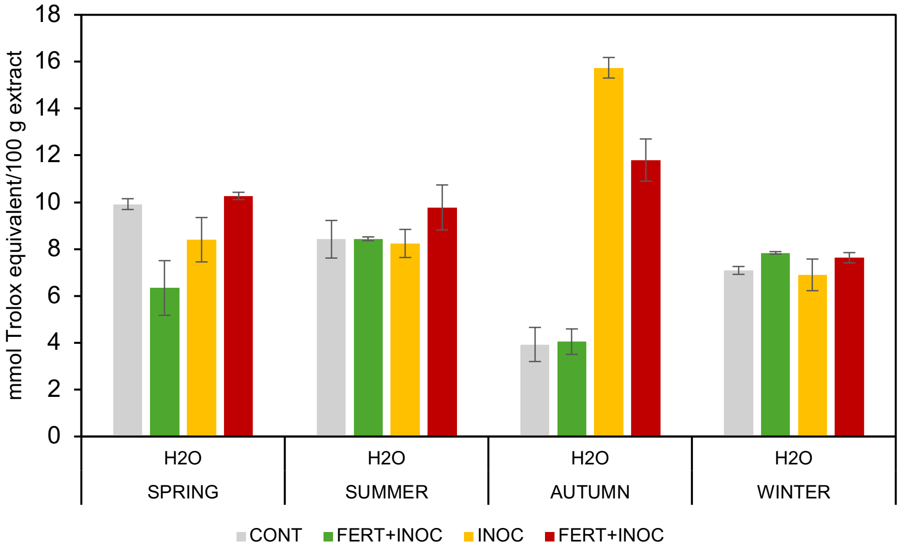

Figure A5 Antioxidant capacity of *C. albidus* aqueous extracts from leaves harvested in four seasons, using Trolox equivalent assay and expressed as 1 mmol equivalent Trolox/100 g extract. No statistically significant differences between treatments were observed (Data represent mean ± SE of n = 3).

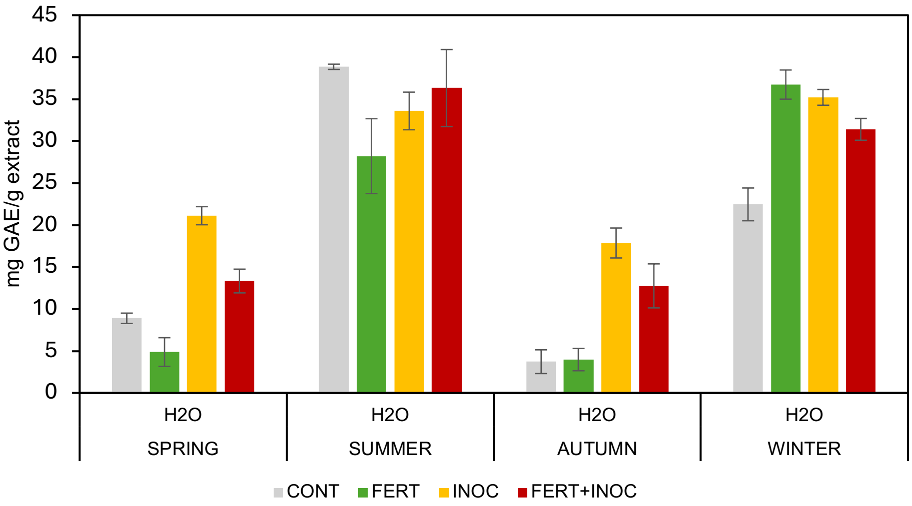

Figure A6 Total phenol content of *C. albidus* aqueous extracts from leaves harvested in four seasons, using Folin–Ciocalteu's assay, expressed in terms of gallic acid equivalent (GAE) per gram of plant extract. No statistically significant differences between treatments were observed. (Data represent mean ± SE of n = 3).

