IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 20, Issue 3 Ser. 4 (May. – June. 2025), PP 39-52
www.iosrjournals.org

Effect of the Phytotherapeutic Citrus Aurantium L. On Adipose Tissue

Ruiz-Silva, C [1]; Ruiz-Silva, CR[2]; Paula-JR, O[3]
[1](*Department, College/ Faculdade Facop,* PHd, MSc, PT, Brasil).
[2](*Department, College/ Faculdade Facop,* Pharmaceutical, Brasil).
[3](Centro Universitario *ETEP,* Graduating in Aesthetics and Cosmetology, Brasil).

Abstract: *Weight loss, although still seen as an aesthetic necessity by most people, is something much more worrying in the present day. Weight gain is related to the development of diseases, which has already become a global concern in the coming years. However, physical activity has been greatly reduced in modern societies, especially in groups with lower socioeconomic status. In developed countries, most occupations are low-energy and physical activities associated with leisure differentiate the most active groups from the least active.*
The uncontrolled use of dietary supplements indicated for weight loss and achieving greater muscle definition has triggered great concern. Among these products, those containing ephedrine (from Ephedra sinica) stand out. Due to the association with heart problems, ischemia and hypertension, some countries have banned the sale of supplements containing these alkaloids, which have been replaced by synephrine (Citrus aurantium). Currently, journals have published reports on the use of C. auratium as a weight loss aid, referring to it as a product that stimulates metabolism and that, unlike ephedrine, does not cause any effect on the cardiovascular system, even though it is claimed that it increases the release of adrenaline.
Therefore, given the high obesity rate in Brazil, the indiscriminate and harmful use of controlled medications that cause adverse effects and chemical dependency, and the new global trend towards healthy living using phytotherapy as a complementary medicine, we present in this paper the beneficial effects of Citrus aurantium on adipose tissue.
Citrus aurantium L., commonly known as sour or bitter orange, can be exceptionally distinguished from other Citrus species by unique characteristics. It is a fruit with a distinct flavor, rich in nutrients and phytochemicals that have different health benefits. This article presents an overview of the most recent studies done on the subject. It aims to provide an in-depth understanding of the biological activities and medicinal uses of the active constituents existing in C. aurantium.
Objective*: Demonstrate the use of Citrus auratium in the treatment of obesity, as it is one of the most serious public health problems, which has been growing in recent decades.*
The interest of individuals in green fruits of C. auratium (bitter orange), due to the toxicological problems of the use of synephrine.
Justify the use of Citrus Auratium by the nutraceutical industry to replace ephedrine with synephrine in food supplements, and the similarities between the chemical structures of amines.
Conclusion: *Obesity is one of the most serious diseases that increases every year, becoming a problem in Public Health today, and the number of people looking for alternatives to lose weight has increased, with dietary supplements (phytotherapeutics). Citrus auratium contains synephrine, a substance similar to ephedrine (Ephedra sinica), which is much safer and more effective, as an aid in weight loss, referring to it as a product that acts on the metabolism, acting on the release of adrenaline and noradrenaline along with beta-3 receptors, which are mainly found in adipose tissue and the liver. Stimulating these receptors triggers the lipolysis process. At the same time, it promotes an increase in the metabolic rate (thermogenesis), burning a greater amount of body calories.*
Key Word*:* ***Key words****: Food supplements, Citrus auratium, and Obesity, synephrine, nutraceuticals, phytotherapy.*

Date of Submission: 25-06-2025 Date of Acceptance: 05-07-2025

I. Introduction

Integrative and Complementary Practices fall under what the World Health Organization (WHO) calls traditional medicine and complementary and alternative medicine (TM/CAM). On this topic, the WHO recommends that its member states develop national policies aimed at integrating/inserting TM/CAM into official health systems, with a focus on Primary Health Care (PHC).

In Brazil, in line with WHO recommendations, the National Policy for Integrative and Complementary Practices in the SUS (PNPIC) was approved in 2006, covering, among others, guidelines and institutional responsibilities for implementing/adapting actions and services of traditional Chinese medicine/acupuncture, homeopathy, medicinal plants and phytotherapy, in addition to establishing health observatories for social thermalism/crenotherapy and anthroposophic medicine in the Unified Health System (SUS).

Citrus aurantium L. is known as bitter orange, originating in Asia, and belongs to the Rutaceae family, one of the important alternatives for treating obesity, which is an exponential factor in becoming a public health problem. Many times, in the desire to obtain ideal physical shape, people end up using therapies without proof of safety and efficacy, and without medical supervision (De SMET, 2004). Among the pharmacological treatments for obesity, the following three groups are distinguished: (1) those that reduce food intake, (2) those that alter metabolism, (3) those that increase thermogenesis (BRAY and RYAN, 1997).

In Brazil, ephedrine-based formulations have not been banned, but they are part of the list of substances that are precursors of narcotics (Brasil, 1998). However, following the global trend, a large number of formulations have been observed on the Brazilian market, including imported food supplements containing C. auratium or p-synephrine.

Weight loss, although still seen as an aesthetic necessity by most people, is something much more worrying in the present day. Weight gain is related to the development of diseases, which has already become a global concern in the years to come. However, physical activity has been greatly reduced in modern societies, especially in groups with lower socioeconomic status.

Since the 1980s, the body has become a fashionable topic. Women's identity increasingly seeks a better quality of life to adapt to the new demands of modern daily life. In addition, women have become increasingly concerned with appearance, aesthetic values and health. According to Russo (2005), for a long time, beautiful women had rounded shapes and were a source of inspiration for many Renaissance painters. This is a huge shock for the standards of the late 20th and early 21st centuries.

In developed countries, most occupations require low energy expenditure and physical activities associated with leisure differentiate the most active groups from the least active. Various studies also show that a sedentary lifestyle is more common among women, the elderly and individuals with lower levels of education (CRESPO et al., 2000; MISIGOJDURAKOVIC et al., 2000; MMWR, 2000). Evidence suggests that a large part of obesity is due to low energy expenditure rather than high food consumption, while physical inactivity in modern life appears to be the major etiological factor in the growth of this disease in industrialized societies. The 20th century was clearly marked by a progressive sedentary lifestyle, which led to extremely high prevalence rates throughout the world, even in more advanced countries, where it reached 40-60% of the population, as well as in our country, where estimates by Rego and Col (1990) indicate rates of approximately 70% (69.3%), being higher among women than men. Furthermore, a natural reduction in energy expenditure is observed with modernization, leading to a more sedentary lifestyle with motorized transportation and mechanized equipment that reduce the physical effort of men and women both at work and at home. Currently, few activities are classified as very active, whereas a few decades ago, several activities had this characteristic. Some more informal surveys conducted by some public opinion research companies such as DATA FOLHA and IBOPE have included the physical activity profile in Brazil.

Continuous trends of increasing obesity have been observed in all socioeconomic and geographic strata of the Brazilian adult population, with the exception of the higher-income adult female population in the Southeast region of the country, where, recently, there seems to have been a decline in the problem. In fact, the trends of increasing obesity have been more pronounced in the lower-income population strata; on the other hand, there has been a decrease in excess obesity in the higher-income strata. In the specific case of the adult female population of the Southeast Region, the prevalence of obesity in the stratum corresponding to the 25% with the lowest family income (14%) is already twice as high as the prevalence in the stratum of the 25% with the highest income (7%).

