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## Herbal and Microbial Products for the Management of Obesity

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**CHAPTER 3****Herbal and Microbial Products for the Management of Obesity****Essam Abdel-Sattar<sup>\*</sup>, Soheir M. El Zalabani and Maha M. Salama***Pharmacognosy Department, College of Pharmacy, Cairo University, 11562, Cairo, Egypt*

**Abstract:** Obesity is a global epidemic and one of the major health burdens of modern times. The prevalence of obesity is increasing worldwide; it constitutes a serious problem in developed as well as developing countries. Beside adults, the number of obese teenagers and children in particular has dramatically increased. Obesity is characterized by accumulation of excess fat in adipose tissues in an extent to produce adverse effects on health, leading to a reduction in life expectancy and/or a raise in health hazards. People are classified as overweight (pre-obese) and obese on the basis of the Body Mass Index (BMI), crude measure which compares weight to height. Obesity is usually associated with and can lead to many disease conditions, mainly type-2 diabetes, cardiac diseases, hypertension, sleep apnea, cerebrovascular incidents, osteoarthritis and certain types of cancers. The tremendously increasing number of reviews on the subject of obesity obviously reflects the amount of investigations currently dedicated to this field. The core of obesity treatment is dieting and physical exercise. The consumption of energy-dense food is reduced *versus* an increase in that of dietary fibers. Conventional medication relies mainly on drugs which either reduce appetite or inhibit fat absorption. However, drug treatment of obesity despite short-term benefits, is often associated with undesirable harmful side effects, rebound weight gain after discontinuation of drug intake, and the incidence of drug abuse. If diet, exercise and pharmacological therapy are ineffective; surgical intervention may be useful. The anti-obesity potential of natural products if accurately explored might provide an excellent alternative strategy for the scientifically-based development of safe and effective drugs. Especially that, they are actually widespread for this purpose as nutritional supplements. OTC anti-obesity natural products are mostly complex in terms of chemical composition and may exert a variety of pharmacological actions leading to weight loss. These include: inhibition of lipases activity, suppression of appetite, stimulation of energy expenditure, inhibition of adipocyte differentiation and regulation of lipid metabolism. A variety of natural products, including crude extracts and isolated compounds induce body weight reduction and prevent diet-induced obesity. Examples of these constituents are polyphenols, triterpenoidal and steroidal saponins, pregnane glycosides, alkaloids, abietane diterpenes and carotenoids amongst others. In addition, a number of lipase inhibitors are obtained from microbial sources.

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The present chapter is intended to survey the vast array of natural products from plant and microbial origin currently suggested as conventional drug alternatives for management of obesity. This will cover the natural sources, extracts, safety assessment and structures of bioactive compounds, as well as the biochemical markers used to evaluate the anti-obese effect and/or determine the mechanism of action. New drug targets that may play a role in the regulation of body weight will also be considered.

**Keywords:** Anti-obesity, herbal medicine, micro-organisms, mechanisms, natural products, phytochemicals, plants.

## **INTRODUCTION**

Obesity, which was once regarded as a cosmetic problem prevalent in high income countries, has been formally recognized by the World Health Organization as a global epidemic in 1997 [1]. Currently, the incidence of overweight and obesity is dramatically rising in low- and middle-income countries due to adoption of western life-style characterized by decreased physical activity and overconsumption of high energy-yielding foods [2]. Together with underweight, malnutrition, and infectious diseases, overweight and obesity are now considered as major health problems threatening the developing world [2, 3]. There is also strong evidence that obesity is associated with morbidity and mortality [4].

### **Definition**

The World Health Organization [5, 6] defines obesity as abnormal or excessive fat accumulation that represents a risk to health. Obesity has also been described as an increased adipose tissue mass, which is the result of an enlargement in fat cells and/or an increase in their number [7] resulting in hypertrophic and/or hyperplastic obesity [8]. A crude measure of underweight, overweight and obesity is the body mass index (BMI) that is a person's weight (in kilograms) divided by the square of his/or her height (in meters) [5, 6].

