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Review Article

OBESITY: DEVELOPMENT, EPIDEMIOLOGY, FACTORS AFFECTING, QUANTITY, HEALTH HAZARDS, MANAGEMENT AND NATURAL TREATMENT-A REVIEW

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ABSTRACT

Due to the advancement in science, enhanced knowledge on the physiological aspects of almost all the tissues and the organs of the human body is gained. One of the most important prevalent topics needed for discussion is obesity and its effect on the metabolic changes leading to disorders in the human body such as diabetes, hypertension, cardiovascular diseases in addition to chronic diseases such as stroke, osteoarthritis, sleep apnea, some cancers, and inflammation-based pathologies. In recent years, obesity is a serious socioeconomic issue, which has become one of the major health problems all over the world, affecting people of all ages, sex, ethnicities and races. Obesity is a complex and multifactorial disease caused by the interaction of a myriad genetics, dietary, lifestyle and environmental factors and it is characterised by an excessive weight for height due to an enlarged fat deposition in the adipose tissue, which is due to a higher calorie intake than the energy expenditure. The pharmaceutical drugs are currently available to treat obesity but generally they have unpleasant side effects. Recent researches demonstrated the potential of natural products to counteract on obesity. Now the novel promising approach is the usage of dietary supplements and plant products and their bioactive compounds that could interfere on pancreatic lipase activity, food intake, lipid metabolism and adipocyte differentiation. In a similar way, hundreds of extracts are currently being isolated from plants, fungi, algae or bacteria and are screened for their potential inhibitions of activity against obesity. Natural products may have a synergistic activity that increases their bioavailability and action on multiple molecular targets.

Keywords: Obesity, Anti-obesity, Lipase inhibitors, Pancreatic lipase, Adipocyte, Appetite suppressant

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INTRODUCTION

Obesity has become a major health problem worldwide, affecting people across all ages, sex, ethnicities, and races. Obesity incidence is increased at an alarming rate and is becoming a major public health concern. Indeed, obesity facilitates the development of metabolic disorders and cardiovascular diseases in addition to chronic diseases [1, 2]. Body mass index (BMI), defined as the weight in kilogrammes divided by the height in meters squared (kg/m^2), is the most widely used measure of obesity due to its low cost and simplicity. The World Health Organization (WHO) and the National Institutes of health (NIH), have defined overweight as having a BMI between 25.0 and 29.9 kg/m^2 and obesity as having a BMI greater than 30.0 kg/m^2 [3]. Some recent WHO global estimates in 2014, more than 1.9 billion adults aged 18 y and older were overweight. Of these, over 600 million adults were obese. In 2014, an estimated 41 million children under the age of 5 y were overweight or obese. Once considered a high-income country problem, overweight and obesity are now on the rise in low and middle-income countries, particularly in urban settings. In Africa, the number of children who are overweight or obese has nearly doubled from 5.4 million in 1990 to 10.6 million in 2014. Nearly half of the children under 5 y who were overweight or obese in 2014 lived in Asia. Obesity is linked to more deaths worldwide than underweight. Globally there are more people who are obese than underweight. This occurs in every region except parts of sub-Saharan Africa and Asia [4].

According to research in different countries an obese individual incurs health care expenditures at least 25% higher than a healthy person [5]. The progress of obesity is characterised by a chronic imbalance of energy intake and energy expenditure [6, 7]. In addition, decreased energy expenditure is often associated with an inherited low basal metabolic rate and low energy cost of physical activity and low capacity for fat oxidation [8]. To reduce body weight and adiposity, a change in lifestyle habits is still the crucial keystone [9]. Physical activity might be the key step in the prevention of obesity by increasing average daily metabolic rate and increased energy expenditure [6]. Unfortunately, this clinical approach is not long lasting and weight regain often seen. Drugs that prevent weight regain appear necessary in obesity treatment [9]. Thus, the development of natural products to treat obesity is a challenging task, which can be launched faster and cheaper than conventional single-entity pharmaceuticals [10]. Many medicinal plants may offer safe, natural, and cost-effective alternatives to synthetic drugs [11-17]. Currently, one of the most significant strategies in the treatment of obesity comprises the development of natural inhibitors for nutrient digestion, absorption and its sequential metabolic reaction pathways [18]. For example, some recent studies are: Ginsenoside F2 and Rh1 from *Panax ginseng* Meyer plant possesses anti-obesity activity via binding with peroxisome proliferator activated receptor-γ (PPARγ) and inhibiting adipocyte differentiation in the 3T3-L1 cell line [19, 20]. Raspberry ketone, a naturally occurring phenolic compound inhibits adipogenic and lipogenic gene expression in 3T3-L1 adipocytes [21]. Aqueous tuber extract of *Cyperus rotundus* L., corn silk extracts show a significant decrease in obesity [22, 23].

In this context, dietary lipids represent the major source of unwanted calories, the attenuation of this fat digestion is an interesting approach for reducing fat absorption [24, 25]. Orlistat is the only authorised anti-obesity drug approved from food and drug administration (FDA). It has been shown to act through inhibition of pancreatic lipase (PL), which is a key enzyme for the digestion of dietary triglycerides [26]. Orlistat is a saturated derivative of lipastatin, an inhibitor of PL isolated from the bacterium *Streptomyces toxytricini* [27]. This molecule exerts a modest weight lowering effect while accompanying a suitable dietary advice. Thus, in a recent meta-analysis [28], the mean BMI change with Orlistat (120 mg three times daily) was a reduction of 0.83 kg/m^2 compared with a placebo. Accompanying this anti-obesity action, Orlistat is also able to modestly reduce blood pressure, improve oral glucose tolerance and prevent the onset of type 2 diabetes [29, 30]. Now, extracts from hundreds of species of medicinal plants, vegetables and fruits [31] as well as products from microorganisms [11], fungi [32], and marine algae [33] are being screened for potential lipase inhibitory activity. Ideally, these treatments will act as adjuncts to behavioural and lifestyle changes, aimed at maintenance of weight

loss and improved health [10]. In this review, we discuss the anti-obesity potential of natural inhibitors and analyse their mechanisms on obesity.