We live in a world beset by two epidemics: sedentary lifestyle and obesity, known as “globesity”. Both are the consequences of multiple factors. One of the factors responsible for the higher prevalence of excess weight and obesity is undoubtedly sedentary lifestyle or insufficient regular physical activity. While obesity has long been accepted as a cardiovascular risk factor, it was only recently, more precisely in 1992, that the World Health Organization, based on the position of the American Heart Association, began to consider physical inactivity as an independent risk factor (MATSUDO, S.; MATSUDO, V., 2007). A sedentary lifestyle is the primary characteristic of most individuals with a body weight above normal (SALLIS et al., 1995). This sedentary behavior

appears to be one of the main causes of excess fat, and, on the other hand, obesity appears to lead to a decrease in the individual's levels of physical activity. 8 The increasing prevalence of overweight and obesity observed in different regions of the world and in various social segments, not only in rich countries but also in developing countries, has caused great concern among health authorities and the general population (WHO, 1998). These nutritional problems are risk factors for several diseases throughout the lives of individuals. They are related to arterial hypertension, hyperlipoproteinemia, coronary heart disease, narial, osteoarticular, diabetes mellitus and some types of cancer (WHO, 1998). According to Silva (2004):

OBESITY

There is confusion about the real meaning of the terms overweight and obesity. However, research and discussion among the various areas of health indicate a need to differentiate the terms. MCArdle et al. cited by Monteiro (2007) define obesity as the excessive accumulation of body fat, being a heterogeneous disorder with a common end in life in which energy intake chronically exceeds energy expenditure. For Guedes and Guedes (cited by MONTEIRO, 2007), obesity is considered an excessive accumulation of fat in adipose tissue, regionalized or throughout the body, triggered by a series of factors associated with environmental and/or endocrine-metabolic aspects. Overweight is body mass that exceeds the average for height and perhaps for a given age (MCARDLE et al. apud MONTEIRO, 2007, p.21).

Overweight is often accompanied by an increase in body fat, with the exception of athletes. However, it may or may not coincide with some pathologies such as glucose intolerance, insulin resistance and hypertension. Another definition for overweight is the excessive increase in total body mass, which may occur as a consequence of changes in just one of its constituents (fat, muscle, bone and water) or in all of them (GUEDES; GUEDES apud MONTEIRO, 2007).

As already mentioned, there is a basic difference between overweight and obesity. In obesity, it can be defined as the body weight as a whole exceeding certain limits, and in the second case, it is the condition in which only the amount of body fat 12 exceeds the desired limits. There are cases in which individuals can be considered heavy and not fat due to muscle and bone development (lean mass) and not due to excess fat, which does not compromise their health status, and there are other cases in which individuals with lower body weight have a certain amount of fat that compromises their health status due to muscle and bone deficiency. (GUEDES; GUEDES apud SALVE, 2006, p.32).

Obesity is a chronic disease characterized by the excessive accumulation of adipose tissue in the body. Its prevalence has been increasing sharply in recent decades and the costs of its complications reach billions of dollars. Obesity is considered when, in men, there is more than 20% fat in the body composition and, in women, more than 30%. (SEGAL; FANDIÑO, 2002). In clinical practice, most studies and the World Health Organization (WHO) classification use the Body Mass Index (BMI), calculated by dividing body weight in kilograms by the square of height in square meters (weight/height²).

According to the U.S. Public Health Service, obesity has become an epidemic. Approximately 20% of the adult population is obese to a degree that directly affects their health and life expectancy. Currently, 1/3 of the population is overweight, and this trend has been increasing in recent decades, especially among the elderly (WHO; MONTEIRO; GOFIN; ABRAMSON; EPSTEIN, cited by CABRERA; JACOBI FILHO, 2001).

Determining factors

Obesity is determined by several factors, such as genetic factors, which determine that children's obesity is inherited from their parents' genotype, inadequate lifestyle, such as poor diet, emotional problems that alter organic functioning, low level of physical exercise, socio-cultural, ethnic and endogenous factors such as hormonal or organic problems (SOUZA, 2005; MELO; TIRAPEGUI; RIBEIRO, 2008). According to McArdle (2003), a series of co-morbidities, called obese syndrome, can also be cited, which is related to obesity: glucose intolerance, insulin resistance, type 2 diabetes, hypertension, high plasma concentrations of leptin, increased visceral adipose tissue, increased risk of cardiovascular diseases and cancer. Genetic factors, such as heredity, could increase weight gain in obese individuals. Body mass can be seen as the end result of the complex interaction between a person's genes and environmental influences, rather than simply being the consequence of psychological factors that affect eating behaviors.

The genetic framework does not necessarily cause excessive fat gain, but in the presence of powerful environmental influences, it lowers the threshold for the development of this condition and contributes to

variability in weight gain among individuals fed daily caloric excesses (MONTEIRO, 2007). Salve (2006) explains that the components that cause variations in determining body weight are: muscles, bones and fats. The changes that occur in these components are due to growth and aging factors, diet, physical exercise and diseases.

Of the determining factors of obesity, two of them are clearly defined in the explanation of a positive energy balance: an increase in energy intake or a decrease in energy expenditure (MATSUDO, S.; MATSUDO, V., 2007). Physical inactivity and inadequate nutrition result in a positive energy balance, which ultimately means an increase in body weight. The complexity of body weight regulation represents one of the greatest challenges for understanding the etiology, treatment and prevention of obesity. (MELO; TIRAPEGUI; RIBEIRO, 2008). Hill et al. (cited by MATSUDO, S.; MATSUDO, V., 2007, p. 15), explain in their proposal that the increase in body fat and BMI can be explained by the change in energy balance due to a decrease in expenditure, as a consequence of the decrease in daily physical activities and an increase in sedentary behavior, as well as an increase in consumption, due to the increase in the size and quantity of fat consumed in the diet. According to the International Association for the Study of Obesity, man in the pre-industrial period maintained a subsistence ratio of 3:1 regarding caloric intake and energy expenditure. However, today, this subsistence ratio has increased to 7:1, largely due to the dramatic reduction in physical activity (MATSUDO, S.; MATSUDO, V., 2007). 15 Matsudo, S. and Matsudo, V. (2007) also emphasize that: [...] it is important to note that this dramatic decrease in physical activity was caused more by the reduction in moderate activity than in vigorous activity, and of the moderate activities, walking suffered the greatest reduction. We no longer walk to visit friends, to work, or even to change the television channel. We have become sedentary, mainly because we have stopped walking!

Types of accumulation

According to Monteiro (2007): Adipose tissue is a form of connective tissue composed of cells (adipocytes) separated from each other by a matrix of collagen fibers and elastic fibers. Fat accumulates by filling existing adipocytes (hypertrophy) and through the formation of new adipose cells (hyperplasia). Normal, non-obese individuals increase their fat reserves from birth to maturity through a combination of hyperplasia and hypertrophy. Ribeiro (2005) explains the dynamics of adipose tissue, stating that body fat is an energy reservoir formed by cells called adipocytes, found in muscles, organs and, mainly, in skin tissue. Adipose cells store almost pure triglycerides (80-95% of their volume). These are mobilized and, consequently, renewed, in periods of two to three weeks. Fatty acids are absorbed into the lymph from the intestine (except short-chain fatty acids) because their stable chemical forms do not allow adhesion to the walls of the lymphatic system. After passing into the lymphatic system, they flow into the venous blood through the jugular and subclavian veins and, one hour after a high-fat meal, plasma concentrations of fatty acids can reach 1-2%. Their half-life is less than 1 hour, and they are rapidly hydrolyzed and stored. 16 Also according to Ribeiro (2005), confirming what was said previously: Adipocytes can increase their fat storage capacity (hypertrophy), as well as increasing the number of cells (hyperplasia). From 30 kg of body fat, increases in adiposity become greater due to the number of adipocytes, and not their size. According to Hermsdorff and Monteiro (2002), adipose tissue is a dynamic organ that secretes several factors called adipokines. These adipokines, in their vast majority, are related, directly or indirectly, to processes that contribute to atherosclerosis, arterial hypertension, insulin resistance (IR) and type 2 diabetes (DM2), dyslipidemias, that is, they represent the link between adiposity, metabolic syndrome and cardiovascular diseases. Among them, the following stand out: tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), activated plasminogen inhibitor-1 (PAI-1), C-reactive protein (CRP), resistin, acylation-stimulating protein (ASP) and factors involved in the renin-angiotensin system. In obesity, body fat deposits are increased, presenting high expression of adipokines, proportional to the greater volume of adipose cells. Hermsdorff and Monteiro (2002) also explain that, in addition to the different expression, a consequence of the increase in adipose tissue, the compartments of this tissue present different values of expression and secretion of adipokines. In general, visceral adipose tissue (VAT) is the most active, i.e., more sensitive to lipolysis via catecholamines and β-adrenoreceptors, and more resistant to the action of insulin, releasing a higher concentration of FFA directly into the portal vein. In addition, VAT secretes higher concentrations of adipokines linked to pro-inflammatory processes such as resistin, angiotensin I, resistin, PAI-1, CRP, IL-6, followed by abdominal subcutaneous adipose tissue (ASA) and gluteal-femoral subcutaneous adipose tissue (GFS). Other adipokines such as leptin and ASP are expressed in greater quantities in both abdominal and gluteal-femoral SAT, probably due to physiological differences between adipocytes in SAT and abdominal adipose tissue (AAT). 2.1.4 Classification According to Melo and Mancini (2009), the assessment of an obese individual consists of verifying the degree of obesity, investigating the etiology and diseases most commonly associated with obesity. It is now well known that not only quantitative excess fat, but also qualitative excess fat, in the form of visceral or central fat, will imply in compromising the individual's health and quality of life. Thus, two types of diagnoses can be established for an obese patient: a quantitative diagnosis, which refers to body mass or the amount of adipose tissue, and a qualitative diagnosis, which refers to

