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Herbal medicines applied to obesity

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Abstract

The study aimed to investigate scientific evidence on the use of herbal medicines "*Camellia sinensis*", "*Citrus aurantium*" and "*Carthamus tinctorius*" to help weight loss. In the development of this research we carried out systematic bibliographical studies on *PubMed*, *ScienceDirect* and *Scielo* databases between the years 2000-2014. According to the studies found, green tea extract of *Camellia sinensis* has several active ingredients, among which catechin stands out, which inhibits the enzyme catechol-o-methyltransferase, responsible for degrading norepinephrine by prolonging the effect of adenosine 3', 5'-cyclic monophosphate on thermogenesis mainly mediated by noradrenaline in combination with caffeine. *Citrus aurantium*s, due to the synephrine action, stimulates the action of the β3-receptors, accelerating lipolysis, and increases basal metabolism through thermogenesis, causing weight reduction. *Carthamus tinctorius*, through the action of linoleic acid, inhibits the enzyme lipoproteinlipase, responsible for carrying triglycerides from the blood to the interior of adipocytes, helping reduce weight, while oleic acid stimulates the enzyme carnitine palmitoltranferase that mobilizes fatty acids into the mitochondria causing the β-oxidation process that contributes to weight loss. It was possible to understand that despite the herbal medicines investigated have shown satisfactory results, data are still incomplete and require further research.

Keywords: Obesity. Phytotherapy. Emaciation. Lipolysis.

Introduction

The first records on phytotherapy date back to the period of 2838-2698 B.C. With the advent of technology and industrialization and the consequent ability to isolate the active ingredients and their synthesis, phytomedicines gained importance worldwide both by increasing production and demand by the population. [1,2]

Over the years, the use of plants for a wide variety of purposes has been known as Phytotherapy, which etymologically has origin in *Phyton*, meaning "plant" and *Therapeia*, which means "therapy", and both words together mean "treatment of diseases with plants".[3]

In the search for new perspectives to treat obesity, phytotherapy arises as one more alternative. Low cost and few side effects are factors that make plant-derived medicines increasingly popular. There are numerous alternatives available in the market to treat obesity but few have consistent evidences concerning their safety and effectiveness.[4]

The incidence of obesity has grown at an alarming rate in recent years, becoming a health problem with uncountable social costs worldwide.[5]

Herbal medicines used for weight loss act in the body as appetite suppressants or metabolism boosters leading to reduced food intake, a decline of cholesterol serum levels and an increased antioxidant, diuretic and lipolytic activity.[6] A large variety of phytomedicines have been exploited for their potential in treating obesity. They are mainly complex products with various components of different chemical and pharmacological features.[7-9]

Obesity is considered a modern disease, being one of the fastest growing pathologies in recent years, according to the World Health Organization (WHO).[10] Overweight and obesity are defined as an abnormal or excessive accumulation of fat, which can be harmful to health, and obese people have higher risk of developing health problems.

The percentage of overweight people rose from 42.7% in 2006 to 48.5% in 2011, while the percentage of obese people rose from 11.4% to 15.8% in the same period. The increased obesity and overweight affects both men and women. In 2006, about 47.2% of men and 38.5% of women were overweight, while in 2011 it rose to 52.6% and 44.7% among men. Overweight problems begin early and affect 29.4% of adults between 18 and 24 years old. In men aged between 25 and 34 years, prevalence of overweight is almost twofold, reaching 55%. From 35 to 45 years old, the percentage is 63%. Among women aged 18 to 24 years, 6.9% are obese. It is also observed that prevalence of obesity is almost twofold in women aged 25 to 34 years (12.4%) and nearly threefold between 35 and 44 years (17.1%). After 45 years old, the rate of obesity remains stable, reaching about a quarter of the female population.[11]

For some time, the cult of thinness has led individuals to a constant search for products to minimize or even eradicate the overweight and/or obesity problem, but the consumption of herbal medicines for weight loss has become an excessive practice mainly due to the lack of more conclusive information. [12] The cult of fitness leads individuals to consume products that contribute to weight loss but sometimes leads to improper use and unrestrained intake, without the supervision of a qualified professional.[13,14]

Among the treatments commonly used for obesity, there are those which diminish foods intake; those which alter the metabolism and others which increase thermogenesis, which are achieved with the use of synthetic or natural drugs such as herbal medicines.[15,16] It should also be mentioned the changes in dietary habits, the practice of physical exercises and surgical and psychological treatments.[17]