Methodology

A well-known scientific search engines viz. Google Scholar, Pubget Medline PubMed, EMBASE, Mendeley, Science Direct, Scopus, Springer Link were used to retrieve online literature. The results were then cross-referenced to generate a total number of 292 references cited in this review (mostly during the time span of 1975-2016). The Current review methodically summarises the anti-obesity effects of phytochemicals of medicinal plants in various models. Table 1 represents a list of existing medicinal plants/plant extracts/fractions and their effects in PL inhibition in *in-vitro* and/or *in-vivo* models. Table 2 represents a list of natural biomaterials showing appetite repressor activity. Table 3 represents existing plant/extracts/bioactive promoting energy expenditure. Table 4 represents plant extracts/bioactive inhibiting adipocyte differentiation. In table 5, natural biomaterials promoting lipid metabolism and acting as anti-obesity agents are shown. In this review, the major biological targets of botanical extracts and isolated compounds are listed with their therapeutic efficacy and possible synergy with other molecules in the extracts is also being discussed.

Factors affecting obesity

Obesity is a complex disease with multifactorial causes, involving a complex interplay of dietary, lifestyle, environmental and genetic factors.

Age

Age factor is one of the important criteria involved in causing obesity. As one gets older, one's body's ability to metabolise food slows down, and we require only a few calories to maintain our weight. This is the reason people at 40 y of age tend to gain weight if they eat the same food and do the same activities as they did when they were 20 y old. There is some evidence that when an older woman gives birth, there is a higher risk of obesity in the newborn [34].

Gender

Women tend to be more overweight than men. Men have a higher resting metabolic rate (means they burn more energy at rest) than women, so men require more calories to maintain their body weight. Additionally, when women become postmenopausal, their metabolic rate decreases. That partly explains why many women gain weight after menopause [35].

Environmental factors

Environmental factors unknowingly affect our metabolism [36]. It is known that hormones are key regulators in our body metabolism, body weight mechanisms and many pollutants affect our hormones [37]. For convenience, we spend time in temperature controlled rooms [38, 39]. Moreover, smoking also reduces weight [40, 41]. Environmental factors include lifestyle behaviours such as the type of food consumed by a person and his/her day to day activities. These factors unknowingly affect our metabolism systems [42]. Other studies of populations, including migration studies, have shown an increase in average body weight in those who move from a traditional to a westernised environment [43, 44].

Psychological factors

The psychological state of a person also influences eating habits and obesity. Many people eat in response to negative emotions such as boredom, sadness and/or anger. Getting too little sleep can also increase body weight [45-47].

Genetic factors

Obesity could be viewed as a consequence of the interaction of environmental factors and the individual genetic predisposition. A child of two obese parents has about 80% chance of becoming obese, whereas the risk is only 15% for the offspring of two parents of normal weight [48]. People with two copies of the fat mass and obesity (FTO) gene have been found on an average to weigh 3-4 kg more and have a 1.67 folds greater risk of obesity compared to those without the risk allele [49]. Some cases of obesity are related to single-gene mutations, e. g. MC4R gene (melano-cortin-4 receptor) [50], DRD4 gene (dopamine receptor D4) [51], PPARγ2 gene [52] or the leptin genes [53]. Some of the genetic factors predispose us to obesity [54]. There is some evidence that the obese people are more fertile than lean ones [55]. If obesity has a genetic component [56] the percentage of obese people in the population should increase. Moreover, union of obese spouses also promotes obesity in the children [57].

Heredity

Heredity influences the distribution of fat tissue. Generally, heavy newborns grow into heavy adolescents, more so when either parent is overweight. Moreover, weight regulation in the human body depends upon various genetically determined factors mainly by hormones. Any abnormality in these factors could result in substantial weight gain. Almost 60% of obese people are said to have inherited this condition. There are several genetic conditions that also contribute or lead to weight gain [58].

Endocrinological causes

Some people in rare cases are genetically predisposed to obesity due to hormonal imbalance or glandular problems. Cushing syndrome, hypothyroidism, hypogonadism in men and polycystic ovarian syndrome in women, hypothalamic lesions like tumours, infections or severe trauma are some of the genetic causes that lead to obesity [58].

Food intake

Some patients eat more during the periods of heavy exercise or during pregnancy and are unable to get back to their former eating habits. The increase in obesity can usually be related to the type of food (containing sugar and fat) consumed [59].

Dietary factors

The world today is more affluent than it ever was; this means that more people have access to a multitude of dietary options. People nowadays are also less active than their predecessors, however, the calorific content of their diet has not decreased; instead, it has increased. Diets around the world have drastically changed; we have transitioned from a high-protein to a high-carbohydrate, high-fat diet. Moreover, the consumption of empty calorie foods like alcohol, aerated drinks, candies, etc. has also been raised sharply. All these coupled with a sedentary lifestyle makes the ideal combination for susceptibility to obesity and diabetes [58].

Sedentary lifestyle

The rise in obesity is due to a sedentary lifestyle which plays a significant role [60]. There is a large shift toward less physically demanding work worldwide. Currently, at least 60% of the world's population gets insufficient exercise, due to increased use of mechanised transportation and a greater prevalence of labor-saving technology at home [61]. The WHO indicates people worldwide are taking up less active recreational pursuits. In both children and adults, there is an association between television viewing time and the risk of obesity [62].

Medical and psychiatric illness

Certain physical and mental illnesses and medication used to treat them can increase the risk of obesity. Medical illnesses that increase obesity risk include several rare genetic syndromes (Crohn's syndrome), as well as some congenital or acquired conditions: hypothyroidism, growth hormone deficiency [63] and eating disorders (binge eating disorder and night eating syndrome)[64]. The risk of overweight and obesity is higher in patients with psychiatric disorders than in persons without psychiatric disorders [65].

Health risks in obesity

The health risks of overweight and obesity are briefly described below

Hypertension

Hypertension leads to increase in high blood pressure progressively with higher levels of BMI in men and women [66]. Obesity and

hypertension are co-morbid risk factors for development of cardiovascular disease. The pathophysiology underlying the development of hypertension associated with obesity includes increased sodium retention and associated increases in vascular resistance, blood volume, increased sympathetic nervous system activity, cardiac output, insulin resistance and suppression of the activity of the rennin-angiotensin-aldosterone system [67-72].

Diabetes mellitus

Accumulated data demonstrate the association between obesity and non-insulin-dependent diabetes mellitus, which is the most common primary form of diabetes and impaired glucose tolerance. In obese individuals, adipose tissue releases a high amount of non-esterified fatty acids, glycerol, pro-inflammatory cytokines, and hormones. They are linked with the development of insulin resistance, which generates compensatory hyperinsulinemia with overstimulation of pancreatic cells and reduction of insulin receptors [73].