the distribution of body fat or the presence of visceral adiposity. Salve (2006) explains that the amount of body fat is divided into essential fat and reserve fat, which are essential components for the body to maintain its balance functions. Essential fat is found in bone marrow, heart, lungs, spleen, kidneys, and in lipid tissues spread throughout the central nervous system. Reserve fat is the fat accumulated in adipose tissue. Obesity can be classified as exogenous, caused by excessive caloric intake, accounting for more than 95% of cases, or endogenous, caused by hormonal and metabolic disorders. Another classification cited by Salve (2006) would be divided into four types: I (characterized by excess total body mass); II (excess fat in the abdominal and trunk-android regions) and III (excess visceral-abdominal fat) and type IV (excess gluteal-femoral fat). 18 Thus, Powers and Howley (2005) state that in addition to the distribution of adipose tissue, it is necessary to determine whether obesity results from an increase in the amount of fat in each adipose cell (hypertrophic obesity), an increase in the number of adipose cells (hyperplastic obesity) or both. In moderate obesity, in which the adipose tissue mass is less than 30 kg, it appears that the increase in adipose cell size is the main means of storing additional fat. Beyond this level, the number of cells is the variable most strongly related to adipose tissue mass. For Souza (2005), obesity is the result of consuming a greater amount of calories than the body uses, and can be classified into two types: Type I is gynoid obesity, which can be called peripheral, characterized by the accumulation of fat in the lower region of the body, in the hips and legs, and is more common among women; and Type II is android obesity, which can also be called central obesity, as it presents a greater accumulation of fat in the central region of the body, such as the abdomen and trunk, and is more prevalent in men. There are classifications according to fat distribution: android, known as central or apple-shaped obesity, which is the accumulation of fat in the trunk region; or gynoid, known as peripheral or pear-shaped obesity, which is the accumulation of fat below the waist, in the gluteal-femoral region (CYRINO; NARDO, 1996). Android, central or abdominal obesity is more frequently observed in men and gynecoid or femoral obesity is common in women, which indicates an estrogenic profile (KIRSCHENER et al., 1990). 19 For evaluation, it is necessary to characterize the obesity pattern: central (android or apple) or peripheral (gynecoid or pear). The risk of diseases is greater for people who accumulate fat in the abdominal region (central), around the viscera.

Mainly when BMI is above 27 and waist circumference is greater than 100 cm for men and greater than 90 cm for women, characterizing central obesity and increased risk of cardiovascular diseases, diabetes and several types of cancer (NAHÁS, 2001). 2.2 Epidemiology of excess weight in Brazil According to Monteiro (2007), in high-income countries, obesity mainly affects the less privileged population; In developing countries, the prevalence of obesity is higher in the population with higher income. However, in the Brazilian population, a higher incidence of obesity has recently been observed among the poorest. Cross-sectional studies on the relationship between the socioeconomic level of individuals and the presence of obesity are quite frequent in developed countries. A systematic review of these studies indicates that, in these countries, obesity tends to be more frequent in the strata of the population with lower income, less education and occupations of lower social prestige, and this trend is particularly evident among adult women (SOBAL; STUNKARD, 1989). In studies prior to the present, based on data collected by national surveys conducted in Brazil between 1975 and 1997, we found a tendency for the positive relationship between family income level and risk of obesity to weaken in the male population and a reversal of this relationship in the female population (MONTEIRO; CONDE, 1999; MONTEIRO et al., 2000a). 20 Applying multivariate analysis techniques to data collected in the survey conducted in 1997, they demonstrate that the level of education is the key variable that accounts for the inverse association currently found in Brazil between socioeconomic status and obesity in women (MONTEIRO et al., 2001). While in the first period (1975-1989), the risk of obesity increased at all levels of education, with the increase tending to be greatest for men and women with higher levels of education, in the second period (1989-1997), the increase in obesity was greatest for individuals without education, with stability or even a decrease in the disease being recorded in female strata with medium or high levels of education. As a result of the recent trend, the positive relationship between education and the risk of obesity in men has decreased and the inverse relationship that had already been observed in the female population has become more pronounced. In Brazil, nationwide surveys show that the prevalence of overweight and obesity has increased in the adult population in a differentiated manner between the sexes. In the period between 1974-75, obesity among men tripled and in the female population with a higher prevalence at the beginning of the period, there was a 50% increase in 2002-2003. This increase in the prevalence of obesity in women focused on the period from 1974-75 to 1989, when the first two nationwide surveys were conducted (National Family Expenditure Study and National Health and Nutrition Survey). Regarding overweight, women also began the period with a higher prevalence, but in 2002-03 the frequency of overweight was similar in men and women. 21 When analyzing the evolution of these prevalences in relation to socioeconomic level, there was an increase in the occurrence of obesity for all income categories among men and only among the poorest women.

On the other hand, among individuals with higher income, there was a decline in the prevalence of obesity and overweight. The association between these outcomes and lower education has also been observed in other populations in several countries. According to data from the Surveillance System for Risk and Protective Factors

for Chronic Diseases by Telephone Survey (VIGITEL, 2006), overweight is more prevalent among men and the prevalence of obesity was similar between men and women. However, overweight and obesity were more prevalent among older women (55 years or older). Prevalence of overweight and obesity increased with age up to 54 years among men, and 64 years among women. According to the information present in (VIGITEL, 2006), it was possible to make associations between some sociodemographic variables and overweight, observing that the prevalence of overweight was 12% higher among non-white women, when compared to white women. Among women, the effects of lower education and non-white skin color were greater for obesity than for overweight. Regarding the variable stable union, it was noted that men and women who lived in stable unions had a greater chance of being overweight. 2.3 Risk factors for excess weight and health implications According to Ades and Kerbauy (2002): Obesity is currently a matter of universal concern. It is considered a chronic, multifactorial disease characterized by the excessive accumulation of adipose tissue in the body. It is a risk factor for serious pathologies, such as diabetes, cardiovascular diseases, hypertension, reproductive disorders in women, some types of cancer and respiratory problems. Obesity can be the cause of suffering, depression and social avoidance behaviors, which impair quality of life. Terres et al. (2006) state that the consequences of obesity have been reported in several studies.