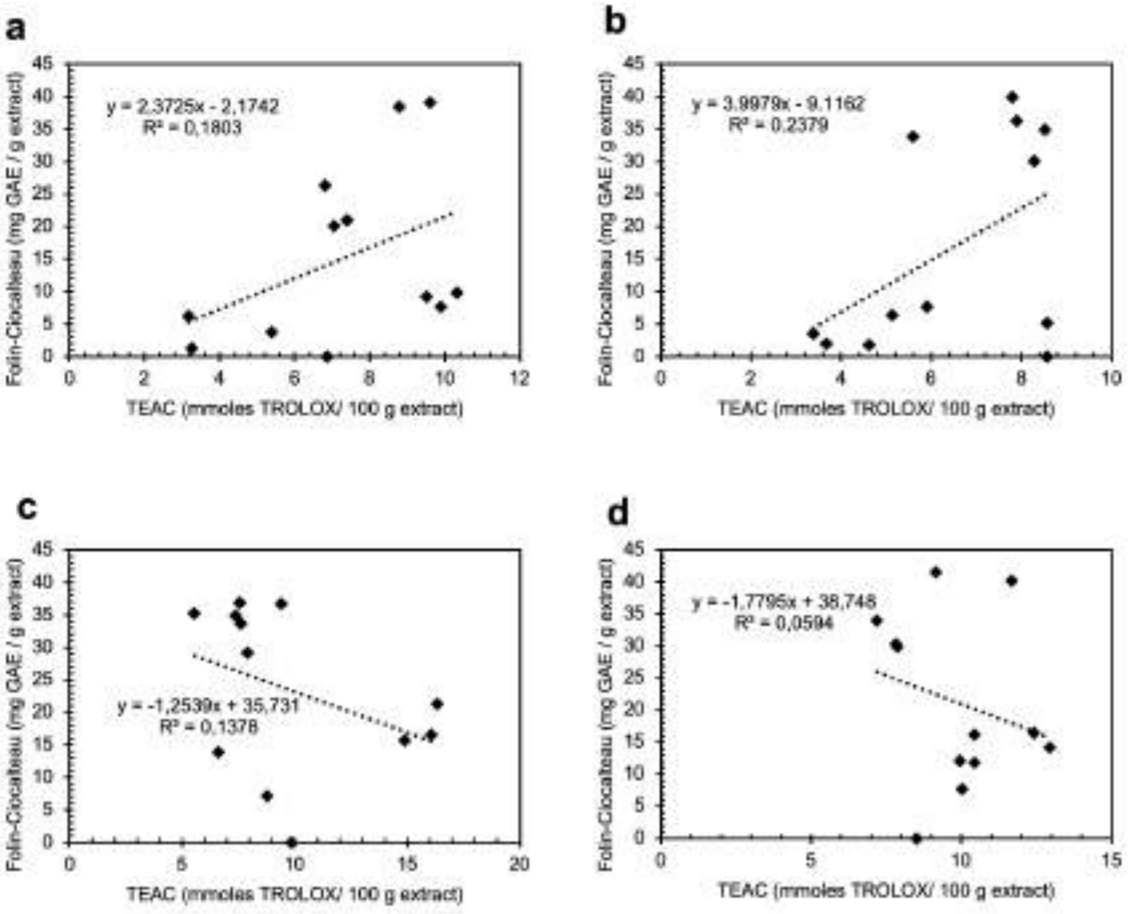

Figure A7 Linear correlation based on treatment between the amount of total phenols and antioxidant capacity measured by ABTS•+ method for the aqueous extracts; (a) CONT, (b) FERT, (c) INOC, (d) FERT+INOC (Data represent mean of n = 3 samples each).