### **Prevalence**

The 2010 IASO/IOTF analysis (International Association for the Study of Obesity/International Obesity Task Force, 2010) estimates that approximately 1.0 billion adults are currently overweight and a further 475 million are obese. In

addition, when Asian-specific thresholds for the definition of overweight (BMI > 23 kg/m<sup>2</sup>) and obesity (BMI > 28 kg/m<sup>2</sup>) are taken into consideration, to adjust for ethnic differences, 1.7 billion people could be classified as overweight worldwide, and the number of adults considered as obese exceeds 600 million [9-11]. About 65% of the world's populations live in countries where overweight and obesity kill more people than underweight (at least 2.8 million adults die each year as a result of being overweight or obese). More than 40 million children under the age of five were overweight in 2011 [12]. Moreover, the most recent WHO fact sheet (2013) recorded that more than 1.4 billion adults (20 years old and older) are overweight (BMI 25-29.9 kg/m<sup>2</sup>) of these over 200 million men and nearly 300 million women were obese, 312 million were clinically obese (BMI > 30 kg/m<sup>2</sup>) [12].

### **Causes and Complications**

Obesity is a multifactorial disease characterized by a chronic imbalance between energy intake and energy expenditure [13-16] together with enlarged fat deposition in adipose tissue [17]. The high calorie intake is often ascribed to change in lifestyle and inadequate dietary habits [2, 13]. Meanwhile, decreased energy expenditure is often associated with an inherited low basal metabolic rate, reduced physical activity and low capacity for fat oxidation [18]. To maintain the energy balance, the energy input in the form of food should be equal to the energy expenditure through exercise, basal metabolism, thermogenesis and fat biosynthesis [8].

Obesity is generally linked with an increased risk of excessive fat-related metabolic disorders and chronic diseases such as type-2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular diseases and certain types of cancer [4, 19-21]. These obesity-associated serious complications are forcing research towards long-term safe solutions for weight management and control [22, 23]. Drugs that prevent weight regain appear necessary in obesity treatment [24].

## **STRATEGIES FOR MANAGEMENT OF OVERWEIGHT AND OBESITY**

### **Overview**

The key strategy to combat overweight and obesity is to prevent chronic positive impairments in the energy equation [17]. A change in lifestyle is still the crucial

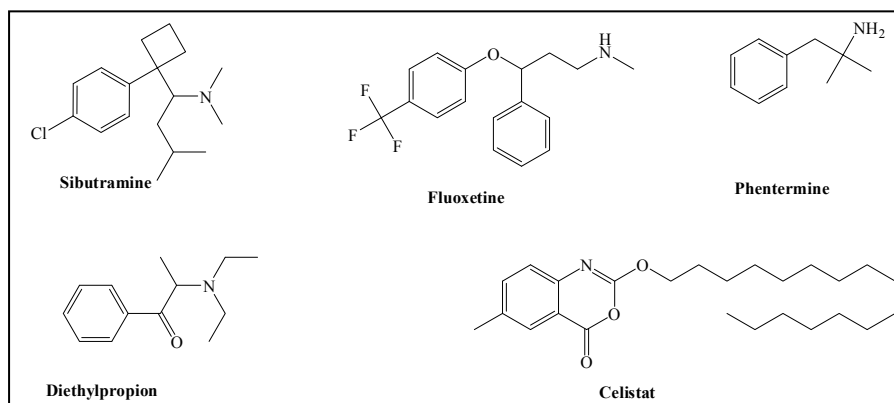
cornerstone [24]; in this respect, physical activity appears to be helpful by elevating average daily metabolic rate and increasing energy expenditure [13], yet this approach is short-term lasting and weight regain is usually observed [24].

Management of obesity usually necessitates a combination of lifestyle modification and pharmacological therapy. Surgical interventions, although effective in some circumstances, are not always appropriate [25, 26]. An alternative strategy to surgery is to develop therapeutic agents that can reduce body weight by decreasing the consumption or absorption of food, and/or by increasing energy expenditure [27, 28]. The ideal anti-obesity drug would produce sustained weight loss with minimal side effects [26]. Unfortunately, drug treatment of obesity despite short-term benefits, is often associated with rebound weight gain after cessation of drug use and side effects from the medication.

### Modern Pharmacotherapy: Present and Future

Pharmacologic options for treatment of obesity include the use of synthetic drugs such as sibutramine, phentermine, diethylpropion, celistat and fluoxetine. Among these phentermine and diethylpropion have potential for abuse [29].