Excess fat on the health of adults has been associated with a greater occurrence of Diabetes Mellitus, hypertension, and increased triglycerides and cholesterol. In children and adolescents, this pathology is associated with the early onset of cardiovascular diseases, type 2 Diabetes Mellitus, psychological problems, in addition to compromising posture and causing changes in the locomotor system, and bringing socioeconomic disadvantages in adult life. Melo and Mancini (2009) explain that obesity is implicated as a triggering or aggravating factor for diseases in practically all organic systems, and its association with type 2 diabetes mellitus is well known (as previously mentioned, dyslipidemia, cardio and cerebrovascular diseases, coagulation disorders, degenerative joint diseases, neoplasias, hepatic steatosis, sleep apnea, etc.). In patients with morbid obesity, these diseases have a higher risk, with a significant increase in mortality (250% compared to non-obese patients).

These data, evidenced in several studies over the last few years, have led to a change in the medical attitude towards obese individuals, with care for the prevention and treatment of obesity being mandatory in good modern medical practice. Also according to Melo and Mancini (2009), obesity increases the risk of neoplasias, particularly breast, endometrial, gallbladder and prostate cancer. Excess weight triggers and aggravates degenerative joint lesions. Obese women are more likely to have infertility, pregnancy-specific hypertensive disease, and gestational diabetes. Psychological changes can be found in obese individuals more frequently than in the general population. In addition, eating disorders, such as bulimia nervosa and binge eating disorder, can be identified in some cases. 23 Obesity is considered one of the main risk factors for arterial hypertension (AH) in adults and children. Studies in animals and humans have demonstrated the potential of weight gain to raise blood pressure. Epidemiological studies report increases of three to eight times in the frequency of AH among obese individuals. Considering the hypertensive population, the prevalence of obesity is considerably higher when compared to normotensive individuals. In the Framingham study, 70% of cases of AH in men and 61% in women were were directly attributed to excess adiposity. The comorbidity of arterial hypertension associated with obesity, which, together with diabetes mellitus, dyslipidemia and atherosclerotic vascular disease, is part of the so-called metabolic syndrome, which includes “insulin resistance”. This condition has been defined as the state in which there is reduced tissue uptake of glucose in response to insulin stimulation, frequently accompanied by a compensatory elevation of circulating insulin levels. In particular, abdominal fat distribution has been implicated in the deterioration of tissue sensitivity to insulin and glucose tolerance and in the elevation of arterial pressure. There is information on the association of hypertension, glucose intolerance and dyslipidemia with obesity, as well as its impact on cardiovascular morbidity and mortality. Matsudo, S. and Matsudo, V. (2007) consider that the world today is being attacked by two epidemics: sedentary lifestyle and obesity, known as “globesity”, and explain that both are the result of multiple factors: While obesity has long been accepted as a cardiovascular risk factor, it was only recently, in 1992 to be precise, that the World Health Organization, based on the position of the American Heart Association, began to consider physical inactivity as an independent risk factor. This inexplicable delay in health authorities recognizing the impact of sedentary lifestyle on health may largely explain the reason for this sedentary lifestyle epidemic. It is important to note that in addition to being one of the causes of chronic diseases, such as diabetes, hypertension, hypercholesterolemia, osteoporosis, depression and, of course, obesity, sedentary lifestyle is also an independent cause of death. A recent WHO report 24 indicated that physical inactivity is responsible for 2 million deaths per year worldwide. 2.4 Pathophysiology of overweight and obesity Understanding the factors that influence energy balance is of fundamental importance for understanding the regulation of body mass. Energy balance is determined by energy intake and expenditure. When out of balance, these factors can lead to excessive accumulation or reduction of energy stored endogenously as body fat. More frequently, however, obesity is the most common result of an imbalance between energy intake and expenditure

(MEIRELLES; GOMES, 2004). Research on the pathophysiology of obesity generally follows two lines of approach: the physiological-biochemical line, in which variations in energy balance are studied; and the molecular biology line, in which specific genes that control the different determining factors of this energy balance are isolated.

However, cases of human obesity characterized by this monogenic inheritance are rare. The polygenic determination of obesity is due to changes that influence several factors, such as metabolic rate, appetite, and growth rate, which ultimately trigger obesity. These genetic predispositions to the development of obesity through high-energy-density diets are a more realistic and appropriate model for studying human obesity than the alteration of a single gene. The causes of obesity are linked to excessive energy intake, reduced expenditure or changes in the regulation of this energy balance. This results in a disorder of energy metabolism in which there is excessive storage of energy, in the form of triglycerides, in adipose tissue. According to Jebb (1999), obesity is not a single disease, but rather a heterogeneous group of conditions with multiple causes that ultimately reflect the obese phenotype. Positive energy balance, which occurs when the caloric value ingested is greater than the expenditure, is an important contributor to the development of obesity, promoting an increase in energy stores and body weight. The beginning of the maintenance of a positive caloric balance relative to the body's needs can be a consequence of either an increase in caloric intake, a reduction in the total caloric expenditure, or both factors combined. The literature indicates that not only the total energy intake and expenditure regulate the quantity of body stores, as proposed by Flatt (44,45) and accepted by many authors. The balance of each macronutrient appears to have a strict control to adjust its consumption with its oxidation (and vice versa) and maintain a state of equilibrium. Flatt (44) states that the balance of nitrogen and carbohydrates is facilitated by the body's ability to adjust the oxidation rates of amino acids and glucose, respectively, in relation to their food consumption. In the case of fats, this adjustment is much less precise and the increase in their consumption does not proportionally stimulate their oxidation. Furthermore, the efficiency with which the dietary lipid is stored as body fat is high, about 96%. The increase in lipid intake will induce a positive lipid balance and, consequently, the accumulation of body fat mass. 26 2.5 General benefits of physical training for health Physical activity can be defined as the body movements produced by skeletal muscles that result in energy expenditure. According to Bouchard et al. (1993), 15% to 40% of total energy expenditure and more than 50% of the variation in energy expenditure between populations (Willett, 1998) is associated with physical activity. According to Powers and Howley (2000), physical activity.

PHYTOTHERAPY

The use of nature for therapeutic purposes is as old as human civilization and, for a long time, mineral, plant and animal products have been fundamental to the health sector. Historically, medicinal plants have been important as phytotherapeutics and in the discovery of new drugs, with the plant kingdom providing the greatest contribution to medicines. The term phytotherapy was given to the therapy that uses medicines whose active constituents are plants or plant derivatives, and which has its origins in popular knowledge and use. The plants used for this purpose are traditionally called medicinal plants (DE PASQUALE, 1984). Therapy with medicines from plant species is reported in ancient medical systems around the world, for example, in Chinese, Tibetan or Indian-Ayurvedic medicine. Ayurveda (traditional Indian medicine) is perhaps older than all medicinal traditions and even older than traditional Chinese medicine. The civilizations of China and India were flourishing and already had numerous writings on medicinal plants, while modest sophisticated cultures were beginning to develop in Europe. The legendary emperor Shen Nung discussed medicinal plants in his works, which, through traditional Chinese medicine, were systematized and written down between 100 and 200 B.C. The most complete reference on Chinese herbal prescriptions is the Modern Day Chinese Encyclopedia of Materia Medica published in 1977. This work lists almost 6,000 medicines, of which 4,800 are of plant origin. As in other healing cultures, traditional recipes are used primarily for chronic diseases, while serious or acute illnesses are cured by Western medicines. The spread of traditional Chinese medicine to most continents has undoubtedly contributed to the current popularity of herbal medicines throughout the world. Examples of famous Chinese medicinal herbs are Angelica polymorpha var. sinensis (Danggui, Dongquai), Artemisia annua (qing ha), Ephedra sinica (ma huang), Paeonia lactiflora (Bai shao yao), Panax ginseng (ren shen) and Rheum palmatum (da huang) (ALONSO, 1998; CARNEIRO, 2001). In the history of Brazil, there are records that the first Portuguese doctors who came here, faced with the scarcity of medicines used in Europe in the colony, were forced very early on to realize the importance of plant-based medicines used by indigenous peoples. Travelers always stocked up on them before traveling through little-known regions. The great voyages brought the discovery of new continents, bequeathing to the modern world a large therapeutic arsenal of plant-based origin that is still indispensable to medicine today. Within Brazilian biodiversity, some important examples of medicinal plants are: Ilex paraguariensis (mate), Myroxylon balsamum (Tolu balsam), Paullinia cupana (guarana), Psidium guajava (guava), Spilanthes acmella (jambu), Tabebuia sp. (lapacho), Uncaria tomentosa (cat's claw), Copaifera sp. (copaiba) (GURIB-FAKIM, 2006). 14 Ministry of Health | Health Care Secretariat | Primary Care Department The magnitude of Brazilian biodiversity

