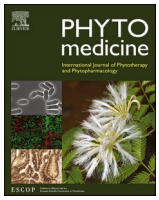
Phytomedicine 113 (2023) 154735

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed



Review

Plant compounds for obesity treatment through neuroendocrine regulation of hunger: A systematic review

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ARTICLE INFO

Keywords:
Adipohormones
Appetite
Energy control
Hunger
Phytochemicals
Satiety

ABSTRACT

Background: Food intake behavior is influenced by both physiological and psychological complex processes, such as appetite, satiety, and hunger. The neuroendocrine regulation of food intake integrates short- and long-term acting signals that modulate the moment of intake and energy storage/expenditure, respectively. These signals are classified as orexigenic, those that activate anabolic pathways and the desire of eating, and anorexigenic, those that activate the catabolic pathways and a sensation of satiety. Appetite control by natural vegetal compounds is an intense area of research and new pharmacological interventions have been emerging based on an understanding of appetite regulation pathways. Several validated psychometric tools are used to assess the efficacy of these plant ingredients. However, these data are not conclusive if they are not complemented with physiological parameters, such as anthropometric evaluations (body weight and composition) and the analysis of hormones related to adipose tissue and appetite in blood.

Purpose: The purpose of this manuscript is the critical analysis of the plant compounds studied to date in the literature with potential for the neuroendocrine regulation of hunger in order to determine if the use of phytochemicals for the treatment of obesity constitutes an effective and/or promising therapeutic tool.

Methods: Relevant information on neuroendocrine regulation of hunger and satiety for the treatment of obesity by plant compounds up to 2022 in English and/or Spanish were derived from online databases using the PubMed search engine and Google Scholar with relevant keywords and operators.

Results: Accordingly, the comparison performed in this review between previous studies showed a high degree of experimental heterogeneity. Among the studies reviewed here, only a few of them establish comprehensively a potential correlation between the effect of the ingredient on hunger or satiety, body changes and a physiological response.

Conclusions: More systematic clinical studies are required in future research. The first approach should be to decode the pattern of circulating hormones regulating hunger, satiety, and appetite in overweight/obese subjects. Thereafter, studies should correlate brain connectivity at the level of the hypothalamus, gut and adipose tissue with the hormone patterns modulating appetite and satiety. Extracts whose mode of action have been well characterized and that are safe, can be used clinically to perform a moderate, but continuous, caloric restriction in overweight patients to lose weight excess into a controlled protocol.

Abbreviations: AgRP, Aguti-related protein; AMPK, adenosine 5'-monophosphate-activated protein kinase; AP, anthropometric parameters; BF, Body fat; BG, β-glucan; BMI, Body mass index; BW, Body weight; CCK, Cholecystokinin; CNS, Central nervous system; CRH, Corticotropin releasing hormone; EGCG, Epigallocatechin gallate; GC, Green coffee; GIMM, Gastrointestinal microbiome modulator; GIP, Glucose-dependent insulinotropic polypeptide; GIT, Gastrointestinal track; GLP-1, glucagon-like peptide-1; HCA, Hydroxycitric acid; MCH, Melanin Concentrating Hormone; NPY, Neuropeptide Y; ORX, Orexin; OXM, Oxynthomodulin; PI-II, Proteinase inhibitor II; POMC, Pro-opiomelanocortin, PP, Pancreatic polypeptide; PYY, Peptide tyrosine-tyrosine; TG, triglycerides; VAS, Visual analog scale; WPI, Whey protein isolate.

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https://doi.org/10.1016/j.phymed.2023.154735
Received 7 November 2022; Received in revised form 7 February 2023; Accepted 22 February 2023
Available online 26 February 2023

Introduction

Being overweight and obesity have become health problems of epidemic proportions at the European and global levels (Aranceta-Bartrina et al., 2005; Kim et al., 2015; WHO, 2015). Both conditions are associated with a metabolic disorder of multifactorial origin related to other chronic degenerative or inflammatory diseases (Ntrigiou V. N.I. et al., 2019), resulting from an energy imbalance between food intake and energy expenditure. Therefore, two main causes give rise to weight gain: overeating and sedentarism. Both have a different participation in obesity and overweight development, but overeating seems to play a trigger role resulting first in weight gain that impairs optimal body motion, which is essential for energy expenditure. Despite scientific efforts to understand the mechanisms that leads to overeating, only a few methods of weight control are effective in the long term. One implies that calorie restriction is difficult to implement with obese patients in cases of overeating but is the most effective strategy in the long term.

Food intake behavior is both physiologically and psychologically influenced and involves different related biological processes, such as appetite, satiety, and hunger. The psychological desire to eat is called appetite and is linked to sensory and pleasure experiences. Once the sensation of filling occurs, the feeding brake called satiety appears, inhibiting eating for a period of time. The term hunger defines the physiological need to eat food (Blundell, 1991). In this process, the central nervous system (CNS) plays a key role as an integrator of most of the actions that maintain energy balance, regulating energy intake, expenditure and storage (Huynh et al., 2016). Nevertheless, food intake control is not a process that occurs exclusively in the CNS; other peripheral signals and extrahypothalamic brain regions are involved (Myers et al., 2012; Waterson et al., 2015). When this complex neuroendocrine circuit system fails, pathologies appear to disturb the metabolic balance between intake and expenditure. Regarding food intake, obesity can result from a strong desire to eat, inappropriate food choices and/or a weak inhibition of eating when fat body stores have been filled.

The neuroendocrine regulation of food intake integrates many signals that can be grouped according to several criteria, as summarized in Fig. 1. Short-term signals act at the moment of food intake, while long-term signals are involved in nutrient storage and expenditure from body compartments, mainly adipose tissue. In this context, food intake is modulated by signals that control the starting and ending of meals through hunger/appetite regulation. In the long term, other signals are responsible for the filling of body stores accompanied by the appearance of a satiety sensation. Hunger and satiety sensations are regulated by several signals that contribute to maintaining or gaining body weight. These signals can be subdivided into i) orexigenic, those that activate anabolic pathways through an intrinsic desire to ingest food due to a strong sensation of hunger and appetite and promote the inhibition of energy expenditure, and ii) anorexigenic, those that activate the catabolic pathways, stimulating signals of gastrointestinal filling and hypothalamic satiety.