Currently, two approved drugs are available on the market, orlistat and sibutramine [26, 30, 31]. Orlistat (Xenical) reduces intestinal fat absorption through inhibition of pancreatic lipase [32-35]; while sibutramine (Reductil) is an anorectic, or appetite suppressant [36-38]. Both drugs have hazardous side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia [35, 39-41].



Moreover, a number of anti-obesity drugs are undergoing clinical development [26, 42, 43] including:

- a. Centrally-acting drugs, such as the noradrenergic and dopaminergic reuptake inhibitor radafaxine, the selective serotonin 5-HT<sub>2c</sub> agonist APD-356, and oleoyl-estrone.
- b. Drugs that target peripheral intermittent satiety signals, such as glucagon-like peptide-1 (*e.g.* exenatide, exenatide-LAR and liraglutide), peptide YY (*e.g.* intranasal PYY3-36 and AC-162325) and amylin (*e.g.* pramlintide).
- c. Drugs that block fat absorption, such as the novel lipase inhibitors cetilistat and GT-389255; and a human growth hormone fragment (AOD-9604) that increases adipose tissue breakdown [42].

However, even for those agents that meet the preliminary requisites for selectivity of action and potential safety profile, extensive testing is still needed, to demonstrate efficacy in terms of weight loss sustainability, as well as long-term benefits for diabetes prevention and treatment, cardiovascular disease, and psychiatric safety [26].

The role of modern medication in weight loss is, thus, controversial and its effectiveness appears too limited. The Food and Drug Administration (FDA) has approved no weight loss drug for use for more than five years. Hence drugs represent a short-term solution for a long-term problem with only modest benefits and unclear risk(s) [44].

### **Naturopathy: A Prospective Solution**

Plants have been used as traditional natural medicines for healing many diseases since antiquity [16]. Many medicinal plants may provide safe, natural, and cost-effective alternatives to synthetic drugs [45, 46].

The potential of natural products for management of overweight and obesity is currently under extensive exploration to overcome high manufacture costs of

synthetic drugs, the rebound of weight gain after stopping medication and the hazardous side effects. Naturotherapy seems, thus, an outstanding alternative strategy for developing future effective, long-term safe drugs for weight management and control [22, 23, 47-49].

A variety of natural products (including crude extracts and isolated compounds from plant and microbial sources) that induce body weight reduction and prevent diet-induced obesity, are widely used in management of these metabolic disorders [50-52]. However, the development of anti-obesity natural drugs appears as a challenging task, which can be launched faster and cheaper than conventional single-entity pharmaceuticals [53].

## **NATURAL PRODUCTS AND MANAGEMENT OF OVERWEIGHT AND OBESITY**

Anti-obesity natural products are supplied in different forms including: comminuted whole plants or plant parts either in the form of teas or encapsulated, in addition to aqueous or alcoholic extracts dispensed in suitable formulations. Extraction and purification are intended to ensure concentration of the bioactive components. Further isolation and formulation of this (these) constituent(s) will possibly enhance the bioavailability of the drug, although in certain cases the synergistic effect of the whole extractives is favored.

The wide variety of anti-obesity natural agents harbored by plants, microbes or their extracts act through various mechanisms to either prevent weight gain or induce weight loss [54-56]. The inhibition of key enzymes involved in lipid and carbohydrate metabolism, disruption of adipogenesis and modulation of the adipocyte life-cycle, as well as, appetite suppression are among the major targeted approaches for development of efficient anti-obesity medications.

On the basis of the mechanisms of action through which they exert their activity, natural anti-obesity products are categorized as follows:

### **Nutrient Digestion and Absorption Inhibitors**

Strategies based on the use of nutrient digestion and/or absorption inhibitors appear the most promising in terms of safety, efficacy and sustainability for

management of overweight and obesity. This approach involves reduction of energy intake through gastrointestinal rather than central mechanisms [45, 57]. The most reputed are the lipase and amylase inhibitors.

### **Lipase Inhibitors**

Dietary fat is absorbed by the intestine only after being subjected to the action of pancreatic lipase (PL) that is a key enzyme in dietary triacylglycerol absorption. Pancreatic lipase hydrolyzes triacylglycerols to monoacylglycerols and fatty acids. The potential of natural products as anti-obesity agents is commonly evaluated through monitoring their pancreatic lipase-inhibitory effect [45].