– the set of all living beings with their integral genetic variability – is not known with precision due to its complexity, with an estimated two million distinct species of plants, animals and microorganisms. This makes Brazil the holder of the greatest biological diversity in the world (WILSON, 1997). Despite this and all the diversity of existing species, the potential for using plants as a source of new medicines is still little explored. Of the estimated 250,000 to 500,000 plant species in the world, only a small percentage have been investigated phytochemically, a fact that also occurs in relation to their pharmacological properties, in which, in many cases, there are only preliminary studies. In relation to medical use, it is estimated that only 5,000 species have been studied (RATES, 2001). In Brazil, with approximately 55,000 plant species, there are reports of investigation of only 0.4% of the flora (GURIB-FAKIM, 2006).

It is estimated that at least 25% of all modern medicines are derived directly or indirectly from medicinal plants, mainly through the application of modern technologies to traditional knowledge. In the case of certain classes of pharmaceutical products, such as antitumor and antimicrobial drugs, this percentage may be greater than 60% (WHO, 2011). The global herbal medicine market currently generates around US$44 billion, according to the consulting firm Analize and Realize, which serves some of the largest pharmaceutical companies in the world. According to the Brazilian Association of Herbal Medicine Companies, there is no official data on the size of this Brazilian market, and estimates vary between US$350 million and US$550 million. Despite its rich biodiversity, Brazil currently has a phytotherapeutic bbased on Brazilian flora, where all stages of development occurred in national territory and, of the phytotherapeutics registered with Anvisa, a small part comes from native species, which demonstrates the need for investment in research with species of the national flora (MIOTO, 2010). Furthermore, paradoxically to the potential and opportunities it offers – such as the scientific and technological park for the development of pharmaceuticals –, the country represents the tenth largest pharmaceutical market in the world and imports approximately 100% of the raw material used in the production of phytotherapeutics (ADAME; JACCOUD; COBRA, 2005). The selection of plant species for pharmacological study can be based on their traditional use by traditional societies, on their chemical content and toxicity, on random selection or by the combination of several criteria. One of the most common strategies is the study of traditional and/or popular medicine in different cultures, known as ethnopharmacology. Drug search strategies based on this line of action have been applied in the treatment of different diseases, such as cancer (KINGHORN, 2003; BALUNAS; KINGHORN, 2005). The approach to medicinal plants, based on their adoption by indigenous societies with oral tradition, can be useful in the preparation of pharmacological, phytochemical and agronomic studies on them, avoiding economic and time losses and demonstrating that it is possible to plan research based on traditional knowledge about medicinal plants, consecrated by continuous use in traditional societies (AMOROZO, 1996 apud RODRIGUES et al., 2002). Modern allopathy generally aims at the development of a single patentable substance that will treat specific circumstances. In most societies today, the 15 MEDICINAL PLANTS AND PHYTOTHERAPY IN FAMILY HEALTH allopathic and traditional systems of medicine occur side by side, in a complementary manner. Traditional medicine often aims to restore balance by using chemically complex plants or by mixing several different plants in order to maximize a synergistic effect or improve the likelihood of interaction with a relevant molecular target. This type of treatment is extremely important for developing countries, where medicinal plants are widely used in Primary Health Care (PHC). In these countries, they are used in their raw form (unprocessed), as teas or decoctions, as phytotherapeutics (standardized and formulated plant extracts) and as a popular alternative to allopathic medicinal products (GURIB-FAKIM, 2006). The World Health Organization (WHO), considering medicinal plants as important instruments of pharmaceutical assistance, through several communications and resolutions, expresses its position regarding the need to value their use in the health field, noting that 70% to 90% of the population in developing countries depends on them for Primary Health Care (WHO, 1993; 2011). In some industrialized countries, the use of traditional medicine products is equally significant, such as Canada, France, Germany and Italy, where 70% to 90% of the population has used these traditional medicine resources under the name of complementary, alternative or unconventional (WHO, 2011). Similarly, in Brazil, approximately 82% of the Brazilian population uses medicinal plant-based products in their health care, whether through traditional knowledge in traditional indigenous medicine, quilombola, among other peoples and traditional communities, or through popular use in folk medicine, transmitted orally between generations, or in official health systems, as a scientific practice, guided by the principles and guidelines of the Unified Health System (SUS). It is a practice that encourages community development, solidarity and social participation (RODRIGUES; DE SIMONI, 2010). In the SUS, the actions/programs with medicinal plants and phytotherapy, distributed in all regions of the country, occur in a differentiated manner, in relation to the products and services offered and, mainly, to the species of medicinal plants made available, due to the different biomes.

Some states/municipalities that have been in existence for many years have specific policies and legislation for phytotherapy services in the SUS and production laboratories, making medicinal plants and/or their derivatives available, primarily in primary care, in addition to publications for health professionals and the

population on the rational use of these products. As for the products, the services make medicinal plants available in one or more of the following forms: natural medicinal plants, dried medicinal plants (plant drug), manipulated phytotherapeutic and industrialized phytotherapeutic (RODRIGUES; SANTOS; DE SIMONI, 2011).

There has been much progress in recent decades with the formulation and implementation of public policies, programs and legislation lation with a view to valuing and enhancing the value of medicinal plants and derivatives in primary health care and their inclusion in the public network, as well as the development of the production chain of medicinal plants and phytotherapeutics (RODRIGUES; SANTOS; AMARAL, 2006). Currently, the main guiding instruments for the development of actions/programs with medicinal plants and phytotherapeutics are: the National Policy of Integrative and Complementary Practices in the SUS, with guidelines and lines of action for "Medicinal Plants 16 Ministry of Health | Health Care Secretariat | Department of Primary Care and Phytotherapy in the SUS", and the "National Policy of Medicinal Plants and Phytotherapeutics", covering the production chain of medicinal plants and phytotherapeutics. These policies were formulated in accordance with WHO recommendations, the principles and guidelines of the Unified Health System (SUS), the potential and opportunities that Brazil offers for the development of the sector, the demand of the Brazilian population for the provision of products and services in the public health system, and the need to standardize existing experiences in the SUS. These national policies are in line with and in tune with others, such as the National Health Policy, Primary Care Policy, Continuing Education Policy, Pharmaceutical Assistance Policy, Traditional Peoples and Communities Policy, Biodiversity Policy, and the Industrial, Technological, and Foreign Trade Policy. The resulting actions are essential for improving health care for the population, expanding therapeutic options for SUS users, sustainable use of Brazilian biodiversity, strengthening family farming, generating employment and income, industrial and technological development, and social and regional inclusion. Regarding the legislation of the sector, ANVISA, based on the guidelines of national policies, promoted a broad review of the legislation for the sector, drafted new standards, such as RDC nº 10/2010, which provides for the notification of herbal drugs, and promoted, through the Brazilian Pharmacopoeia, the review of the monographs of medicinal plants. All of these standards certainly represent progress in the Brazilian regulatory sector, being important for various segments, from Live Pharmacies to the industrial sector. Other advances resulting from the induction of national policies that deserve to be highlighted are: - Expansion of the offer of phytotherapy services and products in the public health system; - Establishment of technical groups to define standards and products for the SUS; - Approval of the National Program and establishment of the National Committee of Medicinal Plants and Phytotherapeutics; - Inclusion of eight phytotherapeutics in the National Reference List of Medicines and Complementary Inputs for pharmaceutical assistance in primary health care; - Incentive for research and development of medicinal plants and phytotherapeutics by the Ministry of Health, in partnership with other funding agencies; - Inclusion of the topic in the National Agenda of Health Research Priorities and in the Primary Health Care Research Network; - Publication of the National List of Medicinal Plants of Interest to the SUS (RENISUS) as a strategy to prioritize the allocation of resources and research in a positive list of medicinal plant species with a view to the development of phytotherapeutics; - Establishment of the Farmácia Viva within the scope of the SUS; - Approval of state and municipal policies and programs. 17 MEDICINAL PLANTS AND PHYTOTHERAPY IN FAMILY HEALTH In view of the advances and potential of our country for the growth of the sector, the challenges remain of allocating specific resources for the development of the actions of these policies; of the training/qualification of health professionals; of the definition of specific standards for the service in the SUS; of the expansion of investment in Research & Development; expanding the supply of services and products in the public network; among others. In this sense, national policies are essential and strategically establish the strengthening and development of the entire production chain of medicinal plants and phytotherapeutics, so that users of the System have access to services and products with quality, efficacy and safety.