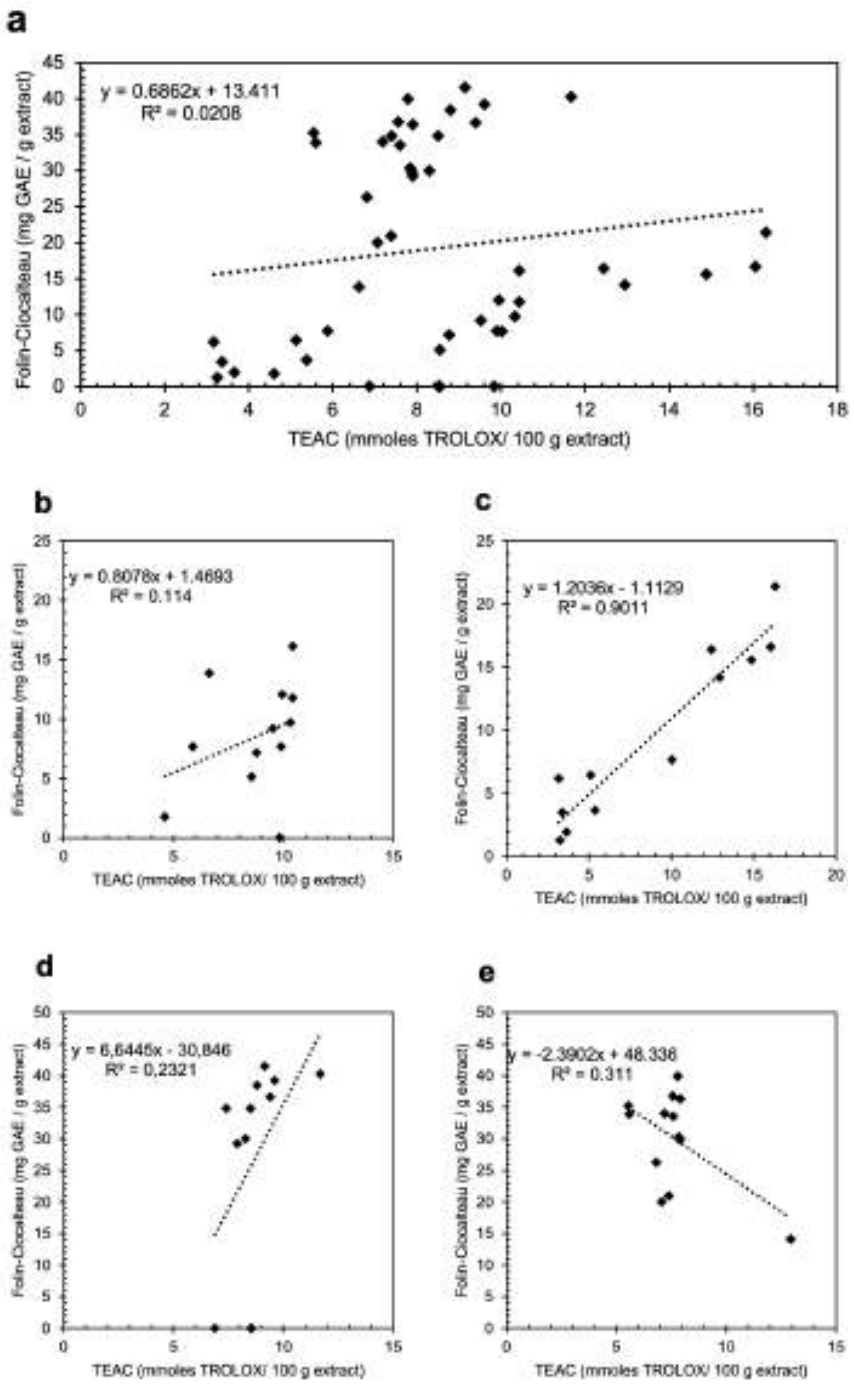

Figure A8 Linear correlation based on harvest timing between the amount of total phenols and antioxidant capacity measured by ABTS•+ method for the aqueous extracts; (a) overall (n = 48 samples); (b) in May, (c) in November, (d) in July and (e) in March harvested leaves (Data represent mean of n = 3 samples each).

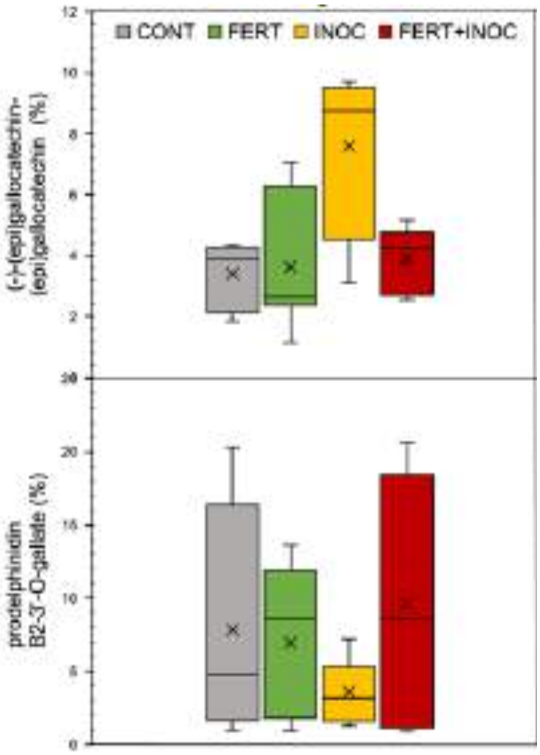

Figure A9 Boxplots of cumulative concentrations (%) of the total of flanan-3-ols studied during one vegetative cycle depending on the treatments (n = 3).