To fight obesity, there are numerous treatments, either via drugs (synthetic or semisynthetic) or *in natura* plants used as supplementary medicines.[18] Among alternative therapies to treat obesity, the following can be highlighted: floral, acupuncture, auriculotherapy, physical activity and phytotherapy.[19]

In 1978, WHO officially recognized the use of herbal medicines to treat obesity.[20] This was because 80% of the population use plants or preparations containing plants for medicinal purposes. In addition, the accessibility and low cost of herbal medicines compared to synthetic drugs contributed to strengthen and disseminate the use of phytomedicines. [18,20] In Brazil, policies for herbal medicines and phytotherapy date back to 1981, by means of the Administrative Rule no. 212, of September 11, issued by the Ministry of Health, which defines herbal therapy as one of the priorities of clinical research.[21]

Afterwards, in 1982, the Ministry of Health launched the Research Program for Medicinal Plants of the Medicine Center (PPPM/CEME), aiming to develop an alternative and supplementary therapy with scientific basis, in view of the pharmacological value of popular plants-derived medicines.[21]

According to the Resolution no. 48, of 2004, of the Collegiate Board of the National Drug and Sanitary Agency (ANVISA), phytomedicines are all medicines made exclusively from plants or parts of plants such as roots, bark, leaves, flowers, fruits or seeds, which have recognized properties for cure, prevention, diagnosis or symptomatic treatment of diseases, validated by ethnopharmacological studies, technical and scientific documentations or phase 3 clinical trials.[22]

Since 2007, with implementation of Resolution no. 402 of August 6, 2007 of the Federal Council of Nutritionists, nutrition professionals are allowed to prescribe herbal medicines and

magistral preparations as a supplement to dietetic prescription for oral use, either as *in natura* plant drugs or in their most diverse pharmaceutical forms, provided that the nutrition professional has a specialized degree on Phytotherapy. According to the same Resolution, prescription is not allowed for herbal medicines that are exempted from medical prescription, which are listed in the Resolution no. 89 dated March 16, 2004.[23]

The use of phytomedicines by health professionals and the acceptance of these medicines by the population has been growing every day and roughly 25% of the drugs prescribed worldwide have a plant origin.[19,23]

The aim of this paper was to show the importance of herbal medicines as an adjuvant to the treatment of obesity and weight loss, but is not intended to compare their effects with the synthetic drugs traditionally used for this purpose. Among the herbal medicines addressed in the present study are *Citrus aurantium* L., Camellia *sinensis* L. and *Carthamus tinctorius* L.

Methodology

A systematic literature review was carried out; search for articles was performed on *Pubmed*, *Science Direct* and *Scielo* databases about the use of "*Camellia sinensis*", "*Citrus aurantium*" and "*Carthamus tinctorius*" phytomedicines for treatment of obesity. The descriptors used in the search were: *"phytotherapy"*, *"obesity"*, "*emaciation"* and *"lipolysis"*, in accordance with the health sciences descriptors (DeCS).

As criteria for inclusion, studies relating herbal medicines with weight loss and pharmacological action for obesity control or reduction were selected. In the study, it was also included *in vivo* researches on the use of herbal medicines with results on loss weight for each herbal medicine related to obesity.

The articles were organized according to the database and keywords, and then quantified, considering the period between 2000 and 2014. Studies that did not have pharmacological data on plants, specifically "*Camellia sinensis*", "*Citrus aurantium*" and "*Carthamus tinctorius*", and which were out of the above cited period of time were disregarded.

The data were analyzed and graphed for better observation using the Microsoft Excel software, version 2013®.

Results and Discussion

The search conducted on the databases resulted in the following number of articles published from 2000 to 2014: *PubMed* (19 articles), *Science Direct* (04 articles) and *Scielo* (02 articles), respectively, as shown in Fig. 1.