History and use of medicinal plants and phytotherapeutics in Brazil

Medicinal plants are an invaluable cultural heritage and represent a very important resource for our health. Brazil is the country with the largest share of biodiversity, around 15 to 20% of the world's total flora, in addition to having around 55,000 cataloged plant species, representing the greatest plant genetic diversity in the world. Despite this, only 8% have been studied for research into bioactive compounds and 1,100 species have been evaluated for their medicinal properties (BRASIL, 2006b). The country can be considered to have advantages in the development of phytotherapy, as it has biodiversity, popular and traditional knowledge of the use of plants, technology to scientifically validate this knowledge, and financial resources. When referring to plants, especially medicinal plants, it is important to emphasize that the knowledge acquired about these species, their uses, indications and management are a legacy of ancestors, who have traditionally passed their knowledge from generation to generation, from the most remote times to the present day. Of all the methods of natural medicine,

phytotherapy is undoubtedly the oldest, the most studied and the one that presents the best results. With the evolution of science and the improvement of research, scholars have sought the answer to the following question: why do plants cure? Based on this question, plants began to be studied from the point of view of their chemical composition and no longer from a mystical perspective.

It was discovered that each plant has active principles that produce effects (beneficial or collateral) when introduced into other living beings. According to Almeida (1993), medicinal plants were the first therapeutic resources used to care for the health of human beings and their families, and are therefore an ancient knowledge that is part of human evolution, since even before the appearance of writing, people were already using plants, sometimes as medicine and sometimes as food.

The Chinese, Egyptians, Hindus and Greeks were the first to catalog medicinal herbs, classifying them according to their shape, color, flavor and aroma, including connections with the stars and, of course, with their magical attributes. In this way, plants were, over the course of several generations, manipulated and used for the most diverse therapeutic purposes, thus generating a rich traditional knowledge (LIMA, 2006). In the literature, there are several citations of people who made some type of use of herbs, both beneficial and harmful. The Druids, Celtic priests, used their magic potions and poisonous herbs, and even devised a horoscope based on the energy of trees, according to the different seasons of the year. To overcome his ills, Achilles used yarrow, an herb that came to be known as Achillea millefolium. Socrates, condemned to death by his adversaries, ingested hemlock, a plant with deadly effects. Charlemagne was one of the first defenders of plants, when he issued an edict protecting the native mint, which was threatened with extinction. For this act, he could have been considered the "patron saint of ecology", today represented by the Englishman William Cobbett (BRUNO; NALDI, 1998). In Brazil, the use of plants not only as food, but also as a therapeutic source began when the first inhabitants arrived here, approximately 12 thousand years ago, giving rise to the Amazonian paleonids, from which the main indigenous tribes of the country derived. Little, however, is known about this period, apart from cave paintings (SILVA, 2004). In 1500, with the arrival of Pedro Álvares Cabral in Brazil, the first official correspondence from Pero Vaz de Caminha to the King of Portugal, D. Manuel, appeared, reporting the discovery of the new land and its characteristics (SILVA, 2004). Father José de Anchieta, from 1560 to 1580, detailed in his letters to the Superiors General of the Society of Jesus the edible and medicinal plants of Brazil. The medicinal plants specifically mentioned were: king grass, marsh rhubarb, black ipecacuanha, red cabriúva, "good herb", peppermint, which were used by the indigenous people against indigestion, relieving neuralgia, rheumatism, and nervous diseases (SILVA, 2004). 16 At the end of the 18th century, one of the greatest contributors to the study of Brazilian phytotherapy came to Brazil, Bernardinho Antonio Gomes, a Portuguese doctor who arrived in the city of Rio de Janeiro as the personal physician of Princess Leopoldina, who was then promised to be married to D. Pedro. According to Gomes (1972), Bernardinho was fascinated by the amount of phytotherapeutic agents extracted from the Brazilian forests and decided to dedicate himself to cataloging these plants botanically, as well as studying their active principles. Thus, until the mid-20th century, the use of medicinal flora was widely used in the country, reflecting the ethnic unions that occurred between the different immigrants who arrived here and the indigenous peoples who lived there. Thus, the dissemination and knowledge about local herbs and the care in their use were transmitted and improved from generation to generation. Until around 1800, conventional medicine, which basically used medicinal plants, was the unquestionable basis for all classic pharmacology textbooks.

From the 1940s onwards, the use of plant-based drugs was relegated to the alternative therapeutic plan, in a second-class sense, as a result of the advances obtained by the chemical synthesis of drugs and the great development of the pharmaceutical industries, increased by capitalism (SCHULZ et al., 2001). In a return to nature, Western society turned its interest to the power of green, starting in the 1960s, determining a progressive increase in the global consumption of products derived from medicinal plants, occurring in the various social classes (DI STASI, 1996). In addition to being used as raw materials in preparations (including teas, oils and various extracts) of Traditional or Popular Medicine in several countries, medicinal plants are also used in the development of phytotherapeutics, as well as in the extraction, isolation and purification of plant compounds to obtain phytopharmaceuticals. These are defined as pharmacologically active substances of plant origin that have a pharmacological action and a defined structure (DI STASI, 1996; YUNES et al., 2001). Phytotherapy, even though its action is based on the pharmacological principles of allopathy, and therefore related to the theory of the causality of disease and its combat, presents characteristics that refer to a more integral notion of the body and its care (BRASIL, 2006a). It is considered here that this therapy has the potential to strengthen the relationship between service-professional-user and to promote comprehensive health practices, whether due to its reduced possibility of chemical aggression to the organism or due to its existing relationship with various medical rationalities and practices and with the culture of a large part of the Brazilian population, among other aspects, such as those related to the traditional knowledge of various communities. Phytotherapy is now widely used

throughout the world as a natural preventive, conservative, regenerative and curative method. Recognition of its value as a clinical, pharmaceutical and economic resource has already led many countries to adopt the practice as a public health policy.

THERMOGENESIS

Thermogenesis corresponds to energy in the form of heat generated at the level of living tissues. The amount of heat produced is directly proportional to the basal metabolic rate, the amount of heat produced in the resting state in the presence of a neutral thermal environment where no heat transfer occurs between the organism and the environment. 40-60% of the energy from the hydrolysis of adenosine triphosphate, ATP, is lost in the form of heat. (MAGALHÃES et al., 2002).