Orlistat, the clinically approved anti-obesity drug, is the tetrahydroderivative of the naturally-occurring lipase inhibitor, lipstatin, a metabolite of *Streptomyces toxytricini* [32]. It acts through irreversible covalent bonding to serine, the active site of PL and thus inactivating the enzyme [58-61]. The unpleasant gastrointestinal side-effects of this drug, such as oily spotting, liquid stools, fecal urgency or incontinence, flatulence, and abdominal cramping [35, 36, 41], directed research towards screening novel natural sources for PL inhibitors derived from either plants or microorganisms [45]. Several biomass-derived extracts and metabolites are claimed to exert PL inhibitory effects. The lipase inhibitory mechanisms of these natural products (extracts and pure isolates) are either reversible or irreversible reaction inhibitor like Orlistat [45, 61].

Among higher plant extracts are those of: *Panax japonicus* (T. Nees) C. A. Mey [62], Platycodi radix (roots of *Platycodon grandiflorum* (Jacq.) A. DC.) [63]; *Salacia reticulata* Wight [64]; and *Nelumbo nucifera* Gaertn [65]. Lower plants including fungi and algae have been also screened in this respect; certain fruiting bodies or mycelia of macrofungi [66, 67] and a number of algae are reported to possess lipase inhibitory activity [60]. However, since crude extracts include both active and inactive components, their lipase inhibitory potencies are usually significantly weak compared to orlistat [68].

Phytochemicals reported as lipase inhibitors comprise saponins, polyphenols, flavonoids, and certain alkaloids such as caffeine [68-71]. Tea leaves polyphenols (L-epicatechin, ECG, EGG, and EGCG) showed strong inhibitory activity against



PL [72-75]. The PL inhibitory activity of polyphenols is enhanced by the presence of galloyl moieties within their chemical structures and/or polymerization of flavan-3-ols [73]. Several carbohydrates are claimed to possess PL inhibitory effects [76]. For example, chitin/chitosan mixtures increase fat excretion in the feces of experimental animals resulting in reduction in body weight [51]. However, the effects of these carbohydrates are said to be controversial in humans [77-85].

Furthermore, various lower plant and microbial metabolites demonstrated PL inhibitory activity. Representatives of lower plant metabolites include: caulerpenyne from the alga, *Caulerpa taxifolia* [86]; vibrallactone from the Basidiomycete, *Boreostereum virans* [87]; and percyquinin from the Basidiomycete, *Stereum complicatum* [88]. Among microbial metabolites are: the aforementioned lipstatin isolated from *Streptomyces toxytricini* [89]; the panclicins from *Streptomyces* sp. NR0619 [90, 91]; valilactone and ebelactones from *Streptomyces albolongus* [92, 93]; and esterastin from *Streptomyces lavendulae* [94].