Plants produce a large amount of bioactive molecules with therapeutic potential in many pathologies, such as cardiovascular disease, diabetes, metabolic syndrome, cancer and obesity (Konstantinidi and Koutelidakis, 2019). In this context, certain compounds presenting biological activity through different in vitro and in vivo models have been the basis for the development of specific pharmacological formulations. Over time, scientific evidence has shown that the consumption of some specific plant bioactive compounds contributes to improving and treating metabolic disorders related to obesity. In this regard, there is a growing interest in the study of the mechanisms involved and the development of dietary supplements focused on the management of body weight and obesity. Some bioactive compounds, such as plant-derived polyphenols, have been shown to regulate energy metabolism and body weight through specific molecular metabolic pathways, including AMPK activation or the secretion of appetite hormones that control caloric intake (Camacho et al., 2015; Herranz-López et al., 2015,

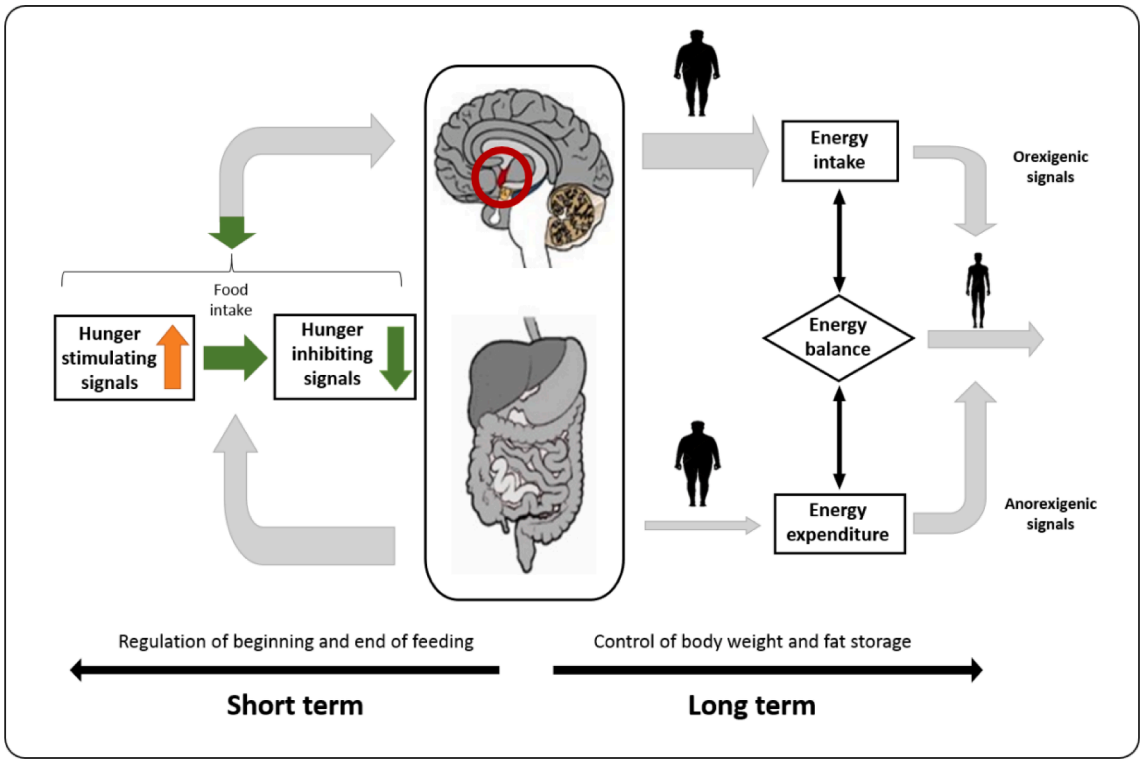

Fig. 1. Short-term (coming mainly from the GIT) and long-term (coming mainly from adipose tissue) regulatory signals of feeding and satiety. Short-term signals control hunger and appetite regulation at the moment of food intake. Long-term signals modulate energy storage to maintain body functions and promote physical activity. The central nervous system and hypothalamus (in red) play a key role as integrators of most of the signals that maintain energy balance, regulating energy intake, expenditure and storage. The disruption of one of these axes leads to obesity development.

2019, 2017; Jimenez-Sanchez et al., 2017; Joven et al., 2014b; Konstantinidi and Koutelidakis, 2019; Olivares-Vicente et al., 2018, 2019). In the long term, obese patients who adopt diets based on caloric restriction have a consequent energy deficit and weight loss, which leads to hunger and reduced energy expenditure. This so-called "energy gap" (Boix-Castejon et al., 2018) is an important barrier to the progress of body weight regulation. In this context, the appetite-suppressing property of certain plant compounds could be useful as a complementary strategy to energy-restricted diets.

The practical application of this manuscript is the critical analysis of the plant compounds studied to date in the literature with potential for the neuroendocrine regulation of hunger in order to determine if the use of phytochemicals for the treatment of obesity constitutes an effective and/or promising therapeutic tool. This knowledge is essential for the possible development of new nutraceutical strategies for the treatment of obesity and associated disorders.

Methodology

In this review, studies focusing on the use of plant compounds bearing satiating and/or appetite-suppressing effects, including information regarding their potential mechanism of action in healthy and overweight or obese individuals, were identified and summarized. A bibliographic search was also carried out on hormones with orexigenic and anorexigenic activity to better understand their physiology. Articles were extracted from the Medline database using the PubMed search engine and Google Scholar with relevant keywords and operators. The following search terms were used: “satiety”, “appetite”, “hunger”, “supplement”, “hormones”, “bioactive ingredient”, “nutraceutical”, “adipohormones”, “weight”, “obesity”, “polyphenol”,” compound”, ”phytochemical”, “CCK”, “GLP-1″, “ghrelin”, “PYY”, and “plant extracts”. No restrictions concerning the type of study were applied. Inclusion criteria for the review were as follows: (1) the study examined the effect of plant compounds on body weight or appetite regulation in humans or animal models; (2) the study was published in a peer-review journal; and (3) the study was published in English and/or Spanish. Contributions up to 2022 were included. 1488 records were identified, from which we reviewed 352 full-text documents after screening. Two reviewers independently screened the titles and abstracts of the identified studies for inclusion in the review. Full-text articles were obtained for all potentially relevant studies and were independently assessed for eligibility by the two reviewers. Finally, 106 papers were included in this review. The PRISMA 2020 flow diagram with the management of the collected information can be seen below in Fig. 2.