From a biochemical point of view, heat production in living beings can be analyzed as a result of: ATP synthesis or ATP hydrolysis. The thermodynamic efficiency of ATP synthesis is approximately 65%, that is, -35% of the energy released during the oxidation of energy substrates (energy transformation) is released in the form of heat. However, the ATP molecule is an intermediate store of energy that must be mobilized again (ATP hydrolysis) for biological work to occur. The efficiency of this second stage is even lower, around 40%. Thus, the thermodynamic efficiency of our organism is around 25-30% (BIANCO, 2000). For ATP synthesis, the energy from the Krebs cycle is processed by the respiratory chain, being temporarily stored in the form of an electrochemical potential of protons through the inner mitochondrial membrane. Since the inner mitochondrial membrane is relatively impermeable to protons, ATP molecules are generated as protons return to the mitochondrial matrix through the enzyme ATP synthase. However, there is an intrinsic "leak" of protons into the mitochondrial matrix, the return of which is accompanied by the release of heat instead of ATP synthesis. It is assumed that this mitochondrial "leak" of protons is in the order of 30 to 40% (BRAND et al, 1999). ATP hydrolysis, in turn, is associated with biological work. Whenever a cell performs work, ATP hydrolysis occurs and energy is lost in the form of heat. In this sense, it is clear that the cellular and molecular mechanisms responsible for heat production during ATP synthesis are distinct from the mechanisms involved in ATP hydrolysis.

While the former is related to mitochondrial function, the latter is closely related to cellular work, being directly influenced by the turnover of a series of ionic, substrate and metabolic cycles, that is, reactions that lead to ATP expenditure. It can therefore be said that almost all biological heat is ultimately the result of processes involving ATP synthesis and hydrolysis (turnover). The faster ATP turnover, the greater the heat production (BIANCO, 2000). From a physiological point of view, it is assumed that heat production in animals can be divided into two categories: obligate thermogenesis and facultative thermogenesis (BIANCO, 2000). Obligatory thermogenesis (BMR - basal metabolic rate) - is the sum of all heat produced in the body, whether awake or at rest, at room temperature and after fasting for at least 12 hours. It is the result of intrinsic mitochondrial inefficiency and ATP turnover, largely associated with: ionic and substrate cell cycles, e.g. Na/K, Ca, glycolysis cycles, particularly in excitable and renal tissues; metabolic cycles, e.g. Cori cycle, lipolysis/lipogenesis, glycogenolysis/glycogenesis, particularly in the liver and adipose tissue; muscle contraction and relaxation resulting from basal muscle work, particularly heartbeats, respiratory movements, striated and vasomotor muscle tone, peristalsis; and basal secretion of exocrine glands and glands attached to the digestive tract (BIANCO, 2000). It is important to note that these foods should not be consumed at night to avoid disrupting sleep. Excessive consumption of these foods can lead to symptoms such as headaches, dizziness, insomnia and gastrointestinal problems. Hypertensive patients and individuals with heart problems should take extra care, as some of these foods make the heart work faster. Due to their influence on metabolism, thermogenics should not be consumed by those with thyroid problems (BENITES et al, 2000). Diet-induced thermogenesis is the energy expenditure generated by the processes of ingestion, digestion, absorption, utilization and storage of ingested food. It represents 5% to 15% of total energy expenditure, which indicates its important role in regulating energy balance and body weight (HERMSDORFF, 2003).

EPHEDRINE

In Brazil, ephedrine-based formulations have not been banned, but they are included in the list of substances that are precursors of narcotics (Brazil, 1998). However, following the global trend, a large number of formulations have been observed on the Brazilian market, including imported dietary supplements containing C. auratium or p-synephrine.

Phytotherapy is often advocated for controlling appetite or increasing thermogenesis. In fact, natural substances can actually help burn calories without causing changes in the body, which is why there is a demand for herbal weight loss products (MORO and BASILE, 2000). The "weight loss" products on the market are available in the form of dietary supplements, phytopharmaceuticals, phytotherapeutics, nutraceuticals, or functional foods. Among other weight loss formulas, the most notable is that based on ephedrine (Ephedra sinica), an adrenergic agonist that acts by stimulating the sympathetic system and promoting lipolysis through beta-3, due to the clinical association of its use with heart problems, hypertension, and stroke. In some countries, dietary supplements containing ephedrine are prohibited.

Due to many problems, ephedrine was replaced by synephrine (SIN), which are adrenergic agents with selective agonist activity at alpha and beta receptors, stimulating lipolysis, increasing basal metabolism and fat oxidation, through thermogenesis, consequently weight loss, improving physical activity through the release of energy from fat reserves, increasing lean muscle, since the protein diet becomes more available for the incorporation of lean mass with physical exercise. Due to its pharmacological interest, synephrine is also marketed as a synthetic drug. The replacement of ephedrine by synephrine is because it does not cross the blood-brain barrier as easily as ephedrine does. However, through studies, synephrine's safety and efficacy are not assured, and it is associated with dietary supplements. (MORO and BASILE, 2000).

CITRUS AURATIUM

The genus Cintrus auratium comprises fruit trees of Oriental origin. There are numerous species, varieties and hybrids, in addition to some related genera, such as fortunella. Citrus fruits are widely used mainly due to their volatile oil content, in addition to being sources of flavonoids, pectins and coumarins (KUSTER AND ROCHA, 2003; ZUANAZZI AND MONTANHA, 2003; MAKSOUND, 2021; KARTHIKEN, 2014; SUNTAR, 2018).

It is popularly known as bitter orange, sour orange, horse orange and Seville orange, wild orange, earth orange. Its fruits, flowers and leaves have been used in folk medicine to treat anxiety, insomnia and as an anticonvulsant (CARVALHO-FREITAS E COSTAS, 2002; PULTRINI et al., 2005). In the Mediterranean region, C. auratium has been used since medieval times as a cardiac and vascular stimulant, digestive, stomachic, sedative, tranquilizer, cholagogue, appetite stimulant and general tonic, as well as an antidote against poisons (ARIES E RAMOM-LACA, 2005). In traditional Chinese medicine, bitter orange, which is known as ''zhi shi'', is used as a stimulant of gastrointestinal function and general tonic (BOUCHARD et al., 2005; MAKSOUND, 2021; KARTHIKEN, 2014; SUNTAR, 2018)

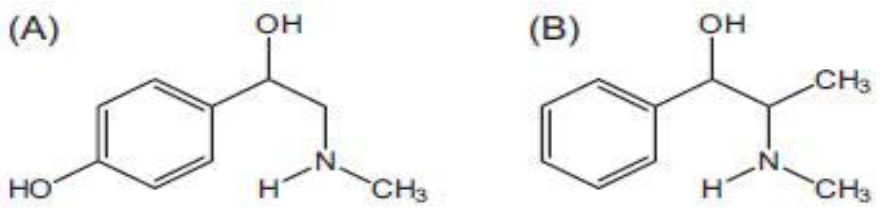

Figure 1. Chemical structure of synephrine (A) and ephedrine (B).

Synephrine

Synephrine is present in the dry extract of Citrus aurantium, which belongs to the Rutaceae family. This extract is used as a raw material in the national market in different dietary products, food supplements and compounds manipulated in compounding pharmacies, but, to date, it does not have a monograph in official codes or pharmacopoeia. In this regard, the biggest problem related to these products is the lack of standardization and poor quality control, both of the extract used and of the final product, facts that directly compromise the guarantee of its chemical composition, active ingredient content, stability, safety and efficacy, reflecting in therapeutic harm to the population, in addition to toxicological potential.

Therapeutic Action:

It is an appetite suppressant, adjuvant in the treatment of obesity.

Active ingredient:

Auratiamarin, stachydrin, hesperidin, quinotin, synephrine, tyramine, myrcene, limonene, citrol, linalool, geraniol, camphene, terpineol, b-pinene, phenylacetic and benzoic acids, calcium, phosphorus and iron salts, vitamins B1, B2 and C.