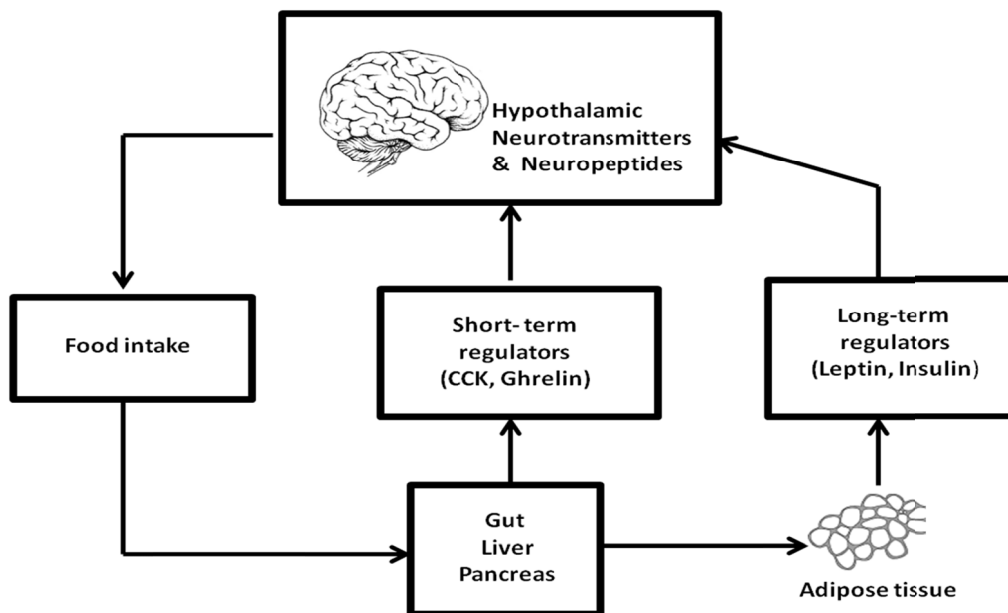
### **Amylase Inhibitors**

Drugs which interfere with the digestion of carbohydrates are called starch blockers. These act mainly through inhibition of the activity of salivary and pancreatic amylases. Theoretically, when amylase activity is blocked, ingested starch escapes digestion in the small intestine, thus contributing no calories. Certain plants extracts or herbal supplements can promote weight loss through interfering with the breakdown of complex carbohydrates (amylase inhibitors) or by providing resistant or inaccessible starches (the third type of dietary fibers) to the lower gastrointestinal tract [95]. On the other hand, some plants' extracts e.g. *Phaseolus vulgaris* (white kidney beans), and whole grains extract of *Triticum aestivum* (wheat) inhibit the activity of salivary and pancreatic amylases [96]. Starch blockers demonstrate potential activity in the treatment of obesity, but further studies are necessary to decisively establish their efficacy.

### **Appetite Suppressants and/or Satiety Inducers**

Generally, regulation of the quantity of food intake (appetite control) may be:

- a. Short-term regulation, which is concerned primarily with preventing overeating at each meal.
- b. Long term regulation, which is primarily related with the maintenance of normal quantities of energy stores in the form of fat in the body [8] (Fig. 1):



**Figure 1:** Schematic presentation of the short- and long-term regulation in appetite and food intake (Through reference [8]).

### ***Factors Influencing Appetite Control***

Regulation of body weight through appetite control is influenced by neurological and hormonal interrelated factors. The neuromodulators serotonin, histamine and dopamine, and their related receptor activities are closely linked with satiety regulation and constitute suitable targets in searching for drugs that could manage obesity through energy intake reduction [97]. In addition, appetite suppression may be induced by acting on the peripheral satiety peptide systems. Bioactive products may, in this respect, act by altering either the CNS levels of various hypothalamic neuropeptides, or the levels of the key CNS appetite monoamine neurotransmitters [98, 99].

### ***Natural Appetite Suppressants***

The first synthetic appetite suppressant to be approved by the FDA within the past 30 years is Sibutramine [38]. The increase in satiety sensation induced by the drug is through controlling noradrenaline, serotonin, 5-hydroxytryptamine, and dopamine levels [36, 37]. The major adverse side effects observed are dry mouth, constipation, and insomnia [30].

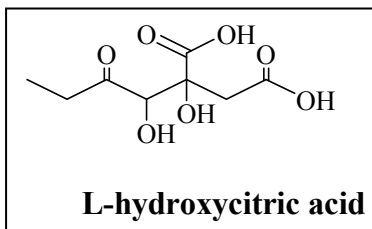
Natural appetite suppressants are usually dietary supplements that control appetite typically through affecting hunger control centers in the brain, resulting in a feeling of satiety. The secretion of the peptide hormone, ghrelin, in human and animal stomach increases with decreased food intake thus stimulating hunger sensation and increased food intake; therefore, development of ghrelin antagonists could provide suitable appetite suppressant candidates for treatment of obesity [100]. Melanin-concentrating hormone (MCH) receptor antagonism may also constitute an important target for appetite control and management of obesity.

Among reputed plant appetite suppressants is *Hoodia gordonii* (Masson) Sweet ex Decne., a succulent plant growing in South African countries. Although, there is still inadequate clinical information to prove its efficacy, yet, the plant extract has been found effective in appetite control resulting in significant reduction of calorie intake and enhancement of weight loss [101-105]. The extract was found to regulate food intake in rats through increasing adenosine triphosphate (ATP) level in the hypothalamic neurons [101]. Another natural appetite depressant available on the drug market is the extract of *Cissus quadrangularis* L. [105].