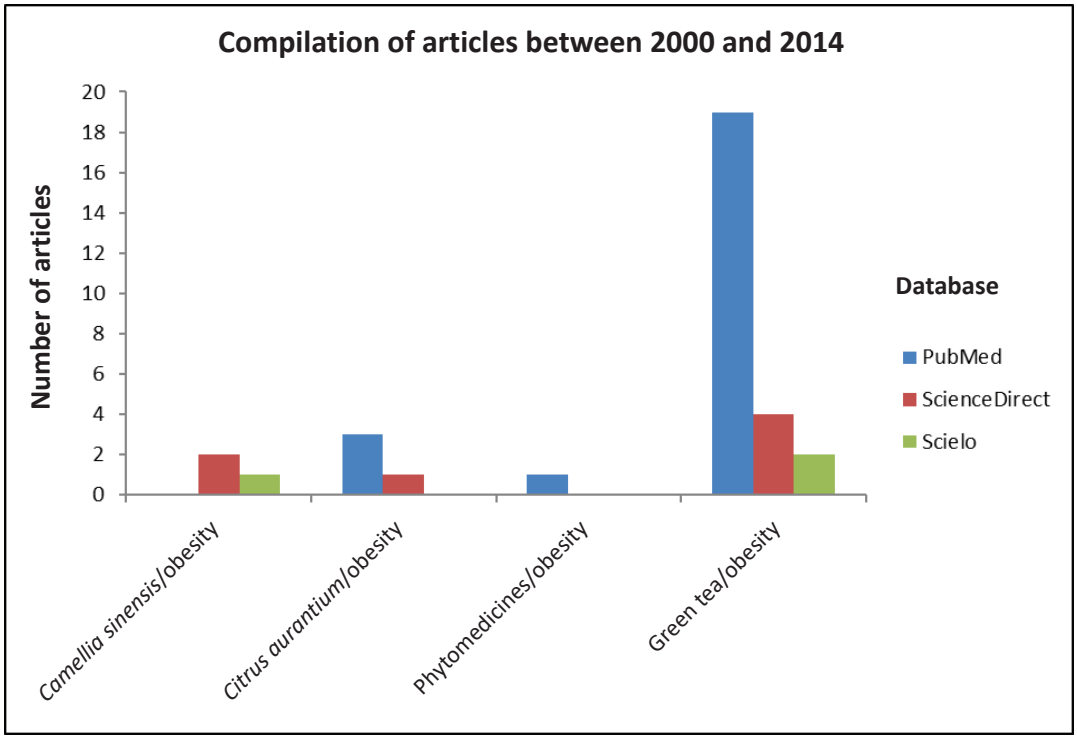


Figure 1. Compilation of articles based on the *Camellia sinensis*, *Citrus aurantium*, obesity, phytomedicines and green tea descriptors published in the period of 2000 to 2014 on *PubMed*, *Science Direct* and *Scielo* databases.

Camellia sinensis L.

Green tea, black tea, Chinese tea or English tea are different commercial types of products made with the leaves of *Camellia sinensis* L., which originated in the East, very popular in China, India and Japan. Tea made from this plant is one of the most consumed beverages in the world. Belonging to the family *Theaceae*, it is a food that is consumed by the population especially as a medicine, making it a functional food for many people.[21]

Cultural, social and economic influences intensify research works with plant extracts and their bioactive constituents. In this context, *C. sinensis* has been highlighted in various studies for their composition rich in phenolic compounds, which are powerful antioxidants.[18,24]

Depending on the production process used, their leaves are used for the production of three main kinds of teas: green tea, oolong and black tea, and the difference between them depends on the degree of inactivation of leaf enzymes during processing.[25]

Green tea is produced from fresh leaves of the plant after a quick inactivation of the polyphenoloxidase enzyme by vaporization and drying, which preserves the polyphenols and makes it richer in catechins compared to other teas. [25,26] The oolong or "partially oxidized" tea is obtained after letting the leaves stand for two to four hours and then heat them to stop the oxidation process. Black tea derives from leaves that aged by aerobic catechins oxidation, enzymatically catalyzed.[26]

Fresh leaves of the *Camellia sinensis* plant, from which green tea is made, have a high amount of flavonoids, known as catechins.[27,28] Among them, the main ones are: epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG), the latter being the most abundant in green tea and which attracts more interests. In addition, they have antioxidants such as polyphenols, manganese, potassium, folic acid, vitamin C, vitamin K, vitamin B1 and B2.[29]

The use of *C. sinensis*-based products has grown significantly in recent years, and there are reports of numerous severe side effects associated with the use of this herbal medicine. As an example, the Spanish Medicine Agency decided to ban the sale of "Exolise, an ethanol dry extract of *Camellia sinensis*", following notification of four cases of hepatotoxicity associated with the extract.[30,31] This product was used as an aid program in weight loss treatments, and the Spanish drug and sanitary system began to demand from all health professionals special attention to detect and characterize potential health problems that the use of this herbal could cause.[31-33]