Indications:

Obtained from bitter orange, it accelerates metabolism, promotes greater calorie expenditure and burns fat stores. Citrus Aurantium contains synephrine, a substance similar to ephedrine (Ephedra sinica), being much safer and more effective. Ephedrine acts as a stimulant, but its use is not recommended, as it accelerates heart rate and blood pressure, which increases the risk of insomnia, heart attack and even stroke. However, synephrine does not have these effects; it binds to receptors found in adipose tissue, activating metabolism and fat burning without interfering with the cardiovascular system. It improves the digestive process, also acting as a liver detoxifier. In addition, some studies have shown that the substance, by promoting more energy, stimulates the release of adrenaline, which makes the person much more energetic. Citrus Aurantium also makes amino acids more accessible for the formation of protein, which is essential for those who want to gain and tone the body's muscles. The substance also has digestive properties, improving the absorption of nutrients and protecting the stomach. Citrus aurantium increases metabolism without affecting the heart rate or blood pressure, because recent research has confirmed that citrus only stimulates the beta-3 receptor, avoiding negative side effects on the cardiovascular system. In addition, since the administration of Citrus Aurantium increases the availability of fats for oxidation (cellular respiration), the body has access to greater amounts of energy. This is important because, when a person performs regular physical exercise, an increase in available energy can reduce muscle tissue mass. And, during aerobic exercise, the greater amount of energy will facilitate better physical performance. When Citrus aurantium is used in combination with a high-protein, low-carbohydrate diet and a moderate weight training program, the body increases its availability of amino acids, which are then incorporated into proteins for the formation of muscle mass. (MAKSOUND, 2021; KARTHIKEN, 2014; SUNTAR, 2018).

Thermogenic Effects:

Citrus increases calorie burning immediately after meals, enhancing the thermic effect of food. In addition, it acts as a sympathomimetic, increasing the release of presynaptic catecholamines. This means that it activates the components necessary to stimulate certain receptors responsible for fat loss. This is because, in addition to synephrine, Citrus has a composition of four adrenergic amines: N-methyltiramyr, hordein, octopamine and tyramine, which act to stimulate beta-3 receptors, specific sites in the cell that regulate fat loss.

Citrus Aurantium extract acts to release adrenaline and noradrenaline along with beta-3 receptors, which are mainly found in adipose tissue and the liver. Stimulating these receptors triggers the lipolysis process. At the same time, it promotes an increase in the metabolic rate (thermogenesis), burning a greater amount of calories.

Dosage: 500mg, 2x/day. NOTE: The extract is standardized to contain 6.0% synephrine.

Precautions: take under medical supervision, but it is important to remember that it does not have the dangerous side effects caused by other supplements. It is contraindicated for pregnant and lactating women.

II. Conclusion

Obesity is one of the most serious diseases that increases every year, becoming a problem in Public Health today, and the number of people looking for alternatives to lose weight has increased, with dietary supplements (phytotherapeutics). Citrus auratium contains synephrine, a substance similar to ephedrine (Ephedra sinica), which is much safer and more effective, as an aid in weight loss, referring to it as a product that acts on the metabolism, acting on the release of adrenaline and noradrenaline along with beta-3 receptors, which are mainly found in adipose tissue and the liver. Stimulating these receptors triggers the lipolysis process. At the same time, it promotes an increase in the metabolic rate (thermogenesis), burning a greater amount of body calories.

References

[1] STRAUSS JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007; 56(4):651-63.
[2] TAN X, Al-Dabagh A, Davis SA, Lin HC, Balkrishnan R, Chang J, Feldman SR. Medication adherence, healthcare costs and utilization associated with acne drugs in Medicaid enrollees with acne vulgaris. Am J Clin Dermatol 2013; 14(3):243-51.
[3] THI M PP, Bich DD, Thi Hai VN, et al. Microneedling Therapy for Atrophic Acne Scar: Effectiveness and Safety in Vietnamese Patients. Open Access Maced J Med Sci 2019; 7(2):293-7.
[4] GOLD MD, Baldwin H, Lin T. Management of comedonal acne vulgaris with fixed-combination topical therapy. J Cosmet Dermatol 2018; 17(2):22 ALONO,J.R. Tratado de Fitomedicina. Argentina :ediciones SRL ,1999
[5] BRASIL. Ministério da saúde. Secretaria de Vigilância Sanitária .Portaria nº 344 regulamento técnico sobre sustâncias e medicamentos sujeitos ao controle especial .D.U.O.-Diário Oficial da União, Brasília, DP,19 de meio de 1998.
[6] BRAY,G.A e RYAN, D.Drungs used in the treatment os obesity .Diabetes Reviews, v.8, p.83-100, 1997.
[7] De SMET, P.A.G.M Health risks of herbal remedies:an update.Clinical pharmacology e Therapeutics ,v.76, p.1-17, 2004.
[8] GRAY ,S. E WOOF,A.D. Citrus auratium used for weightloss by an adolestent with anorexia .Journal of adolestent health ,v.37, p.415-416, 2005.
[9] MORO, C.O, e BASILE,G.Obesity and medicinal plants.Fitoterapia ,v.71, p.74-S82, 2000.
[10] MURRAY ,M.T. The Health Power of Herbs .2 ed .USA :Prima Health ,1995.
[11] BLUNDELL J. E. Appetite disturbance and the problems of overweight. Drugs 1990; 39 (Suppl 3):1-19. Disponível em Acesso dia 10 de setembro de 2011.

[12] BENITES J.,CARDOSO J., CONTI T., MARTINS J., SONH V. Uso de alimentos termogênicos no tratamento da obesidade. Rio de Janeiro, junho de 2010. Disponível em . Acesso dia 10 de setembro de 2011.
[13] BIANCO, A. C. Hormônios Tireóideos, UCPs e Termogênese. Arquivos Brasileiros de Endocrinologia e Metabolismo. vol.44 no.4 São Paulo Ago. 2000.
[14] MAHAN, L. Kathleen; ESCOTT-STUMP, Sylvia; tradução Andéa Favano. Krause – Alimentos, Nutrição e Dietoterapia. 11ª edição. São Paulo: Roca, 2005.
[15] Carl Germano, RD, CNS. The Natural way to lose Weight Safely. Ed Kensington Health, New York, NY, EUA. Copyright 1998. CAIRO, N. Guia de Medicina Homeopática. 1983. American Herbal Pharmacopoeia and Therapeutic Compendium – Chaste Tree Fruit, 2001.
[16] SIMÕES, C. M. O. Farmacognosia da Planta ao Medicamento. 1ª edição. Editora da Universidade.
[17] TESKE, M.; TRENTINI, A. M. Herbarium Compêndio de Fitoterapia. Herbarium. Curitiba. 1994. - 2 - It_Citrus Auratium.
[18] SAAD, G. A. et al. Fitoterapia contemporânea: tradição e ciência na prática clínica. 2ª edição, Rio de Janeiro: Guanabara Koogan, 2018. DRUGS.COM. Bitter Orange. 2022. Disponível em: https://www.drugs.com/npp/bitter-orange.html.
[19] KARTHIKEYAN, V.; KARTHIKEYAN, J. Citrus aurantium (bitter orange): A review of its traditional uses, phytochemistry and pharmacology. International journal of drug discovery and herbal research, v. 4, n. 4, p. 766-772, 2014.
[20] SUNTAR, I. et al. An Overview on Citrus aurantium L.: Its Functions as Food Ingredient and Therapeutic Agent. Oxid Med Cell Longev, v. 2018, n. 7864269, 2018.
[21] Maksoud S, Abdel-Massih RM, Rajha HN, Louka N, Chemat F, Barba FJ, Debs E. *Citrus aurantium* L. Active Constituents, Biological Effects and Extraction Methods. An Updated Review. Molecules. 2021 Sep 26;26(19):5832. doi: 10.3390/molecules26195832. PMID: 34641373; PMCID: PMC8510401.