Dyslipidemia

Obesity is the most common cause of dyslipidemia. Lipid oversupply in a state of obesity, hyperinsulinemia and/or insulin resistance results in increased non-esterified fatty acid availability and, in turn, higher triglyceride (TG) stores in non-adipose tissues, e. g. the muscle, liver, and pancreas [74, 75]. Fatty acid-induced disorders are referred to as lipotoxicity. Thus, elevated TG level is often accompanied by a slight increase in total cholesterol and a marked drop in high-density lipoprotein (HDL) cholesterol. Moreover, low-density lipoproteins (LDL) rich in TG, partially metabolised by hepatic lipase, are converted into small LDL, with higher atherogenic potential [76].

Cardiac alterations

Observation studies have shown that obesity and excess abdominal fat are directly related to cardiovascular risk factors, including high levels of total cholesterol, LDL cholesterol, triglycerides, blood pressure, fibrinogen and insulin [77] and low levels of HDL cholesterol [78], plasminogen activator inhibitor-1 causing impaired fibrinolytic activity is elevated in persons with abdominal obesity [79]. Obesity increases the risk of heart failure, sudden cardiac death, chest pain, and abnormal heart rhythm [80]. Increased electrical alterations in obesity lead to frequent ventricular dysrhythmias even in the absence of heart dysfunction. The annual sudden cardiac death rate was nearly 40 times higher in obese people than in non-obese population [81, 82].

Lung disease

Obesity is associated with an increased risk of chronic respiratory disorders (e. g. asthma, hypoventilation syndrome and sleep apnea). Accordingly, weight loss often leads to symptomatic improvement [83].

Cancer

The line between diet, obesity and cancer is not completely understood, but the rising worldwide trend in obesity and cancer might be at least in part causal. The putative cause of these obesity-related cancers has been primarily ascribed to excess oestrogen production by the adipose tissue, inflammation due to adipocytokines secreted by adipocytes, infiltrating macrophages or associated stromal cells that might also play an important role [84, 85].

Neurological disorders

Psychological damage caused by overweight and obesity ranges from lowered self-esteem to frank clinical depression. Indeed, rates of anxiety and depression are three to four times higher among obese individuals [86]. Obesity significantly increases the risk of Alzheimer's disease. A strong correlation exists between BMI and high levels of amyloid, i.e. the protein that accumulates in the Alzheimer's brain, destroying nerve cells and producing cognitive and behavioural problems [87].

Clinical management of obesity: drugs and surgery

Although reduction of caloric intake by diet and increased level of physical activity are very well-known approaches to lose weight, in most cases patients who lose weight, regain the weight in subsequent years suggesting obesity has a high relapse rate making difficulty in treatment. So the treatment has to be a lifelong commitment with proper dietary habits increased physical activities. Many diets have been advocated for weight loss, but there is little scientific evidence to recommend one diet over another [88]. Due to the inconsistent effort in achieving a negative balance through diet and exercise, the needs for drugs and other supplements are fast gaining acceptance. However, drug discovery for anti-obesity agents has long been plagued with inconsistency and side effects. Strategic anti-obesity treatments broadly act through peripherally and centrally. The current scenario in drug discovery for anti-obesity therapeutics mainly focuses on the following mechanisms for energy homoeostasis. 1) Centrally acting: by regulation of food intake 2) Peripherally acting: by affecting absorption of dietary fat, affecting storage and metabolism of fat and/or increasing heat generation from dietary fat [89]. Body weight regulation and energy homeostasis can be viewed as multi-component feedback regulatory mechanisms which provide a vast number of intervening points as targets. In the long term, single point target for body weight management may activate compensatory mechanisms leading to failure of treatment [90].

Currently available synthetic analogues for anti-obesity

Sibutramine

Sibutramine (trade names Reductil and Meridia), is an anorectic or appetite suppressant [91]. It is a dual monoamine form, there arenor-adrenaline and serotonin (5-Hydroxytryptamine) reuptake inhibitor [92-94] noradrenaline in the nerve ending of central nervous system(CNS), and this action has anorexigenic and satiety effects, effective in improving metabolic syndrome parameters such as fasting glucose, triglycerides and HDL [95]. The sibutramine is contraindicated in patients with a history of cardiovascular disease, including coronary artery disease, stroke or transient ischemic attack, cardiac arrhythmia, congestive heart failure, peripheral arterial disease, or uncontrolled hypertension [96]. Sibutramine (Meridia) may cause an increase in blood pressure [97].

Orlistat

The orlistat (Xenical) has intestinal action, acts by inhibiting pancreatic lipase [98], and thus reduction of triglyceride absorption, and its long-term administration accompanying an energy restricted diet, results in weight loss [99]. Compared with sibutramine, the orlistat reduced waist circumference, BMI, systolic and diastolic blood pressure, fasting blood glucose, glycated haemoglobin, total cholesterol and LDL cholesterol in patients with type 2 diabetes mellitus [100]. The common symptoms are a loose stool, the presence of oil in the feces, fecal urgency, fecal incontinence, flatulence and, less frequently abdominal pain and rectal pain [101].

Rimonabant

Rimonabant's (Acomplia) mode of action in appetite regulation poses involvement of cannabinoid-1-receptors (CB1r) which on stimulation increases demand of food. Rimonabant reduces food intake by blocking CB1r and enhances thermogenesis. Side effects include mood changes, nausea, vomiting, diarrhea, headache, dizziness and anxiety [102].

Lorcaserin

Lorcaserin, a selective 5-hydroxytryptamine (5-HT2c) receptor agonist developed by Arena Pharmaceuticals, has serotonergic properties and acts as an anorectic. 5-HT2c receptors are located in various parts of the brain, including the hypothalamus, activation of which leads to pro-opiomelanocortin production and results in the weight loss through hypophagia [103]. Fluoxetine and Sertraline have been evaluated in patients with overweight, but without formal indication in the treatment of obesity. Its indication is the treatment of depression and bulimia nervosa [104]. The bupropion is an atypical antidepressant noradrenaline dopamine reuptake inhibitor and a smoking cessation aid; it's also demonstrated decreased food intake and dose-dependent weight loss [105]. Topiramate enhances the activity of gamma aminobutyric acid (GABA); blocks sodium

channel dependents, antagonises glutamate receptors and inhibits carbonic anhydrase. Secondly, used in epilepsy, mood stabiliser prophylaxis of a migraine and in weight loss [106].