Hormones with orexigenic and anorexigenic activity

As previously stated, anorexigenic hormones suppress appetite and decrease food consumption, while orexigenic hormones stimulate appetite and increase food intake. Anorexigenic hormones include leptin, which is produced by adipose cells. Leptin acts on receptors in the hypothalamus to suppress appetite and decrease food intake (Perry et al., 2019). Other anorexigenic hormones include insulin, which is produced by the pancreas (Qiu et al., 2018), and peptide YY (PYY), which is produced by cells in the intestine (Hamamah and Covasa, 2022). Both insulin and PYY act on receptors in the hypothalamus to decrease appetite and food intake. The main anorexigenic hormones involved in appetite regulation are briefly described in Table 1. The role

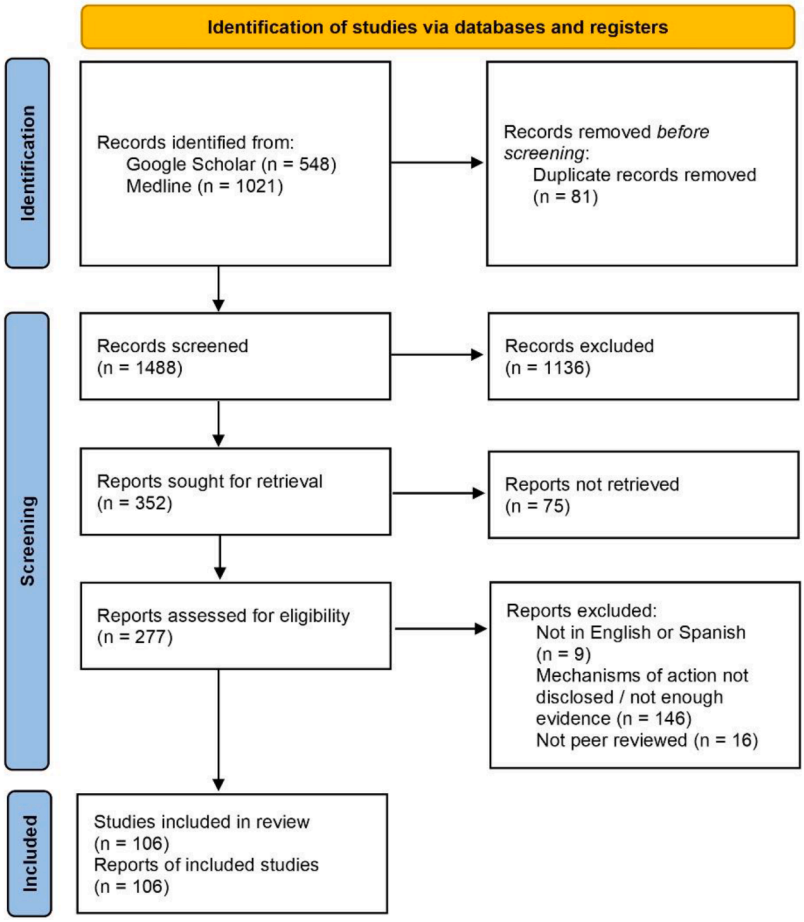

Fig. 2. PRISMA 2020 flow diagram.

Table 1
Main peptide hormones with anorexigenic activity, their synthesis, targets and functions.

Anorexigenic	Synthesis	Target	Function
Glucagon-like peptide-1 (GLP-1)	Small intestine (l cells), mainly ileum and colon. CNS areas	Receptors in the GIT, heart, vessels, kidney, muscle, and lung. At the CNS level, it acts in the hypothalamus	It regulates glucose homeostasis by increasing insulin synthesis and secretion and inhibiting glucagon production. It slows gastric emptying (Carranza Quispe, 2016; Jaimes et al., 2005; Näslund E et al., 2004; Verdich et al. C, 2001)
Insulin	Endocrine pancreas. CNS areas.	Receptors at the CNS level, liver, skeletal muscles, and adipose tissue	It regulates anabolic metabolism. It favors the formation of fatty tissue and increases leptin production. It decreases NPY expression (Mitchell and Begg, 2021)
Obestatin	GIT	AgRP neurons of the arcuate nucleus of the hypothalamus	It participates in the process of gastric emptying, insulin release and pancreatic β cell survival (Alvarez-Crespo et al., 2009; Zhang et al., 2005)
Resistin	Adipose tissue	Liver	It participates in energy homeostasis and modulates insulin resistance (Heilbronn et al., 2004; Rajala et al., 2004)
Oxynthomodulin (OXM)	Small intestine (l cells). CNS areas	GLP-1 receptors and hypothalamus	It reduces circulating ghrelin (Cohen et al., 2003), causing a reduction in the feeling of hunger. It decreases gastric emptying and inhibits gastric secretion
Peptide Tyrosine-Tyrosine (PYY)	Small intestine (l cells) from the distal ileum and colon. CNS regions	Y receptors in the CNS at the level of the hypothalamus	It increases satiety (postpones the consumption of the next meal) and delays gastric emptying (Batterham et al., 2003; Nicolaïdis, 2008). It inhibits NPY secretion
Cholecystokinin (CK)	Small intestine CNS areas	CCK-1 receptors, in the gastrointestinal tract, and CCK-2 receptors, in the nervous system	It inhibits ghrelin and stimulates the release of PYY. It is involved in the secretion of pancreatic enzymes and in thermoregulation processes. It delays gastric emptying (Cummings and Overduin, 2007; Frühbeck, 2005; Gibbs and McHugh, 1976)
Pancreatic polypeptide (PP)	Endocrine and exocrine pancreas and in distal regions of the gastrointestinal tract such as colon or rectum	Y receptors in the CNS at the level of the hypothalamus	It modulates satiety and controls energy homeostasis. PP is secreted after food ingestion correlating with the amount of calories ingested (Alvarez-Crespo et al., 2009)
Pro-opiomelanocortin (POMC)	CNS: arcuate nucleus of hypothalamus, anterior pituitary	Different areas of the brain	It signals satiety and reduces food intake. It controls body energy status by integrating signals from peripheral ghrelin, leptin, and insulin to regulate feeding and energy expenditure (Vohra et al., 2022)
Glucose-dependent insulinotropic polypeptide (GIP)	K cells of the small intestine, located mainly in duodenum, and in smaller amounts in jejunum and ileum	Adipocytes	It stimulates insulin secretion, increases the sensation of gastric fullness (Daousi et al., 2009). Controversial results regarding food intake
Leptin	Mainly expressed and produced by adipose tissue	Hypothalamus stimulating POMC and inhibiting NPY production	It regulates energy expenditure and eating behavior. Increased adiposity is related to leptin production (lipostatic action). Leptin suppresses appetite by stimulating anorexigenic signals (POMC) and decreasing orexigenic signals (NPY) (Frühbeck, 2005)
Adiponectin	Adipose tissue. CNS	It can cross the blood brain barrier and binds to receptors located in the CNS (Bassi et al., 2012)	It regulates energy homeostasis. It stimulates the oxidation of fatty acids. It improves insulin sensitivity. It stimulates food intake and decreases energy expenditure during fasting by acting on the CNS (Kubota et al., 2007)
Amylin	Pancreatic β cells	Hypothalamus, interacting with peptides such as leptin, CCK or GLP-1	It reduces gastric intake, promoting a reduction in body weight and improving glycemic control (Zhang et al., 2016)
Corticotropin releasing hormone (CRH)	Hypothalamic paraventricular nucleus	Pituitary	Regulates energy balance and modulates the response to stress (Frühbeck, 2005)