Green tea catechins (GTC) are polyphenolic compounds present in unfermented dry leaves of the C. *sinensis*. Test results showed that the intake of GTC can reduce body weight. The hypothesis is that GTC influences the activity of the sympathetic nervous system (SNS), enhancing energy expenditure and causing fat oxidation.[34,35]

Caffeine, which is naturally present in green tea, also influences the SNS activity and can act synergistically with GTC to enhance energy expenditure and fat oxidation. Other possible alterations were: reduced appetite, increased regulation of enzymes involved in hepatic fat oxidation and diminished nutrients absorption.[35]

Study with human cells culture showed that the green tea components and caffeine enhance lipid oxidation and thermogenesis, thus leading to an increased energy expenditure, probably due to the synergistic effect between the molecules.[28]

Researchers demonstrated an increase in energy expenditure, a reduction of the 12-hour respiratory quotient and an increase of urinary excretion of noradrenaline in humans who consumed green tea extract, containing 90mg of epigallocatechin gallate (EGCG) and 50 mg of caffeine. [36] However, the same 50-g amount of caffeine, when administered alone, did not have an effect on the 24-h energy expenditure.

Therefore (Fig. 2), the most abundant flavonoid in tea – epicatechin gallate – stimulates lipid oxidation and thermogenesis.[29,35]

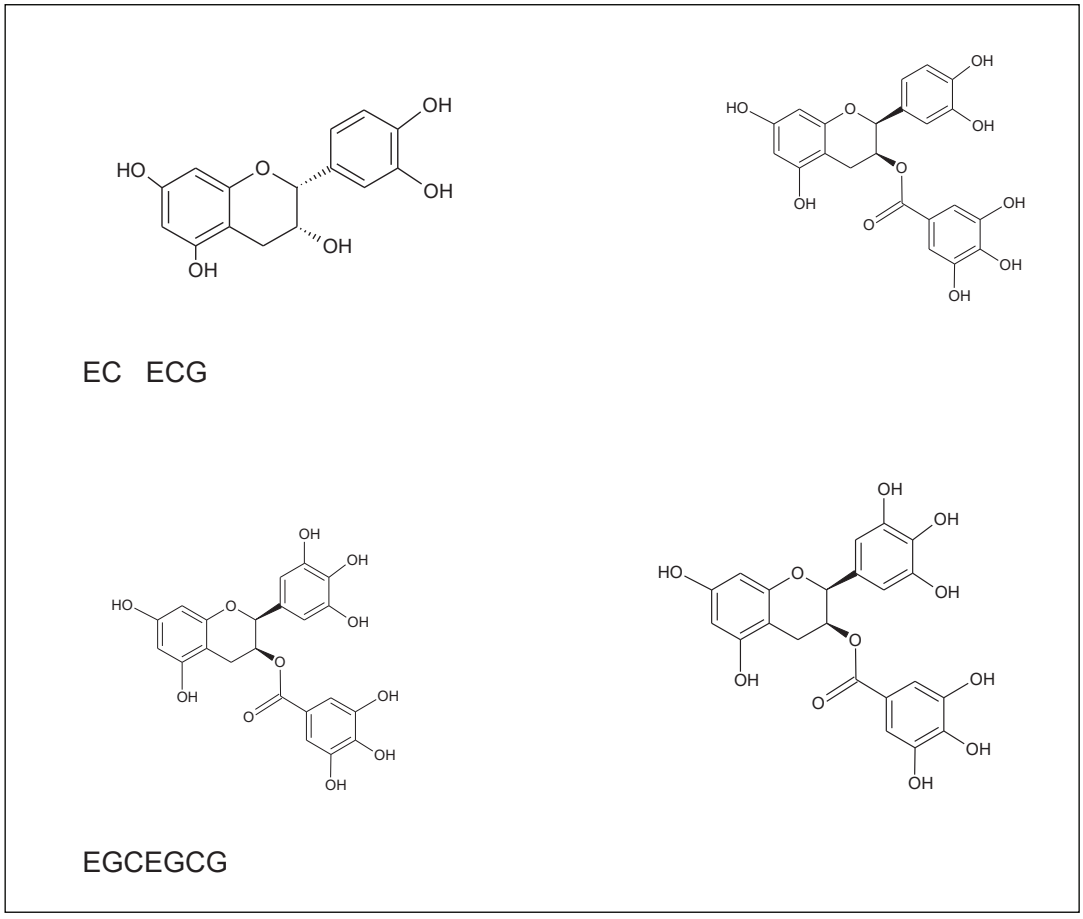


Figure 2. Epicatechin (EC), Epicatechin gallate (ECG), Epigallocatechin (EGC), Epigallocatechin gallate (EGCG).