Surgical treatment

The unsatisfactory results of treatment with diet, exercise or physical, pharmacological therapy reflect the difficulty of the obese patient in changing the lifestyle. With these non-surgical methods often cannot be a significant and sustained weight loss (>5 y), with many recurrences [107]. In 1991, NIH demonstrated safety and the long-term success of several anti-obesity surgeries. Two bariatric surgical procedures have gained popularity for treating obesity [108]. They are gastric bypass surgery and the laparoscopic adjustable gastric band (Lap-Band). Gastric bypass is a permanent surgical option. The surgeon will divide the stomach into two parts and then reconnect the intestine. There are several techniques used to reconnect the intestine, and many gastric bypass surgeries have different names. Gastric bypass surgery causes permanent changes to the stomach and digestive tract and its effects usually cannot be reversed [109].

The laparoscopic adjustable gastric band is an inflatable tube made up of silicone, in the surgery doctor places the band around the top portion of the stomach. The band helps to create a space at the top of the stomach that limits how much food patients can eat at any given time. The band helps a person to feel full and eat less at each meal. Over time, the lap-band patient will lose weight. Doctors recommend the lap-band for patients who have a BMI above 40. Unlike other weight loss surgeries, the lap-band does not permanently alter the digestive tract. Doctors can deflate and remove the band in order to reverse the surgery [109].

Natural inhibitors for treatment of obesity

Because of dissatisfaction with the high cost and potentially hazardous side effects, a number of researchers demonstrate the potential of natural products and their bioactive compounds for treating obesity. This is currently undergoing exploration of clinical trials and this may be an excellent alternative strategy for developing future effective and safe anti-obesity drugs [110, 111]. A vast number of natural products, including crude extracts and isolated bioactive compounds from plants can induce body weight reduction and prevent diet-induced obesity. Based on that, they have been widely used in the treatment of obesity [112, 113].

A wealth of information suggested that numerous bioactive components from nature are potentially useful in obesity treatments. The best example is polyphenols and saponins. These show strong anti-obesity activity and include apigenin, catechins and genistein [114, 115]. A growing body of evidence indicates that natural products having anti-obesity effects can be arranged into five categories based on their distinct mechanisms; they produce (i) decreased lipid absorption, (ii) decreased energy intake, (iii) increased energy expenditure, (iv) decreased pre-adipocyte differentiation and proliferation, (v) decreased lipogenesis and increased lipolysis. Thus, this review emphasises the importance of natural inhibitor along with anti-obesity potential and reviewed the scientific data, including experimental methodologies, bioactive components and its mechanisms of action against obesity.

Inhibitory effect on pancreatic lipase enzyme

The treatment for obesity makes one of the most important promising criteria in the effort to reduce energy intake through gastrointestinal mechanisms, without altering the central mechanisms, is the development of nutrient digestion and absorption inhibitors [116]. Dietary fat is not directly absorbed by the intestine unless the fat has been subjected to the action of PL. Therefore, PL is one of the most widely studied mechanisms for determining natural products potential efficacy as anti-obesity agents [116, 117].

PL is a key enzyme in dietary triacylglycerol absorption, hydrolyzing triacylglycerols to monoacylglycerols and fatty acids. Few natural substances interact directly with the lipases, example orlistat. It is a derivative of naturally occurring lipase inhibitor from *Streptomyces toxytricinni* [98]. Orlistat lipase inhibition mechanism acts through a covalent bond to the lipase's serine active site [118-120]. Although it is clinically approved for obesity treatment, it has certain unpleasant gastrointestinal side effects [121, 122]. These side effects result from orlistat include oily spotting, liquid stools, fecal urgency, flatulence, abdominal cramping [123]. Therefore, now researchers are screening novel inhibitors, derived from plants or other natural sources that lack some of these unpleasant side effects [116]. Recent evidence that ethanolic extract of jasmine flowers shown inhibition of PL activity in both *in vitro* and *in vivo* [124]. Malaysian researcher screened 32 medicinal plants for anti-lipase activity *in vitro* assay, in that *Eleusine indica* (31.36%), *Myristica fragrans* (20.23%), *Melastoma candidum* (19.67%) and *Phyla nodiflora* (18.26%), respectively showing potential candidates [125], pomegranate leaves [126], *Achyranthes aspera* L., and *Coffea canephora* [127], plants possess PL inhibition effects. In 2012, Korean researchers examined 400 plant species, 44 extracts from plants, showed high anti-lipase activity using 2, 4-dinitrophenylbutyrate as a substrate in porcine pancreatic lipase (PPL). Furthermore, 44 plant extracts were investigated for their inhibition of lipid accumulation in 3T3-L1 cells. Among these 44 extracts examined, crude extracts from 4 natural plant species were active. *Salicis radicis* cortex showed highest fat inhibitory activity; whereas *Rubi fructus*, *Corni fructus* and *Geranium nepalense* exhibited fat inhibitory capacity higher than 30% at 100μg/ml in 3T3-L adipocytes cell lines, suggesting anti-obesity activity [128]. Similarly, in 2011 Korean researchers screened 61medicinal plants out of those, *Sorbus commixta* (stem, leaf) and *Viscum album* (whole plant) exhibited antilipase activity with IC_{50} values of 29.6 mg/ml and 33.3 mg/ml, respectively [129]. Twenty three medicinal plants were screened which are belonging to 15 different families and compared their PPL effects. Thirteen plants were found to show *in vitro* inhibitory activities. The nine most active plants have shown an IC_{50} range of 107.7-342.7 μg/ml. The plants are *Anthemis palaestina* Boiss. *Salvia spinosa* L., *Ononis natrix* L., *Fagonia arabica* L., *Origanum syriaca* L., *Majorana syriaca* (L.) Rafin., *Hypericum triquetrifolium Turra, Malva nicaeensis, Chrysanthemum coronarium* L., *Paronychia argentea* Lam [130]. A study was reported on methanolic extracts of 37 traditional Chinese herbal medicines of different families. They were assayed for *in vitro* activity against PPL activity, among that, *Prunella vulgaris* L. and *Rheum palmatum* L. showed significant inhibition [131].