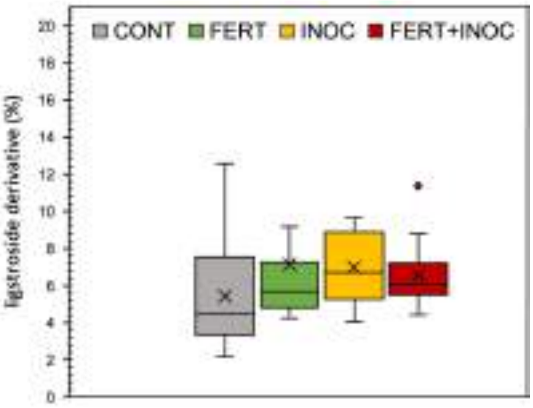

Figure A10 Boxplots of cumulative concentrations (%) of the total of the secoiridoid glycoside studied during one vegetative cycle depending on the treatments (n = 3).

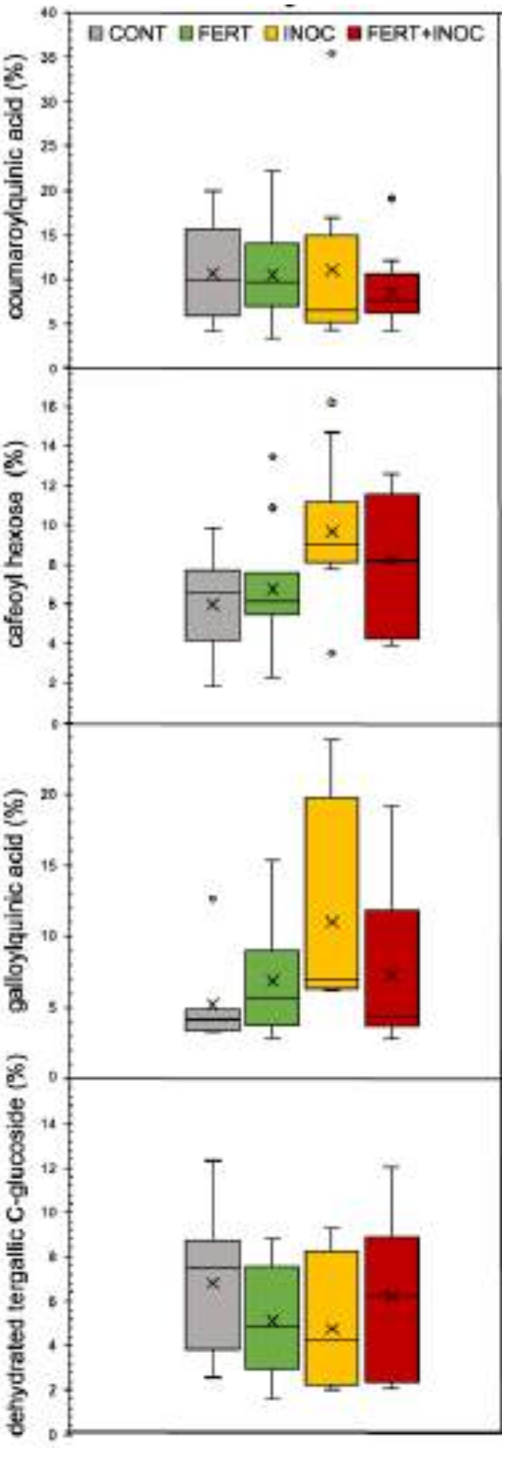

Figure A11 Boxplots of cumulative concentrations (%) of the total of phenolic acids studied during one vegetative cycle depending on the treatments (n = 3).