Source: adapted from Alfonso (2004).[29]

In other study using epigallocatechin gallate associated or not with caffeine, thermogenesis was triggered in cells of brown adipose tissue (BAT) of *Sprague Dawley* strain rats. The results showed that treatment based on epigallocatechin alone, in doses of 200 μM, increased oxygen intake by the BAT.[36] However, when 100 μM of caffeine was added to this EGCG concentration, oxygen intake was even greater than just as an isolate phytotherapeutic agent. However, treatment with just 100 μM of caffeine did not have any effect.[35,36]

The thermogenic effects of green tea would result in synergistic interactions between catechins, caffeine and noradrenaline (Fig. 3). Catechin would inhibit the hepatic catechol-o-methyltransferase (COMT), an enzyme responsible for degrading noradrenaline in the synaptic cleft, prolonging its effect. C-AMP, a second intracellular messenger for noradrenaline-mediated thermogenesis, prolongs its effect on the cell, increasing consumption of ATP, as it is known that c-AMP is caused by the degradation of ATP, which contributes to higher energy expenditure.[36]

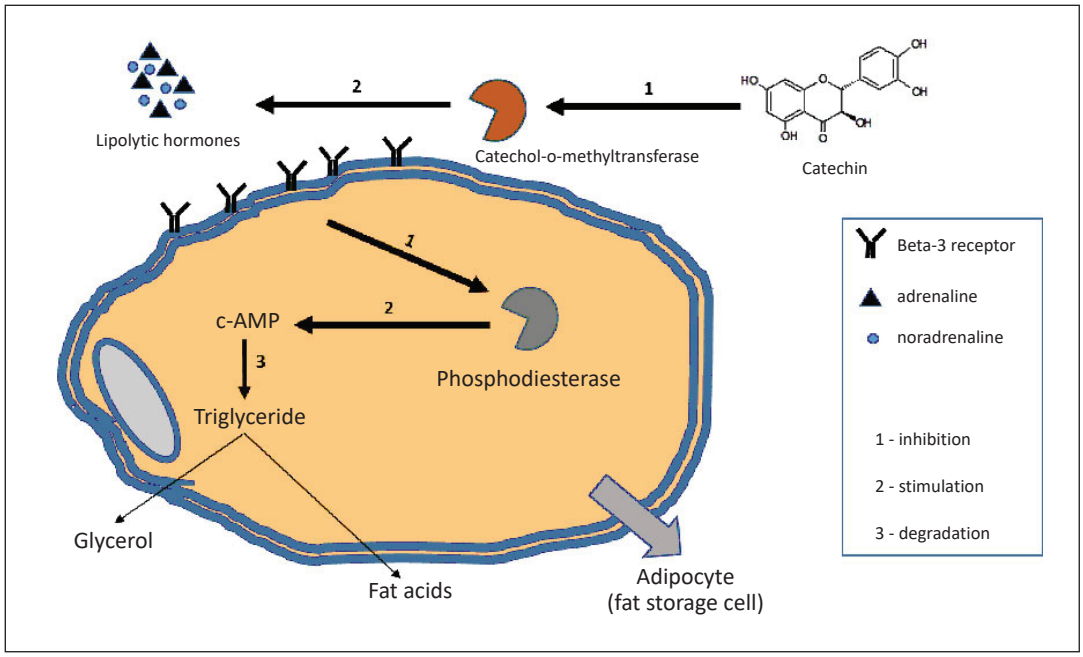


Figure 3. Catechin inhibits catechol-o-methyltransferase (COMT), an enzyme responsible for degrading noradrenaline in the synaptic cleft, prolonging its effect on the cell. The c-AMP is the second intracellular messenger for noradrenaline-mediated thermogenesis.

Source: Dulloo et al.[36]

In another study, it was found that the association of caffeine and green tea (25 mg of caffeine), 45 mg of epigallocatechin gallate and 380 mg of placebo induced weight gain prevention or limitation, with a variation of 5 to 10% in obese individuals. [37] On the other hand, weight loss with a treatment with 300 mg/day of caffeine alone was more effective as well as in maintaining the body mass of the individuals that participated in the study. Weight regain was also observed in cases where probably there was a reduction of sensitivity to caffeine and a relation with the saturation of the enzymatic system via leptin.