Other abbreviations used: AgRP, aguti-related protein; CNS, central nervous system; GIT, gastrointestinal track; NPY, neuropeptide Y.

of some of them has been known for decades, and the theoretical postulates about the processes of hunger and satiety regulation have been expanded and modified over several scientific reports. However, the physiological relevance of these hormones and the mechanisms that regulate their secretion and action have not been precisely determined (Yoshihiro Suzuki, 2014). Numerous drugs can reduce body weight, including those derived from hormones produced and secreted by the gastrointestinal tract (i.e., glucagon-like peptide-1/GLP-1) or adipose tissue (i.e., leptin). In particular, these two hormones have been extensively studied and seem to have clear anti-obesity action, reducing body weight and regulating glucose metabolism (Müller et al., 2018).

Orexigenic hormones act on receptors in the brain, particularly in the hypothalamus, to regulate energy balance and hunger. They include ghrelin, which is produced by cells in the stomach and hypothalamus. Ghrelin primarily stimulates receptors in the hypothalamus to promote appetite and food intake. Table 2 describes the main orexigenic hormones involved in appetite regulation.

Psychometric assessment of appetite, hunger, satiety, and fullness in clinical trials

First, appetite modulation by plant ingredients and compounds can be assessed based on subjective aspects obtained through validated questionnaires. One of these tools is the visual analog scale (VAS), a psychometric response scale able to quantify the feeling of hunger, satiety, desire to consume food or the feeling of fullness. In addition, VAS assesses the amount of food consumed over a period of time using a food consumption log. However, these data are not conclusive if they are not supported by complementary physiological parameters, such as body weight control, specific anthropometric evaluations (body composition), bioimpedance or adipohormone analysis. The effects of various bioactive phytochemicals have been evaluated by means of the VAS, but very few reports complete the obtained information by analyzing anorexigenic/orexigenic circulating hormones. Therefore, a comparison between studies is difficult due to the high degree of heterogeneity. More systematic clinical studies are required in future research.

The first heterogeneity results from the use of the terms “hunger,

Table 2
Main peptide hormones with orexigenic activity, their synthesis, targets and functions.

Orexigenic	Synthesis	Target	Function
Ghrelin	Parasympathetic nervous system, GIT and oxyntic glands of the stomach (Cummings et al., 2001). It is also synthesized in a lesser extent throughout the intestine and in the CNS	Hypothalamus. Receptors in stomach, intestine, pancreas, adipose tissue, cardiovascular system, testis, ovary and muscle	It induces appetite and accelerates gastric emptying by increasing plasma levels before meals (Goldstein et al., 2011; González-Jiménez and Schmidt Río-Valle, 2012; Tschop et al., 2000) Excitatory effect on neurons producing NPY and AgRP; and inhibitory effect on neurons that produce POMC
Neuropeptide Y (NPY)	GIT and arcuate nucleus of the hypothalamus	Y receptors in the CNS at the level of the hypothalamus	It promotes feeding, reduces energy expenditure, regulates energy balance, controlling whole-body energy homeostasis (Beck, 2006; Loh et al., 2015, 2017)
Orexin (ORX)/ Hypocretin	Neurons located mainly in the perifornical area of the posterolateral hypothalamus	Adipose tissue	It contributes to early hyperphagia (Linehan et al., 2020), stimulates feeding, controls energy regulation and participates in the neuroendocrine regulation of GIT (Ebrahim et al., 2002; Nuñez et al., 2009)
Melanin Concentrating Hormone (MCH)	Hypothalamus	MCH receptor 1 in brain and other areas of the CNS	MCH overexpression promotes hyperphagia, weight gain, and lipogenesis (Carranza Quispe, 2016). It participates in energy balance and emotional control (Torterolo et al., 2010)
Agouti-related protein (AgRP)	Hypothalamus	NPY neurons	It blocks the MC3 and MC4 receptors of melanocortin, thus preventing its anorectic effect (Frühbeck, 2005)

Other abbreviations used: CNS, central nervous system; GIT, gastrointestinal track; POMC, pro-opiomelanocortin.

appetite and satiety". This ambiguity causes misinterpretations when comparing different studies. A consensus definition of these terms is instrumental to compare the results obtained from different reports. Furthermore, the methodology for evaluating appetite, satiety, hunger, or food consumption is not lineal. Moreover, conformity in the use of VAS is lacking for the evaluation of subjective sensations, such as indicators of regulation, feelings of hunger or satiety and prospective consumption or desire to consume some type of specific or general food. In addition, methods to validate individual states of mind and motivations vary between studies (Blundell et al., 2010). Due to these limitations, the record of food consumption ad libitum has been proposed as an alternative and more precise methodology to assess satiety.

In addition, the length of the studies varied, challenging subsequent analysis. Numerous studies show significant effects on appetite suppression, hunger suppression, or increased satiety, but most are short-term trials. This observation suggests that the ingestion of certain nutraceuticals over longer periods should be further investigated. Moreover, new studies that strictly control the macronutrient content of participants are warranted to draw conclusions regarding food preferences. Overall, scientific consensus is necessary to standardize experimental conditions between studies and establish a more general methodology.

Recently, neuroimaging technology has added a new perspective in the research of human brain-gut interactions. In this context, Zanchi et al. (Zanchi et al., 2017) demonstrated a direct link between changes in the plasma concentrations of certain hormones and changes in the brain regions that form part of the neural circuit of appetite. To date, the main discrepancy in the different studies lies in the variability of the experimental designs.

Knowledge of the mechanism of action of endocrine signals could provide a candidate pathway to develop new therapies for the prevention and even treatment of metabolic syndrome. In-depth studies of appetite regulation demonstrate the complexity of the participating mechanisms. This new knowledge clearly supports that pathologies such as being overweight or obese, are not only metabolic disorders but also neurological imbalances.