A wide range of plants have possess potent pancreatic lipase inhibition effects, including *Panaxjaponicas* [132], *Platycodi radix* [133], *Salacia reticulate* [134], *Nelumbo nucifera* [135], and so on described in table 1. This pancreatic lipase inhibitory phytochemicals include mainly, polyphenols, flavonoids, saponins and caffeine [136-139]. Many carbohydrates also possess potent PL inhibitory effects [140, 141]. But, the effects of these carbohydrates on body weight reduction in animals and humans are controversial [142-150].

Many active metabolites from microorganisms, including lipstatin from *Streptomyces toxytricini* [151], panclicins from *Strepomyces sp.* NRO619 [152], valilactone and ebelactone from *Strepto-mycesalbolongus* [153, 154], esterasin from *Streptomyces lavendulae* [155], caulerpenyne from *Caulerpa taxifolia* [156], vibralactone from *Boreosterem virans* [157], and percyguinin from Basidiomycete *Stereum Complicatum* [158] also possess PL inhibitory activity. Moreover, certain fruiting bodies or mycelia of macrofungi reportedly possess lipase inhibitory activity [159, 160].

Some of the most widely studied materials among the many natural sources of PL inhibitions are the different types of tea (e. g green, oolong, and black tea). A significantly different type of tea polyphenols [e. g. L-epicatechin, Epigallocatechin Gallate (ECG), Epigallocatechin gallate (EGG) and (-)-Epigallo-catechin-3-gallate (EGCG)], isolated from tea leaves, showed strong inhibitory activity against PL [114, 161, 162]. These polyphenols require galloyl moieties within their chemical structures and or polymerization of their flavan-3-ols for enhanced PL inhibition [162]. In their search for a PL 54 marine algae were screened. Interestingly, almost all algae showed lipase inhibition activity in either methanol or ethyl acetate extracts [158].

Table 1: Plant extracts and isolated compounds showing inhibition on pancreatic lipase

Source	Active component	Major activity	References
Rubus coreanus Miquel (fruit)	Crude ethanolic extract	32.5±1.1% inhibition	[128]
Cornus officinalis Siebold et Zuccarini (fruit)	Crude ethanolic extract	34.8±2.3% inhibition	[128]
Ulmus darvidian for. *Suberose* (bark)	Crude ethanolic extract	38.0±1.9 % inhibition	[128]
Geranium thunbergii Siebold et Zuccarini (whole grass)	Crude ethanolic extract	31.4±0.7% inhibition	[128]
Ephedra sinia Stapf. (Herbaceous stem)	Crude ethanolic extract	25.9±4.3 % inhibition	[131]
Milettia reticuiata Benth. (Rattan cane)	Crude ethanolic extract	33.3±4.2% inhibition	[131]
Polygonum cuspidatum Sieb. (root and rhizome)	Crude ethanolic extract	37.8±6.5% inhibition	[131]
Prunella vulgaris L.(ear)	Crude ethanolic extract	74.7±10.0% inhibition	[131]
Rheum palmatum L. (root and rhizome)	Crude ethanolic extract	53.8±9.0% inhibition	[131]
Salvia miltiorrhiza Bge. (root and rhizome)	Crude ethanolic extract	32.7±3.8% inhibition	[131]
Uncaria macrophylla Wall (aerial part)	Crude ethanolic extract	30.1±3.3% inhibition	[131]
Juniperus communis(bark*)* and *Illicium religiosum* (wood)	Crude ethanol/water extract	IC_{50} =20.4 and 21.9 µg/ml, respectively	[136]
Panax japonicas (rhizomes)	Chikusetsusaponins	22% decrease in body weight gain	[132]
Carica papaya L.	Crude aqueous extract	55.77±0.4 % inhibition	[159]
Thea sinesis (oolong tea)	Crude aqueous extract (caffeine)	10% decrease in body weight gain	[163]
Platycodi radix	Platycodin saponins	13% decrease in body weight gain	[164-167]
Platycodi radix	Crude aqueous/ethanolic extract (saponin)	12% decrease in body weight gain	[133]
Acanthopanax santicosus	10.6% ellagic acid	54% decrease in body weight gain	[168]
Cassia mimosoides	Proanthocyanidin	IC_{50} = 0.11 mg/ml; 60% decrease in body weight gain	[169]
Kochia scoparia (fruits)	Crude aqueous extract (saponins)	19% decrease in body weight gain	[137]
Afromomum meleguetta and *Spilanthes acmella*	Crude ethanolic extract	90%, 40% lipase inhibition respectively	[170]
*Salacia reticulate (*mixed with cyclodextrin)	Crude aqueous extract	27% decrease in body weight gain	[133]
Thea sinensis (leaf)	Saponins	17% decrease in body weight gain	[163, 171]
Nelumbo nucifera (leaf)	Crude ethanolic extract	28% decrease in body weight gain	[135]
Trigonella foenum graecum L. (seed)	Crude ethanolic extract	14% decrease in body weight gain	[172]
Salix matsudana (leaf)	Poly phenol (PP), Flavonoid glucoside	20% decrease in body weight gain 19% decrease in body weight gain	[173, 174]
Vitis vinifera	Crude ethanolic extract	Inhibitory effect on lipase activity = 80%	[10]
Eriochloa villosa	Crude methanolic extract	Inhibitory effect on lipase activity = 83%	[175]
Orixa japonica	Crude methanolic extract	Inhibitory effect on lipase activity = 81%	[175]
Setariia italic	Crude methanolic extract	Inhibitory effect on lipase activity = 80%	[175]
Salvia officinalis L.	Methanolic extract (carnosic acid)	IC_{50} = 36 µg/ml	[176]
Scabiose tschiliesis Gun.	Triterpenoid saponins	Maximum activity: almost 100% with prosapogenin 1B (1 mg/ml)	[177]
Acanthopanax sessiliflorous	Lupane-type saponins	40% decrease in body weight gain	[178]
Aesoulus turbinate (seed)	Escin	IC_{50}=14 µg/ml with escinIIb	[179]
Cyclocarya paliurus (Batal) *Ilinskaja*	Crude aqueous extract	IC_{50} = 9.1 µg/ml	[180]
Ziziphus Mauritiana	Crude extract	68% decrease in body weight gain	[181]
Gardenia jasminoides (fructus)	Croci, crocetin	IC_{50} =2.1 mg/ml with crocetin; 25% decrease in body weight gain with crocin	[182,183]
Dioscorea nipponica	Crude methanolic extract	IC_{50} =5-10 µg/ml, 37% decrease in body weight gain	[184]
Coffea canephora	Caffeine, chlorogenic acid, neochlorogenic acid, feruloyquinic acids	157% decrease in body weight gain	[159]
Glycyrrhiza uralensis	Licochalcone A	IC_{50} = 35 µg/ml, K_i = 11.2 µg/ml	[185]
Spirulina platensis (marine algae)	Crude methanolic extract	55±0.23 % inhibition	[186]
Gracilaria corticata (marine algae)	Crude methanolic extract	45±0.21 % inhibition	[186]
Fungus*, Leetiporus sulphureus*	Mycelia extract	Inhibitory effect on lipase activity = 83%	[187]
Fungus*, Tylopilus felleus*	Mycelia extract	Inhibitory effect on lipase activity = 96%	[187]
Fungus, *Hygrocybe conica*	Mycelia extract	Inhibitory effect on lipase activity = 97%	[187]
Streptomyces toxytricini	Lipistatin	IC_{50} = 0.14 µg/mol	[27]
Actinomycetes sp.	Valilactone	IC_{50} = 0.00014 µg/ml	[153]
Citrus unshiu	Hesperidin	IC_{50} = 32 µg/ml	[188]