Another study showed the relationship between body fat and green tea intake. According to the study, of 1103 individuals assessed, about 43% were regular consumers of green tea and exhibited a smaller amount of body fat and lower waist-to-hip ratio compared to individuals who did not consume green tea regularly. This result was more effective in individuals who have consumed green tea for more than ten years. [38]

In another research work, the researchers evaluated the effects of oolong tea, which has large amounts of catechins.[39] It was a 12-week double-blind study where Japanese individuals drank one bottle of oolong tea/day containing 690 mg of catechins, and the control group drank one bottle of oolong tea/day containing only 22 mg of catechins. The control group exhibited less satisfactory results compared to the group that consumed oolong tea extract. This group exhibited a reduction of skinfolds, of subcutaneous and overall body fat as well as a decreased waist circumference and reduced rates of oxidized LDL.[39]

Similar studies were conducted with animals (*Cherry Valley* ducks), in which a reduction of the subcutaneous fat thickness, intramuscular fat width, as well as a reduced production of abdominal fat and triglycerides in serum were observed.[38]

Studies with cells suggest that green tea can reduce glucose absorption and fat by inhibiting digestive enzymes.[27] Green tea extract (AR25) inhibited marked digestive lipases *in vitro* and might reduce fat digestion in humans. [40]

In a research work with methanolic extract from flower buds of *Camellia sinensis*, the researchers reported an inhibitory effect on body weight gain and visceral fats in diabetic mice (TSOD - *Tsumura Suzuki Obese Diabetes*) fed a high-fat diet.[41] In this study, the researchers suggested that the anti-obesity effect also occurred due to chakasaponin II and the n-butanol fraction, which inhibited gastric emptying and food intake due to suppression of mRNA levels of neuropeptide Y, acting on energy expenditure in the hypothalamus by means of sensory nerves, probably vagal afferent nerves, or enhancement of 5-HT release, with consequent reduction of fat intake and body weight gain.

Citrus aurantium L.

Citrus aurantium is commonly known as bitter orange, sour orange, bigarade orange or Seville orange tree. Its leaves, flowers and fruits have been used as herbal medicine to treat some disorders such as insomnia, anxiety, and as an anticonvulsant medicine.[42,43]

C. aurantium is used since the medieval times in the Mediterranean region as a sedative, cholagogue, cardiac and digestive stimulant, and as an antidote against poisons. It is found in warm tropic regions in both hemispheres.[44]

Currently, there has been a growing interest on the green fruits of *C. aurantium* due to its weight-loss nature in plant-based products.[45,46] Extracts from immature fruit of *C.aurantium* are often used for weight loss but are reported to produce adverse cardiovascular effects, which are smaller if compared to the benefits regarding weight loss, due to stimulation of B-3 receptors of the adipose tissue and liver, and its antispasmodic, sedative and hypnotic effect.[46,47] Furthermore, in tests with administration of C. *aurantium* and *Rhodiolarosea* resulted in a rise of the hypothalamic norepinephrine levels and in the frontal cortex dopamine, results that suggest that treatments with *C. aurantium* with *R. rosea* have actions on central monoamine pathways and have the potential to be beneficial in obesity treatments.[47]

Immature dry fruits of *C. aurantium* contain nearly 10% of flavonoids and five adrenergic amines: synephrine, hodermine, octopamine, tyramine and N-methylthyramine.[45,46] Of these amines, synephrine stands out: it is sold in its synthetic form, developed as a sympathomimetic agent, being a α-adrenergic agonist with some β-adrenergic properties called oxedrine.[45] Sometimes it is used at higher dosages, similar to the use of high doses of ephedrine via intravenous route for asthma outbreaks.[47,48]

In nature, synephrine occurs in all citrus products derived from *Citrus* sp., Rutaceae, including juices, and is consumed in small amounts if citrus-derived products are included in the diet.[49]

Synephrine is a substance present in *C. aurantium* L. extract, having an effective thermogenesis property and similarity with the alkaloids of *Ephedra sinica* such as ephedrine. [50] Studies indicate that adrenergic amines of *C. aurantium* L., as is the case of synephrine, cause little or no effect at all on the central nervous system and/or cardiovascular system.[16,47,49,50]