Phytochemicals with anorexigenic activity: molecular mechanism

The scientific literature is extensive in relation to medicinal plants or plant-based nutraceuticals that have shown benefits in preventing metabolic syndrome, improving insulin sensitivity, or improving glucose tolerance. However, data on nutraceuticals acting specifically as appetite modulators are scarce (Zuñiga et al., 2017). To date, few studies have confirmed a clear decrease in appetite or hunger or an increase in satiety or fullness using plant extracts or nutraceuticals compared to a placebo. Nevertheless, molecular mechanisms have been studied in more detail in cell or animal models. Therefore, the results obtained in these systems need to be interpreted with caution due to their difficulty to be extrapolated to humans (Timper et al., 2017). Table 3 lists the plant ingredients and phytochemicals with anorexigenic activity together with their active components, effects, mechanisms of action and methods of measuring their effect.

The extracts shown in Table 3 have provided evidence for a potential modulation of the feeling of plenitude that likely act in the appetite centers of the brain. The putative mechanism of action might be similar to that of gut hormones by inducing signals of satiety and fullness, which regulates energy homeostasis in humans (Murphy and Bloom, 2006). Examples of hunger neuroendocrine regulators presented in Table 3 include EGCG that increased adiponectin levels, maintaining glucose, insulin and leptin levels, achieving a delayed gastric emptying in healthy women (Fernandes et al., 2018). Consumption of MetabolAid®, composed of polyphenolic extracts of *H. sabdariffa* and *L. citriodora*, generated improvement of anthropometric measurements, decreased blood pressure and heart rate and a more positive perception in the overall health status by increasing anorexigenic hormones (GLP-1) and decreasing orexigenic hormones (ghrelin) (Herranz-López et al., 2019). Slendesta®, a standardized potato extract, achieved lower postprandial hunger, desire to eat, and prospective consumption, as well as significantly higher postprandial fullness by increasing plasma levels of CCK (Zhu et al., 2017). These plant ingredients exert their metabolic effect through the increase of anorexigenic hormones present in Table 1 or by decreasing the levels of orexigenic hormones present in Table 2. The state of energy balance is sent to key brain regions, such as the hypothalamus and brainstem, using central and peripheral signals. In addition, some of these ingredients show a decrease in hunger ratings and an increase in satiety hormone levels. Overall, energy intake and expenditure are homeostatically regulated, leading to a cascade of reactions that reduces the sensation of hunger. This cascade results in a significant reduction of appetite sensation or a stimulation in early satiety, leading to a decrease in body weight.

Some of the studies shown in Table 3 did not exhibit conclusive results, and larger and more rigorous trials are needed to objectively assess the effects of the proposed polyphenolic compounds (Brum et al., 2016; Onakpoya et al., 2011b; Rebello et al., 2012). For example, the dosage for Garcinia extracts and HCA are not conclusive in the reports, and to date, the correct dose of HCA is unknown because each study has concluded different optimal doses (Onakpoya et al., 2011b).

Table 3
Main plant ingredients and phytochemicals with anorexigenic activity, their herbal parts used, extraction solvents, experimental models, routes of administration, active components, effects on appetite/satiety, body changes, other relevant effects, target/mechanisms of action and appetite/weight measurements used.

Plant/Extract (*scientific name*)	Herbal part used	Extraction solvent	Dosage	Experimental models	Route of administration	Description/ Active components	Effect on Appetite/ Satiety	Body Changes	Other relevant effects	Target/ Mechanism	Appetite/ Weight measurements	References
Baobab extract (*Adansonia digitata* l. (*Bombacaceae*))	Fruit	Not disclosed	15 g	Human	Oral	Smoothie of baobab extract	↓Hunger	Possible effect on weight maintenance.	No significant difference in calorie intake at an ad libitum meal	Unclear	Subjective ratings with VAS	(Garvey et al., 2017)
Oat β-glucan (BG) (*Avena sativa* l. (*Poaceae*))	Seed	Not applicable	3–4 g	Human	Oral	Varying doses of β-glucan in extruded breakfast cereals	↑Satiety	No other effects	↓Post-prandial glycemia	↑ The viscosity of the meal bolus in the stomach and delays gastric emptying	Glycemia	(Tosh, 2013)
Caraway extract (*Carum carvi* l. (*Apiaceae*))	Seed	Water	30 ml per day	Human	Oral	Tannins, alkaloids and terpenoids. Carvone and limonene. Aqueous extract from the seeds	↓Appetite	↓AP ↓Carbohydrate intake	Indigestion and pneumonia treatment. Galactagogue and carminative. Management of functional dyspepsia	↑ The secretion of gastric juice and promotes bile release.	Calorie, macronutrient intake and AP. VAS and an ad libitum pizza test	(Kazemipoor et al., 2016; Mahboubi, 2019)
Whey protein isolate (WPI) and cocoa polyphenols (*Theobroma cacao* l. (*Sterculiaceae*))	Cocoa seed	Not disclosed	340 g beverage	Human	Oral	Food formulation with bioactive ingredients:WPI is rich in leucine. Cocoa is rich in polyphenols	↓Hunger ↑Satiety	No other effects	Improve markers of metabolic syndrome	↑ Adiponectin levels and regulates insulin receptor expression	Glycemia, adiponectin levels and hunger ratings	(Campbell et al., 2016)
Coffee extract (*Coffea arabica* l. (*Rubiaceae*))	Fruit	Water	3–4 cups per day	Human	Oral	Coffee bean extracts	↓Hunger	↓BW ↓BF	Antioxidant activity	↑Plasmatic PYY	Biomarkers of oxidative stress response in blood. BW and intake of energy	(Bakuradze et al., 2011; Greenberg, 2012; Schubert et al., 2014)
Garcinia extract (*Garcinia cambogia*Desr. (*Clusiaceae*), *Garcinia indica* (Thouars) Choisy (*Clusiaceae*), *and Garcinia atroviridis* Griff. ex T.Anderson (*Clusiaceae*))	Not disclosed	Not disclosed	1–2.8 g of HCA per day	Human	Oral	Hydroxycitric acid (HCA)	↓Appetite	↓BW ↓BF		Inhibition of the lipogenic enzyme ATP-citrate lyase and increased release of serotonin in the brain, resulting in appetite suppression.	BW	(Onakpoya et al., 2011b)
Green tea extract (*Camellia sinensis* (l.) Kuntze (*Theaceae*))	Not disclosed	Not disclosed	752 mg of EGCG	Human	Oral	EGCG	↑Fullness ↑Satiety	↓BW ↓BMI ↓BF	EGCG reduces TBK1 activity, reducing TLR4, which impacts insulin resistance, inflammation, and hepatic lipid storage in obesity-related symptoms of high-fat diets. This downregulatess the production of TBK1-	Hormonal modulation. Acute EGCG supplementation is able to delay gastric emptying	Gastric emptying, VAS, insulinemia, glycemia, adiponectin and leptin levels	(Fernandes et al., 2018; Li et al., 2022)