Suppressive effect on food intake

For the past30 y, Sibutramine is the first new drug approved by FDA for treating obesity via appetite suppression [91]. Its main mechanism involves an increase in the feeling of satiety by controlling noradrenalin, serotonin/5-hydroxytryptamine, and dopamine [189,190]. However, sibutramine shown some known side effects, including dry mouth, constipation, and insomnia [143]. Body weight regulation through appetite control is multifactorial events resulting from neurological and hormonal interrelationships. A line of evidence indicates that dopamine, histamine, serotonin, and their associated receptor activities are closely connected with satiety regulation. These receptors may enable researchers to target better their searches for drugs that treat obesity through energy intake reduction [191]. Molecules that act via peripheral satiety peptide systems alter the various hypothalamic neuropeptide levels. Also, they change the main CNS appetite monoamine neurotransmitter levels and they may be the suitable candidates for appetite suppressant [192, 193].

Appetite suppressants control hunger centres in the brain, providing a satiety signal. However, ghrelin secretion in the stomach may increase with decreased food intake, stimulating more food intake. Therefore, ghrelin antagonism may decrease the appetite that potentially occurs with decreased feeding, thus, may be a potential adjunctive treatment for obesity. An example of a natural appetite suppressant is *Hoodia gordonii*. It regulates appetite and significantly reduces calorie intake and boosts weight loss [194].

Natural (_)-hydroxy citric acid (HCA) from *Garcinia cambogia*, is a potential natural appetite suppressant. It is available under the names HCA-SX and Super CitriMax [195]. HCA is a competitive inhibitor of adenosine 5-triphosphate-citrate lyase, leading to a decreased acetyl coenzyme A production and decreased fatty acid synthesis. HCA is also thought to suppress food intake via loss of appetite by stimulating liver gluconeogenesis. HCA is also reported to act by increasing the availability of 5-hydroxytryptamine or serotonin, which is a neurotransmitter implicated in regulating eating behaviour and appetite control. The central metabolism of glucose also suppresses food intake, mediated by the hypothalamic Adenosine monophosphate-activated protein kinase activation (AMPK)/malonyl-CoA signalling system [196]. Central administration of glucose increases hypothalamic malonyl-CoA decreases orexigenic neuropeptide expression and suppresses food intake. Centrally-administered fructose provokes feeding, via the AMPK/malonyl-CoA signalling pathway. Thus, decoctions prepared from natural sources containing excessively high fructose levels may suppress the hypothalamic malonyl-CoA signalling pathway, thereby exerting an orexigenic effect [197]. *Hypericum perforatum* increases the serotonin quantity present within synaptosomes by inhibiting synaptosomal uptake of serotonin, which suppresses the appetite and reduces food intake. Thus increased serotogenic transmission might be the link between antidepressant and anti-obesity activities of *H. perforatum* [194]. Some natural appetite suppressants are listed in table 2.

Table 2: Anti-obesity biomaterials showing appetite-repression activity

Source	Used part and/or active constituent	References
Caralluma fimbriata	Total dry extract	[198]
Panax ginseng (root)	Crude saponins	[199]
Terminalia paniculat Roth.(bark) Family: *Combretaceae*	Crude ethanolic extract	[200]
Bauhinia variegate *Bauhinia variegate* (root)	Crude aqueous extract	[201]
Pinellia ternate	Crude aqueous extract	[202]
Garcinia cambogia	(-)-HCA	[203]
Camellia sinensis (leaf)	(-)-EGCG	[204]
Hoodia gordonii and *H. pilifera*	Steroidal glycoside (P57AS3)	[205,206]
Phaseolus vulgaris and *Robinia pseudoacacia*	Lectins	[207]
Pinus koraienis(pine nut)	Pine nut fatty acids	[208]
Ephedra species	Ephedrine	[209]
Citrus aurantum	Synephrine	[210]
Hypericum perforatum	Total extract	[211]
Nelumbo nucifera (leaf)	Crude ethanolic extract (flavonoid)	[212]
Panax ginseng(berry)	Crude ethanolic extract	[213]
Glycine max (soybean)	b-conglycinin,glycinin(globulins)	[214,215]
Undaria pinnatifida(sea weed)	Fucoxanthin	[216-218]
Undaria pinnatifida (seaweed)	Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)	[219]
Sterculic foetida (seeds)	Petroleum ether extract	[220]
Caralluma fimbriata	Total dry extract	[198]
Panax ginseng (root)	Crude saponins	[199]
Terminalia paniculat Roth.(bark) Family: *Combretaceae*	Crude ethanolic extract	[200]
Bauhinia variegate *Bauhinia variegate* (root)	Crude aqueous extract	[201]
Pinellia ternate	Crude aqueous extract	[202]
Garcinia cambogia	(-)-HCA	[203]
Camellia sinensis (leaf)	(-)-EGCG	[204]
Hoodia gordonii and *H. pilifera*	Steroidal glycoside (P57AS3)	[205,206]
Phaseolus vulgaris and *Robinia pseudoacacia*	Lectins	[207]
Pinus koraienis(pine nut)	Pine nut fatty acids	[208]
Ephedra species	Ephedrine	[209]
Citrus aurantum	Synephrine	[210]
Hypericum perforatum	Total extract	[211]
Nelumbo nucifera (leaf)	Crude ethanolic extract (flavonoid)	[212]
Panax ginseng(berry)	Crude ethanolic extract	[213]
Glycine max (soybean)	b-conglycinin, glycinin(globulins)	[214,215]
Undaria pinnatifida(sea weed)	Fucoxanthin	[216-218]
Undaria pinnatifida (seaweed)	EPA and DHA	[219]
Sterculic foetida (seeds)	Petroleum ether extract	[220]