Tests conducted with female S*prague-Dawley* rats using 95% synephrine extract during 28 days showed minimal effects on heartbeat and blood pressure. With addition of caffeine, increase of heart rate and blood pressure was more pronounced, suggesting that other botanic components may alter these physiological parameters.[51]

The extract of *C. aurantium* L. enhances the metabolism without affecting the heart rate or blood pressure, because recent researches confirm that this extract stimulates only the β-3 adrenergic receptor, preventing negative side effects on the cardiovascular system.[51,52]

Synephrine (Fig. 4) is a substance used for treatment of obesity due to its ability of connecting to β-3 adrenergic receptors in specific cell sites that regulate fat loss.[47,52]

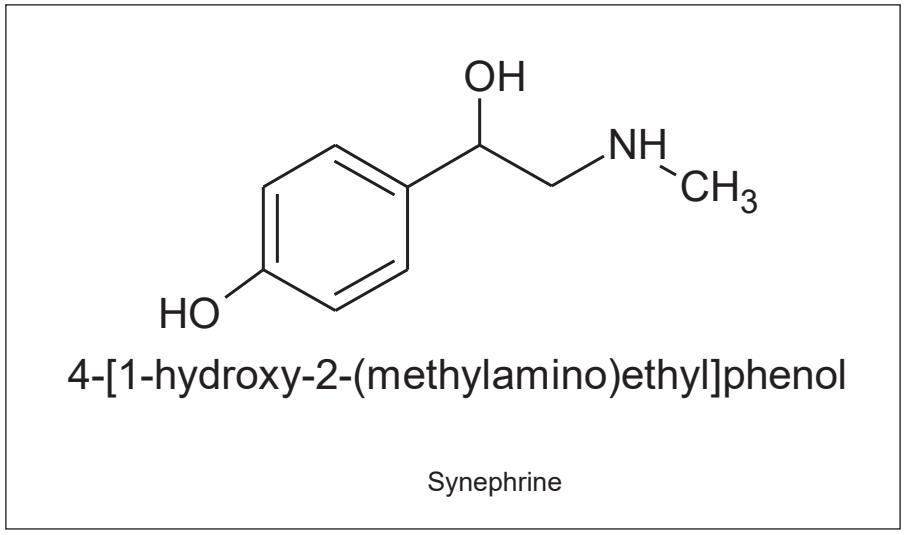


Figure 4. Synephrine chemical structure

The β- 3 adrenergic receptors accelerate lipolysis and enhance basal metabolism through thermogenesis. Few are the substances capable of activating directly the β-3 adrenergic receptors, without acting on α-1, α-2, β-1, β-2 receptors, which are related to blood pressure and heart rate.[50,53,54]

The β-3 adrenergic receptors are present in different cells, acting on diverse functions, among them modulation of hormones release, metabolic control and cardiovascular regulation.[54,55]

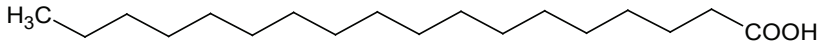
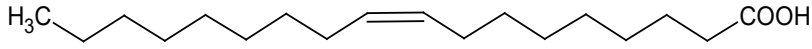
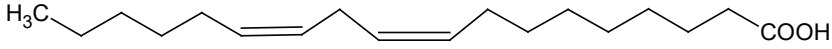
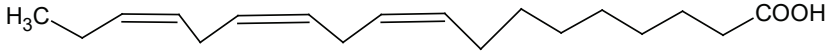
In adipocytes, it has been reported that β-3 adrenergic receptors play a role in leptin release.[50,56] In addition, the balance between lipogenesis and lipolysis is associated with the stimulation of α and β-adrenergic receptors, respectively.[53,54]

Carthamus tinctorius L.

Safflower, *Carthamus tinctorius L.*, belongs to the family *Compositae* and *Asteraceae*, and is an herbal plant originated from Asia and Africa. Its flowers have a red colorant called carthamin, widely used for dyeing fabrics, and the yellow colorant is very used for cooking (Table 1). Dissemination of the species is made with the seeds, from which oil is obtained,[57] and production increased in the last 30 or 40 years for use in human foods.[58]

Among the vegetable oils, safflower oil is one of the most common. The seeds are rich in omega 6 linoleic acid (around 70%), and omega 9 oleic acid (around 20%).[59]

Table 1. Chemical structure of vegetable oils: omegas 3, 6 and 9, and stearic acid.