(*continued on next page*)

Table 3 (*continued*)

Plant/Extract (*scientific name*)	Herbal part used	Extraction solvent	Dosage	Experimental models	Route of administration	Description/ Active components	Effect on Appetite/ Satiety	Body Changes	Other relevant effects	Target/ Mechanism	Appetite/ Weight measurements	References
									targeted genes, including TNF- and IL-6.			
Decaffeinated green coffee (GC) phenolic extract alone or combined with oat β-glucans (GC/BG)	Not disclosed	Not disclosed	5 g per day of GC/BG	Human	Oral	B-CAN™: 5 g/ day of 70% oat BG and 600 mg/ day of GC polyphenols	↓Hunger GC/BC is more efficient than GC	No other effects		↓ Maximum ghrelin levels. GC/ BG more efficient than GC	Subjective ratings with VAS. In a subgroup of participants blood levels of CK, PYY, GLP-1, ghrelin and leptin	(Redondo-Puente et al., 2021)
Gastrointestinal microbiome modulator (GIMM)	Not applicable	Not applicable	4 g of inulin, blueberry extract equivalent to two cups of whole blueberries, and 2.5 g of oat β-glucan	Human	Oral	Inulin, BG, blueberry anthocyanins, and blueberry polyphenols	↑Satiety		Improved blood glucose tolerance	↑ In fasting plasma PYY and ↓ in plasma ghrelin. Effects on serum glucose may be through insulin-independent pathways	Blood levels of gut microbiota, satiety hormones, glycemic control and lipid determination. Subjective ratings.	(Rebello et al., 2015)
MetabolAid® (*Hibiscus sabdariffa* l. (*Malvaceae*) + *Lippia citriodora* (Paláu) Kunth (*Verbenaceae*))	Not disclosed	Not disclosed	500 mg per day	Oral	Human	Combination of polyphenolic extracts	↑Satiety	↓BW ↓AP	Modulating the plasma concentrations of adipohormones, through the release of adiposity factors and intestinal peptides that control appetite and satiety	Activation of the AMPK pathway	Blood pressure, BW, AP and VAS. Serum adipohormones	(Arluison et al., 2004; Barrajon-Catalan et al., 2014; Boix-Castejon et al., 2018; Fernández-Arroyo et al., 2011; Herranz-López et al., 2019; Joven et al., 2014a; Turnley et al., 1999)
Psyllium	Not applicable	Not applicable	6.8 g once or twice a day	Human	Oral	Soluble fiber obtained from *Plantago major subvar. ovata Pilg.* (*Plantaginaceae*).	↓Hunger ↑Satiety ↑Fullness	↓BMI ↓BF	Reduction in plasma TG	↑ In fiber intake is linked to a ↓ in energy intake.	Hunger and desire to eat. AP, lipids, TG, BW and BF	(Brum et al., 2016; Pal et al., 2011)
Red pepper, chili, cayenne, or paprika extracts (*Capsicum annuum* l. (*Solanaceae*))	Not disclosed	Not disclosed	1.03 g of red chili pepper (2.56 mg capsaicin) per meal	Human	Oral	Capsaicin	↑Fullness ↑Satiety	↓BW ↓Energy intake ↑Energy expenditure	↑ Fat oxidation and thermogenesis.	Effect might be related to ↑ in sympathetic nervous system activity.	VAS. Energy expenditure, core body and skin temperature, and subjective ratings	(Janssens and Westerterp-Plantenga , 2014) (Ludy, 2011)
Slendesta®: Standardized potato (*Solanum tuberosum*l. (*Solanaceae*)) extract	Tuber	Water	15 mg of proteinase inhibitor II (PI-II)	Human	Oral	The active compound is a proteinase inhibitor II (PI-II)	↓Food consumption ↑Satiety ↑Fullness	↓BW	↓Epididymal fat. Histomorphological changes of fat and pancreas.	↑ CCK secretion ↑ UCP1 and beige-specific genes causing elevated energy expenditure.	VAS, and blood levels of CCK, insulinemia and glycemia	(Zhang et al., 2022; Zhu et al., 2017)
Satiereal® (*Crocus sativus* l. (*Iridaceae*))	Stigma	Not disclosed	176.5 mg extract per day	Human	Oral	Extract from saffron stigma.	↓Caloric intake ↑Satiety	↓BW ↓Snacking frequency		Suggested mood-improving effect	BW and subjective ratings	(Gout et al., 2010)

(*continued on next page*)

Table 3 (*continued*)

Plant/Extract (*scientific name*)	Herbal part used	Extraction solvent	Dosage	Experimental models	Route of administration	Description/ Active components	Effect on Appetite/ Satiety	Body Changes	Other relevant effects	Target/ Mechanism	Appetite/ Weight measurements	References
White bean + Artichoke (*Phaseolus vulgaris* l. (*Leguminosae*) + *Cynara scolymus* l. (*Asteraceae*))	*P. vulgaris*: beans. *C. scolymus*: flowering buds.	Not disclosed	100 mg *P. vulgaris* extract + 200 mg *C. scolymus* extract 3 times a day.	Human	Oral	Crocetin and safranal α-amylase inhibitor	↑Satiety	↓AP ↓BMI ↓BW ↓BF	↓Carbohydrate absorption. Hypoglycemic effect. Improvements in glucose and lipid profiles		Lipidemia and glycemia VAS BW, AP and BF	(Barrett and Udani, 2011; Onakpoya et al., 2011a; Rondanelli et al., 2011)
Sorghum (*Sorghum bicolor* (l.) Moench (*Poaceae*)) flaked biscuits	Grain	Not applicable	50 g per day	Human	Oral	Sorghum whole grain	↑Satiety compared to bread	No other effects		↑ Postprandial GLP-1 and GIP levels. Hormonal modulation	VAS, glycemia, insulinemia and blood levels of GIP, GLP-1, PYY, and ghrelin	(Stefoska-Needham et al., 2016)

Other abbreviations and symbols used: AP, anthropometric parameters; BF, body fat; BG: β-glucan; BMI, body mass index; BW, body weight; CCK: Cholecystokinin; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine-tyrosine; TBK1: TANK-binding kinase 1; TG, triglycerides; TLR4: toll-like receptor 4; UCP1: uncoupling protein 1; VAS: visual analog scale; (↑) increase; (↓) decrease.