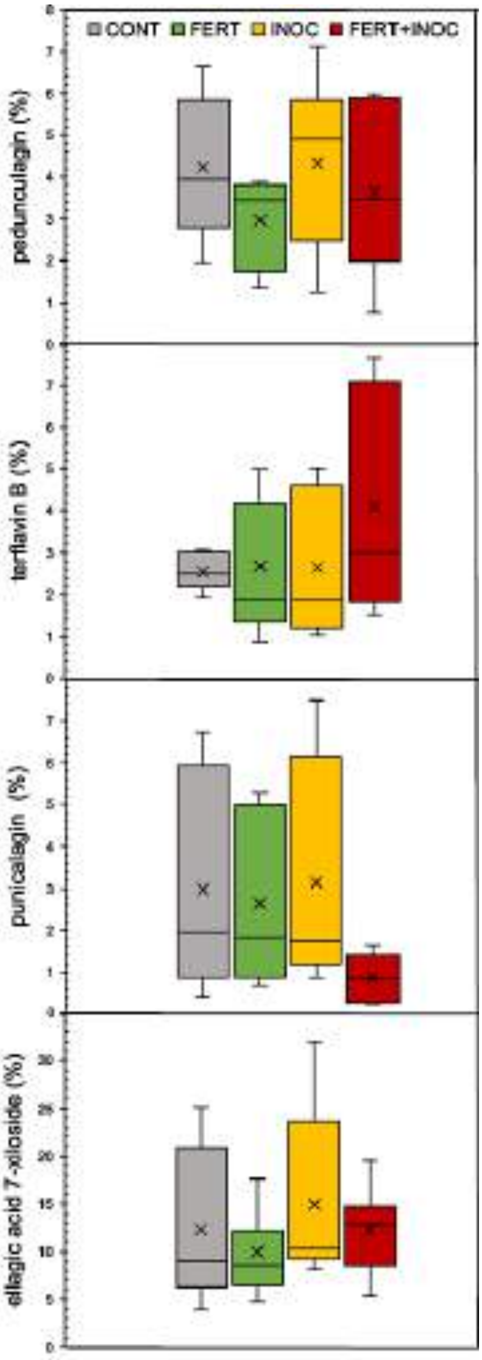

Figure A12 Boxplots of cumulative concentrations (%) of the total of ellagitannins studied during one vegetative cycle depending on the treatments (n = 3).

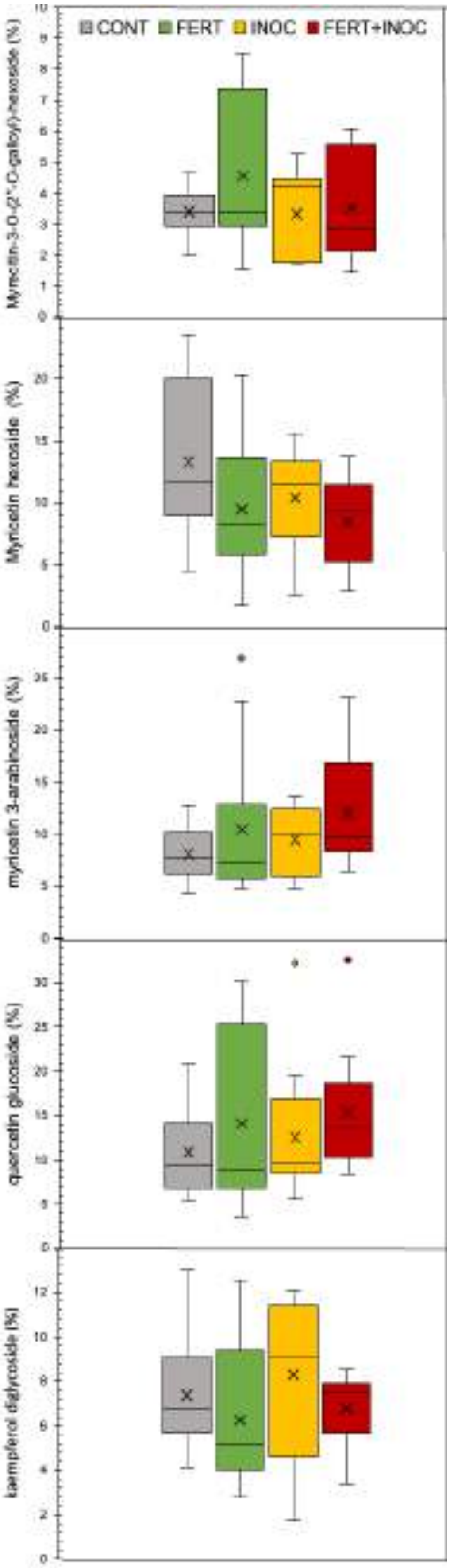

Figure A13 Boxplots of cumulative concentrations (%) of the total of flavonols studied during one vegetative cycle depending on the treatments (n = 3)

Figure A14 Pairwise (Pearson) correlation matrix of all analysed parameters. * means statistically significant: *** for $p \leq 0.001$, ** for $0.001 < p \leq 0.01$, * for $0.01 < p \leq 0.05$.

APPENDIX B

A.2. Article published in Plants (Ed. MDPI)

Cistus albidus L.—Review of a Traditional Mediterranean Medicinal Plant with Pharmacological Potential

Autores: Daniel Raus de Baviera; Antonio Ruiz-Canales; Enrique Barrajón-Catalán

Revista: Plants

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Editorial: MDPI

Ambito de la publicacion: Campo científico

Categoria JCR	Categoria de cuartil	Rango	Factor de impacto
Plant Science	Q1	96/721	4,0