Stimulatory effects on energy expenditure

Stimulation of energy expenditure is one of the important cretiria in obesity. Results of recent experiments showed that natural inhibitors active against energy expenditure stimulants are more effective. Excessive adiposity results from an imbalance in energy homoeostasis, in which the consequences of excessive food intake are not balanced by increased energy expenditure [221, 222]. Energy expenditure components can be separated into a number of different categories. The simplest scheme divides energy expenditure into three categories: (1) physical activity (2) obligatory energy expenditure, and (3) adaptive thermogenesis. To regulate body weight and energy expenditure, mammalian brown adipocyte tissue (BAT) establishes non-shivering thermogenesis, through dissipation of excess energy as heat [223]. BAT plays an important role in obesity control by controlling energy balance through uncoupling protein (UCP1) responsible for oxidative phosphorylation. Thus, searching for substances that up regulate UCP1 gene expression may be a worth strategy for achieving obesity control through increased energy expenditure [224]. An example is the ethanolic extract of Solanum tuberosum, which activated the expression of UCP3 in BAT and liver which significantly reduced fat weight in HFD fed rats [225]. Many natural compounds have been proposed as treatments for obesity via enhanced energy expenditure including caffeine, capsaicin, green tea and its extracts [112]. Some natural appetite suppressants are listed in table 3.

Table 3: Anti-obesity plant extracts and bio-molecules promoting energy expenditure

Source	Active component	Major activity	References
Pinellia ternate	Crude aqueous extract	Slight decrease in body weight gain	[202]
Nelumbo nucifera (leaf)	Crude ethanolic extract	15% decrease in body weight gain	[114, 191, 212]
Camellia sinensis	EGCG	8% decrease in body weight	[114, 191, 227]
Panax ginseng (berry)	Crude ethanolic extract	13% decrease in body weight gain	[213]
Glycine max (soybean)	β-conglycinin, glycinin (globulins)	10% decrease in body weight gain	[214,215]
Undariapinnatifida (sea weed)	Fucoxanthin	17% decrease in body weight gain	[217,218]

Inhibitory effect on adipocyte differentiation

Adipocyte plays a central role in the maintenance of lipid homoeostasis and energy balance, by storing triglycerides and releasing free fatty acids in response to changing energy demands. Because adipocyte tissue growth can be due to both hyperplasia and hypertrophy of adipocytes. Several studies screening for anti-obesity materials have focused on the processes of adipocyte proliferation and differentiation [226]. In this search, 3T3-L1 preadipocyte cells are currently used as an *in vitro* model for the study of obesity, because such cells accumulate triglycerides upon differentiating in culture [227, 228]. This is due to the expression of adipocyte-specific genes, such as PPARc and enhancer binding protein [229, 230]. For this reason, natural products that specifically target adipogenesis inhibition had been considered promising with regard to their potential in the treatment of obesity. However, current research suggests that inhibiting adipogenesis or adipose tissue expansion is unhealthy, leading to type 2 diabetes and other metabolic diseases, such as atherosclerosis [229].

Fatty acids, particularly polyunsaturated fatty acid (PUFA), acts as signal transducing molecules in adipocyte differentiation. In adipocyte tissue, saturated and monounsaturated fatty acids are more readily acylated into triglycerides than PUFA [231-233]. Thus, PUFA plays a central role in suppressing fatty acid synthesis and regulating adipocyte differentiation through suppression of late phase adipocyte differentiation [233, 234]. Recent reports have demonstrated another interesting mechanism, in the extract of macro fungus *Cordyceps militaris* mycelia, which suppressed 3T3-L1 adipocyte differentiation through activation of the aryl hydrocarbon receptor [235]. The wide variety of natural products found to inhibit preadipocyte proliferation and/or the apoptotic effect. In addition, to showing inhibitory activity against adipocyte differentiation, several naturally occurring compounds have displayed apoptotic effects on maturing preadipocytes (esculetin, resveratrol, guercetin, genistein, EGCG, capsaicin, and conjugated linoleic acids). Examples of some natural products and isolated biomolecules with adipocyte differentiation inhibitory effects are given in table 4.

Table 4: Anti-obesity plant extracts and bio-molecules inhibiting adipocyte differentiation

Source	Active component	References
Garcinia cambogia	(-)-HCA	[236]
Cassia auriculata(leaf)	Crude aqueous extract	[237]
Pinusdensiflora	Crude aqueous extract	[238]
Corsrhizometidi	Berberine	[241]
Chili pepper (Capsicum)	Capsaicin	[242]
LagerstroemiaSpeciosa L. (banana leaf)	Hot water extract (tannic acid)	[246]
Undariapinnatifida (brown algae)	Fucoxanthin	[247]
Camellia sinensis(green tea)	(-)-ECG	[248-250]
Lithospermumerythrorhizon	Shikonin	[251]
Zizyphus jujube (fruit)	Extract of chloroform Fraction	[252]
Garlic	Ajoene	[253]
Humuluslupulus	Xanthohumol	[254, 255]
Lagerstroemia speciosa(leaf)	Ellagitannins	[246]
AscophyllumNodosum	Aqueous methanolic extract	[256]
Wasabia japonica (leaf)	Hot water extract	[257]
Coriolous versicolor (mushroom fruit body)	(-)Ternatin	[258]
Cordycepsmilitaris	Mycelial extract	[194]
Ipomoea batatas(root)	Sporamin	[259]
Rosmarinusofficinalis	Carnosic	[260]
Curcuma longa	Curcumin	[261-263]
Linumusitatissimum (flax seed)	(-)Secoisolariciresinol	[264]
Hibiscus sabdariffa	Flower extract	[265]
Solanum tuberosum	Ethanolic extract	[225]
Soy isoflavone	Genistein	[266]
Undariapinnatifida	Neoxanthin	[267]
Commiphoramukul	Cis-guggulsterone	[268]
Rehmanniaglutinosa	Crude ethanolic extract	[269]
Eriobotrta japonica	Corosolic acid	[270]
Irvingiagabonesis(seed)	Extract	[271]
Terminalia paniculatRoth.(bark) Family: Combretaceae	Crude ethanolic extract	[200]