Additionally, some results show no solid evidence or show contradictions (Logan et al. , 2006; Rebello et al., 2012). Therefore, larger, well-controlled randomized clinical trials are needed, particularly in the case of Garcinia and red pepper.

Another factor necessary to increase consistency between studies is the length of interventions. Most of the studies are short-term; therefore, longer studies are needed to evaluate the long-term effect of polyphenolic extracts (Zhu et al., 2017). Inconsistencies in the composition of the sources from which polyphenols were obtained have been noticed when comparing different studies. For instance, extracts containing BG from different sources provide similar benefits, but each product requires individual testing to assess the possible role of other compounds present in the extract (Tosh, 2013). Additionally, studies using coffee extracts to decrease appetite (Campbell et al., 2016; Kazemipoor et al., 2016; Mahboubi, 2019) are incomplete, as they suggest that one or more noncaffeine ingredients that remain to be identified may have the potential to decrease body weight (Bakuradze et al., 2011; Greenberg , 2012; Redondo-Puente et al., 2021; Schubert et al., 2014).

Other reports show no significant differences when comparing appetite/satiety-related hormones (Redondo-Puente et al., 2021) or in insulin sensitivity, plasma satiety hormones, or serum lipid concentrations between the intervention groups (Rebello et al., 2015). Moreover, the subjective feeling of satiety in response to nutraceutical supplements derived from plant extracts, such as nopal (El-Mostafa et al., 2014) or baobab (Garvey et al., 2017), has been studied without assessing the levels of circulating hormones. The considerable variability and inadequacy of the presented randomized clinical trials necessitate larger and more rigorous designs to objectively assess the effects of polyphenolic extracts on body weight reduction (Onakpoya et al., 2011a). In some studies present in Table 3, adverse events were reported, including nausea, gastric intolerance or headache (Gout et al., 2010; Onakpoya et al., 2011b). Therefore, the optimum dosage needs to be assessed.

Plant preparations are generally safer than synthetic anti-obesity medications. This is attributed to the variety of metabolites contained in these formulations in addition to their active substances, which cause a variety of targeted reactions and can control side effects (Kazemipoor et al., 2015). In addition, most of the agents with anorexigenic capacity included in Table 3 come from plant ingredients or phytochemicals that are regularly consumed in the human diet and are known not to present toxicity at the levels used. However, this can depend on the specific plant extract. Garcinia extracts have been used as weight loss supplement in a variety of clinical trials (Onakpoya et al., 2011b). Their action can be attributed to hydroxycitric acid (HCA), a derivative of citric acid. The anti-obesity effects of HCA are known to be caused by a number of mechanisms. HCA inhibits the enzyme adenosine triphosphatase-citrate-lyase, an enzyme for the extra-mitochondrial catalysis of citrate into oxaloacetate and acetyl coenzyme A (acetyl-CoA), a component of the synthesis of fatty acids. Thus, HCA limits the availability of two carbon groups needed for the production of lipids and cholesterol by decreasing the acetyl-CoA and subsequently the malonyl-CoA pool (Tomar et al., 2019). However, there might be a potential causal association between consumption of Garcinia products and development of acute liver injury (Crescioli et al., 2018). HCA has shown to increase the amount of hepatic collagen, lipid peroxidation, mRNA levels of oxidative stress-related genes (such as glutathione peroxidase and superoxide dismutase), and inflammatory responses (Kim et al., 2013) (such as tumor necrosis factor and monocyte chemoattractant protein-1). Therefore, further research should be done in this clinical setting to identify, isolate, and analyze the toxicological effects of plant active principles.

The plant-based nutraceuticals described in Table 3 may exert anti-obesity effects due to their active components. These active components may have a variety of mechanisms of action that can contribute to weight loss or weight management. For example, leucine has shown to promote a decrease in adiposity by inhibiting lipogenesis, promoting lipolysis and fatty acid oxidation, and greatly increasing leptin release in

adipocytes via the mTOR signaling pathway. Dietary leucine lowers hyperglycemia, lowers the rate of fat formation, lowers body fat, and raises insulin sensitivity, all of which are brought on by the high fat diet (Zhang et al., 2020). EGCG inhibits TLR4 signaling by specifically inhibiting TANK binding kinase 1 (TBK1) activity and consequently downregulating the expression of TBK1-targeted genes, including TNF-α, and IL-6. TNF-α is crucial for lipid metabolism and hepatocyte cell death in the emergence of obesity (Li et al., 2022). Inulin can alter the gut microbiota of obese individuals, increase the abundance of bifidobacteria and *Akkermansia muciniphila* in obese individuals, and improve metabolic disorders. Short-chain fatty acids in the colon, such as acetic acid, propionic acid, and butyric acid, change in response to inulin administration. Dietary treatment with these metabolites has been demonstrated to considerably reduce body weight gain by boosting beige adipogenesis, mitochondrial biogenesis, and triglyceride hydrolysis and fatty acid oxidation in adipose tissue (Wu et al., 2022).

The anti-obesity properties of capsaicin may be mediated via a variety of mechanisms. By increasing the expression of PPARγ and UCP-1 in preadipocytes and adipocytes, capsaicin can suppress adipogenesis (Szallasi, 2022). As a result, it will promote the release of adiponectin and lead to an increase in body fat storage. Capsaicin can cause an increase in UCP-1 and PGC-1α expression and brown adipose tissue activity (Takeda and Dai, 2022). It can also decrease insulin resistance, promote satiety, and reduce appetite. Finally, capsaicin can influence the function of the gastrointestinal tract and gut microbiota stimulating GLP-1 secretion and increasing the population of the gut bacterium *Akkermansia muciniphila* (Zheng et al., 2017),

Recently, PPI II increased the expression of the uncoupling protein 1 (UCP1) protein and gene and beige-specific genes, including Cd137, Cited1, Tbx1, and Tmem26 in vitro. PPI II treatment for three months in diet-induced obesity mice increased the levels of the UCP1 protein in white adipose tissue, causing elevated energy expenditure, thus preventing obesity and improving glucose tolerance (Zhang et al., 2022). α-Amylase inhibitors are effective in reducing postprandial hyperglycemia by slowing the digestion of carbohydrates and absorbing postprandial glucose. The formation and accumulation of triacylglycerol are inhibited by reducing postprandial hyperglycemia via preventing glucose uptake into adipose tissue (Kim et al., 2020). Additionally, α -amylase inhibitors might alter the gut microbiota, potentially boosting the diversity of species such as Bacteroidetes and Akkermansia as well as short fatty-acid-producing bacteria (Peddio et al., 2022).