Substance	Chemical structure
Stearic acid C18:0	
Oleic acid C18:1 Omega 9	
Linoleic acid C18:2 Omega 6	
Alfa-linoleic acid C18:3 Omega 3	

Source: Adapted from Fan et al.[59]

Safflower seeds have been used in Korea as a substance that promote bone formation and in the prevention of thrombi development by lowering blood viscosity. The flowers have been widely used in treatment of cardiovascular, cerebrovascular and hepatic diseases and more rarely in gynecological problems. [38,59-61]

Safflower oil, through the linoleic acid, reduces body fat by inhibiting the lipoprotein lipase (LPL), an enzyme responsible for transferring the lipids present in the blood current into the adipose cells. These cells are responsible for storing body fat and make up the adipose tissue of the human body.[62]

The more expressive the activity of LPL, the greater the number of lipids stored in the adipose cells, thus increasing the volume of the adipose tissue. By blocking the action of LPL, transfer of the lipids into the cells is also inhibited, forcing the body to use the existing fat store as a source of energy for the muscular activities, causing the lipolysis process.[62,63]

The linoleic acid increases the activity of an enzyme present in the body, the carnitine-palmitoyl-transferase (CPT). This enzyme is present in the voluntary-contraction skeletal muscles, such as the biceps, being responsible for the mobilization of lipids in the form of fatty acids into the mitochondria, in order to achieve β-oxidation, which increases the amount of energy that will be provided to the cell with consequent reduction of the fat stores.[64,65]

The oleic acid, known as omega 9, primarily found in olive oil, helps control hunger and body weight. Studies conducted by the University of California in the United States demonstrated that the oleic acid stimulates the production of the oleoyilethanolamide lipid, an appetite suppressant substance, thus increasing weight loss and reducing LDL.[62]

Based on the compiled information found in the articles of this review, table 2 was prepared, containing information on the chemical components such as alkaloids (synephrine), in some phytomedicines, as well as their indications, contraindications and other information for the health professional, as auxiliary instruments for body weight reduction.

Table 2. Summary of the information relating to the phytomedicines presented

Scientific name: *Camellia sinenses* L. Part used: leaves Active ingredients: antioxidants, polyphenols, flavonoids, catechins. Effects: inhibition of hepatic catechol-o-methyltransferase Indications: asthma, physical ad psychic asthenia, weight loss supplement, prevention of cardiovascular diseases. Posology: infusion: 1 dessert spoon per cup, infusing for 10 minutes: 50 to 100 drops/ dose, take 3 times/ day; powder: 0.8 to 1.6 g/day. Side effects: nervousness; insomnia and tachycardia may occur. Contraindications: gastritis, duodenal ulcers, insomnia and tachycardia.
Scientific name: *Citrus aurantium* L. Part used: fruit Active ingredientss: adrenergic amines: synephrine, N-methyltyramine, hordenine, octopamine and thyramine. Effect: specific action on β-3 adrenergic receptors. Indications: weight loss diets; stimulates weight loss and increases muscular mass. Posology: limited to 1600 mg per day divided into 5 times maximum; take always before main meals: lunch and dinner. Side effects: not found Contraindications: Pregnant women and infants.
Scientific name: *Carthamus tinctorius* L. Part used: seeds Active ingredients: monounsaturated and polyunsaturated fatty acids such as omega 6 linoleic acid and omega 9 oleic acid. Effects: inhibition of lipase lipoprotein enzyme (LPL). Indications: antioxidant and weight loss. Posology: 0.3 to 1.5 g/person/day, depending on sex and intake of animal and vegetable foods. Side effects: discomfort, abdominal pain and dyspepsia. Contraindications: pregnant and nursing women.

Source: Adapted from Olszewer.[65]

Conclusion

Either overweight or obesity can pose high risks to human health. This paper proposed a compilation of data relating to three phytomedicines largely used in the control and prevention of obesity.

It was possible to observe that *Camellia sinensis, Citrus aurantium* and *Carthamus tinctorius,* and their associations with caffeine, can promote weight loss, since caffeine is more effective in lipolytic processes due to the synergetic activity on the adipose tissue. Therefore, the herbal medicines herein described can be alternatives for treatment of overweight or obese individuals and can only the prescribed by qualified professionals, having previous knowledge on physicochemical and pharmacological properties.

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