Regulatory effects on lipid metabolism

The pharmacological targeting of lipolysis can be achieved by stimulating triglyceride hydrolysis in order to diminish fat stores, thereby combating obesity. This option requires the associated oxidation of the newly released fatty acids which led to the development of the b3-adrenergic agonists [272]. The flavonoids from *Nelumbo nucifera* leaves are examples of the biomaterial inhibitors involved in b3-adrenergic receptor activation [212]. The activity of oolong tea is a good example of another anti-obesity mechanism. Caffeine, one of the major bioactive components in oolong tea, possesses both a positive charge and a hydrophobic area like that of adrenaline. Caffeine's mechanism of lipolytic action might be due to its binding to the phospholipid phosphate groups and the subsequent interactions between the lipase and triglyceride portions of lipid droplets, eliciting lipolysis [163]. Examples of some natural products with adipocyte differentiation inhibitory effects are given in table 5.

Table 5: Anti-obesity biomaterials promoting lipid metabolism

Source	Active component	Major activity	Mechanism of action	References
Salacia oblonga (root)	Mangiferin	40% decrease in liver/body weight ratio	Hepatic PPARa activator	[273,274]
Lex paraguariensis	Crude water extract	11% decrease in body weight gain	Downregulation of adipose tissue genes	[275]
Mixture of *Morus alba, Melissa officinalis, Artemisia* (leaf)	Crude aqueous extract	7% decrease in body weight gain	Hepatic PPARa activator	[276]
Cortidis Rhizome	Berberine	13% decrease in body weight gain	AMPK	[277]
Nelumbo nucifera (leaf)	Crude ethanolic extract (flavonoid)	15% decrease in body weight gain	Activation of β-adrenegic receptor	[212]
Curcuma longa L.	Curcumin Curcuminoids	7% decrease in body weight gain 11% decrease in body weight gain	Reversal of inflammatory and metabolic derangement Alteration in fatty acid metabolism	[278-280]
Eucommia Ulmoides(leaf)	Crude aqueous extract	No data	Downregulation of lipogenic enzymes	[281]
Coixlachrymajobi var. mayeun (seed)	Crude aqueous extract	36% decrease in body weight gain	Modulation of lepin and tumour necrosis factor (TNF-α)	[282]
Salacia reticulate (root)	Aqueous extract (polyphenolic compounds)	7% decrease in body weight gain	Inhibition of lipid metabolising enzymes and stimulation of lipolysis	[283]
Glycyrrhiza glabra L.(root)	Licorice flavonoid oil	30% decrease in body weight gain	PPARγ agonistic activity	[284]
Diospyros kaki (leaf)	Crude methanolic extract	11% decrease in body weight gain	Modulation of leptin and lipogenic enzymes	[277]
Morus alba L.(leaf)	Crude aqueous extract	7% decrease in body weight gain	PPARs agonistic activity	[110]
Panax ginseng	Crude aqueous extract	8% decrease in body weight gain	PPARs agonistic activity	[110]
Lagestroemia speciosa L. (leaf)	Crude aqueous extract	3% decrease in body weight gain	PPARs agonistic activity	[110]
Glycyrrhizauralensis	Crude ethanolic extract (flavonoid)	22% decrease in body weight gain	PPARγ agonistic activity	[285]
Evodia ruraecarpa(fruit)	Crude ethanolic extract (evodiamine)	23% decrease in body weight gain	Vanilloid receptor agonistic activity	[286]
RhynchosiaVolubilis (black soybean)	Tripepide (Ile-Gln-Asn)	IC_{50}=0.014 mg protein/mol	AMPK activation	[287]
Soybean	Genistein+L-carnitine (soy isoflavone)	254% decrease in body weight gain	PPARs agonistic activity	[288]
Coffea canephora	Caffeine, chlorogenic acid, neochlorogenic acid, feruloyl quinic acids	157% decrease in body weight gain	Inhibition of fat absorption, activation of fat metabolism	[159]
Glycine max (Soy) Isoflavone	Genistein	90% inhibition of adipocyte differentiation, 43% decrease in cell adipocyte viability	AMPK activation, Adipocyte apoptosis	[270]
Rubus idaeus (rasberry)	4-(4-Hydroxyphenyl) Butan-2-one (RK)	17% decrease in body weight gain	Increase lipolysis	[289]
Solanum tuberosum	Crude extract	5% decrease in body weight gain	Downregulation of P38 MAPK and Upregulation of UCP3	[225]
Momordica charantia	Crude ethanolic extract	61% increase in glucose uptake with 0.5 nmol insulin and 75% increase in adiponectin secretion	Enhance glucose uptake and adiponectin secretion	[290]
Toona sinensis (leaf)	Crude ethanolic extract	156% increase in glycerol release Lipolytic activity	Lipolytic activity	[291]
Cinnamoni cassia	Cinnamon	3.1 fold increase in PPARγ levels	PPARγ agonistic activity	[292]

Conclusion and future prospects

Body weight management is a lifelong process, and permanent weight reduction is difficult to achieve. The ultimate cause of obesity is an imbalance between calorie intake and energy expenditure resulting from complex interactions between many genetic and environmental factors. Obesity is multifactorial and the chronological disease that affects millions of people worldwide and contributes substantial morbidity and mortality. Anti-obesity pharmacological treatment should be administered only when BMI above 25 and considered safe and effective for the obese subject.

Over the past 30 y, few obesity treatment drugs have been developed or approved. Only two drugs are currently available, and

some drugs have been withdrawn from the market due to its serious side effects. Sibutramine and orlistat may cause weight loss of up to 10% when used in combination with dieatary, behavioural and exercise therapy. Natural bio-molecules, inhibitors or products can play a safe and effective role in obesity especially those containing fibres, polyphenols, alkaloids and sterols. Natural biomaterials with potential action on causative metabolic pathways of obesity work without affecting CNS. The need exists for anti-obesity drugs having greater effectiveness, which are better tolerated. In the future, the active exploration of many natural sources may provide hope for new developments based on a growing understanding of the complex mechanism involved in body fat content regulation. Ideally, such exploration and research will lead to a safer and more effective pharmacological treatment for obesity.

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CONFLICTS OF INTERESTS

Declared none

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