Data from Table 3 demonstrate a lack of rigorous studies on the effects of nutraceuticals based on plant ingredients. Among the studies reviewed that claimed an effect of the ingredient on hunger or satiety for the management of obesity, only a few of them (Boix-Castejon et al., 2018; Fernandes et al., 2018; Rebello et al., 2012; Zhu et al., 2017) have measured in some extent anthropometric parameters, food intake and appetite in correlation with the levels of gut or adipohormones. Therefore, the study of nutraceuticals that can modulate key adipohormones release may be an opportunity for the development of new lines of research in the treatment of obesity and other metabolic disorders. To this end, appetite control is a new field with more active research. The growing demand for new products of natural origin for weight control and appetite suppression has generated new lines of investigation in the field. Furthermore, certain in vitro studies can be extrapolated to human intervention conditions. Overall, more human clinical studies are needed.

Multiple peripheral signals control energy homeostasis, but all are integrated in the hypothalamus, specifically in the arcuate nucleus, which is mainly responsible for the control of food intake. This neurological center is especially sensitive to biochemical messengers, such as leptin, insulin and ghrelin. Other regions are responsible for eating behavior control and brain responses directly to the presence of nutrients, such as glucose, amino acids or fatty acids. We found that most studies have focused on the mechanisms involved in the regulation of energy homeostasis mediated by adenosine 5′-monophosphate-activated protein kinase (AMPK) in tissues, such as muscle, liver or adipose tissue (Hardie et al., 2012; Herranz-López et al., 2015; Jimenez-Sanchez et al., 2017). Nevertheless, the role of this enzyme is not limited to this homeostasis. Several studies indicate that AMPK plays a fundamental role in the regulation of appetite and that the enzyme is widely expressed in hypothalamic areas that control food intake (Huynh et al., 2016; Kola et al., 2006; Minokoshi et al., 2004). Increased energy expenditure leads to energy intake through appetite stimulation, simultaneously inhibiting energy expenditure through various metabolic pathways, including those regulated by AMPK. The inhibition of AMPK expression in the hypothalamus reduces food intake and body weight. Kola et al. suggested AMPK kinase as a mediator of orexigenic effects (Kola et al., 2006). Evidence has shown that the brain-intestine axis is responsible for neuronal functions, including the control of eating behavior. In conclusion, changes in the plasma concentrations of various hormones, such as ghrelin, GLP-1, PYY, CCK, leptin and insulin, as well as nutrients, such as glucose, are key influencers of the function of regions of the brain that regulate appetite and satiety in which AMPK seems to be expressed.

Concluding remarks

The use of plant extracts for weight control is increasingly noticeable. Various plant ingredients have been shown to be potentially effective in alleviating the signs and pathologies resulting from obesity, such as hyperlipidemia, hypercholesterolemia and hypertension. However, most recent research has opened a challenging area of research indicating that some herbal supplements seem to play an important role in food intake disorders, especially in hyperphagia, which is also related to obesity. Caloric restriction, under normal conditions in the face of weight reduction, can be associated with anxiety states accompanied by a significant increase in appetite in the individual, which is mitigated by uncontrolled eating. Therefore, the investigation of nutraceuticals that can modulate satiety or appetite for the treatment of obesity would become a very interesting and novel area of research. Nevertheless, new studies are needed to precisely determine the participating molecular mechanisms and the physiological effects and psychological response elicited by plant extracts and their bioactive compounds. Among all the studies reviewed that claimed an effect of the ingredient on hunger or satiety, only a few of them have rigorously determined the effect of the ingredient on food intake, appetite or body weight in correlation with the levels of gut or adipohormones.

The main limitations of this study lie in the general lack of studies that perform quantitative measurements of anorexigenic and/or orexigenic hormones during the different stages of clinical interventions. Future research should decipher the plasmatic pattern of hormones that regulate hunger, satiety and appetite in overweight and/or obese subjects in different phases, including fasting and the postprandial state, and compare these patterns with those in healthy subjects. In turn, subsequent studies should assess brain connectivity at the level of the hypothalamus, gut and adipose tissue and correlate this connectivity with the hormone patterns involved in the regulation of appetite and satiety. Following these study guidelines will provide a more solid understanding of the effect of phytochemicals on the neuroendocrine regulation of hunger.

Translating these findings to clinical practice will be the challenge in the future treatment of obesity. At the moment, the extracts seem to work best in overweight people. An efficient use of the extracts in patients with obesity needs further research, since this group presents a strong hormonal and metabolic dysregulation. Safe extracts whose mode of action have been well characterized, may be prescribed into a context of diet and exercise, which are the variables that will determine effective weight loss. It is important to identify the active ingredients of the extracts to ensure their effectiveness during treatments. In addition, it will be necessary to prescribe the extract more in line with the profiles of appetite hormones that appear dysregulated in the patient,

personalizing the treatment. The diet should be balanced and slightly hypocaloric, to generate no anxiety in the patient during the weight loss process. It is important to educate the patient to autonomously control their nutritional status. Once the goal of normal weight has been reached by the patient, taking the extracts should not be necessary, although this is still an aspect to investigate. In conclusion, future research in the use of appetite-controlling plant extracts might improve existing protocols for safe and effective weight reduction in cases of overweight and obesity.

Author contributions

All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Disclosure statement

The authors report that there are no competing interests to declare.

CRediT authorship contribution statement

M. Boix-Castejón: Data curation, Investigation, Methodology, Writing – original draft. **E. Roche:** Data curation, Visualization, Writing – review & editing. **M. Olivares-Vicente:** Data curation, Visualization, Writing – review & editing. **F.J. Álvarez-Martínez:** Investigation, Software, Writing – review & editing. **M. Herranz-López:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **V. Micol:** Funding acquisition, Resources, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This study was supported by the official funding agency for biomedical research of the Spanish government, Institute of Health Carlos III (ISCIII) through CIBEROBN CB12/03/30038). F.J.A.-M. has been supported by Margarita Salas grant for the training of young doctors 2021/2023 and M.H.-L. has been also supported by the Requalification of the Spanish University System for 2021/2024, funded by the European Union NextGenerationEU. This work has also been funded by the Project PROMETEO/2021/059 from Generalitat Valenciana and The Spanish Ministry of Economy and Competitiveness (MINECO, Project RTI2018–096724-B-C21 and PID2021–125188OB-C31).

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