Other plant extracts and herbal supplements reported as appetite suppressants are derived from *Panax ginseng* C. A. Meyer (Korean red ginseng) [106], *Camellia sinensis* (L.) Kuntze [107-110], *Caralluma fimbriata* Wall. [111], *Ephedra sinica* Stapf. [112], *Citrus aurantium* L. [113], *Phaseolus vulgaris* L. [114, 95] and *Robinia pseudoaccacia* L. [114]; as well as the oil of the seeds of *Helianthus annuus* L. (sunflower oil) [115-118]. The mechanisms of appetite regulation reported for these herbal products are different. These mechanisms will be discussed individually in “plant and microbial sources with multi-functional anti-obesity activity” section.

Several active metabolites derived from the aforementioned plants were found to possess appetite-suppressive properties including saponins, flavonoids and other polyphenols. However, in most cases, the exact mechanism of action of these constituents is still unclear; they are thought to intensify signaling in the basal energy-sensing function of the hypothalamus.

The most famous among these metabolites is (-)-hydroxycitric acid (HCA), isolated from the fruits of *Garcinia cambogia* Desr., which is a potential natural appetite suppressant; it acts by increasing the release of serotonin, a neurotransmitter involved in regulation of eating behavior and appetite control [119]. Central metabolism of glucose suppresses food intake, mediated by the hypothalamic adenosine monophosphate-activated protein kinase (AMPK)/malonyl-CoA signaling system [120]. In fact, glucose administration increases hypothalamic malonyl-CoA resulting in a decrease in orexigenic neuropeptide expression and suppression of food intake [120, 121]. Certain natural appetite suppressants induce a decrease in expression of either neuropeptide Y (NPY) in the hypothalamus or of serum leptin levels [106, 122], such as the crude saponin mixture isolated from Korean ginseng [106]. The oxypregnane steroidal glycoside P57, reported as major active constituent from Hoodia, was found responsible for ATP level increase in hypothalamic neurons [123].



The alkaloid ephedrine has also been associated with significant weight loss, by either enhancing thermogenesis or inducing anorexia [124-129]. As anorexic it acts by inhibiting gastric emptying, which may result in a feeling of satiety and thereby aiding weight loss [130]. Its effects have been enhanced by combination with aspirin and/or methyl xanthines (caffeine or theophylline) [131-136].

Certain dietary fats (*e.g.* conjugated linoleic acid, lauric acid, and salatrim) have suppressive effects on energy intake; yet, significant body weight reduction was not recorded [137-139].

### Stimulators of Energy Expenditure

The influence of reduced energy expenditure in the development of human obesity is still not obvious, despite its evidence in many rodent models. Adiposity is a consequence of imbalance in energy homeostasis where food intake is not balanced by energy expenditure [140, 141]. Energy is usually expended through [142]:

- a. Physical activity.
- b. Obligatory energy expenditure.
- c. Adaptive thermogenesis.

Mammalian brown adipose tissue (BAT) plays an important role in obesity management by controlling energy balance through dissipation of excess energy as heat to establish non-shivering thermogenesis [143]. The major participant in this process is the proton-carrier mitochondrial uncoupling protein 1 (UCP1), which discharges the proton gradient generated in oxidative phosphorylation, thus dissipating energy as heat. Therefore, the search for upregulators of UCP1 gene expression may constitute a valuable approach for achieving obesity control through increased energy expenditure [144]. UCP3, an analogue of UCP1 is, as well, an effective anti-obesity agent, which mediates thyroid hormone-regulated thermogenesis  $\beta_3$ -adrenergic agonists, and/or leptin levels in some organs [145]. The ethanol extract of *Solanum tuberosum* L. was found to activate the expression of UCP3 in BAT and liver rats fed with high fat diet (HFD) and consequently appreciable reduction in weight or fat mass was observed [54].

On the other hand, BAT can be recruited under certain conditions; thus searching for natural compounds that can recruit BAT within white adipose tissue (WAT) may provide another helpful anti-obesity strategy [142], this on the basis that the remodeling of mature WAT into mitochondria-rich cells with a high capacity for fatty acid oxidation has been reported [146, 147]. Several natural products, including  $\omega$ -3 polyunsaturated fatty acids and fucoxanthin, a marine-derived xanthophyll, stimulate thermogenesis in BAT and promote the *in vivo* acquisition of WAT deposits BAT features in rodents [148-151].

In addition, numerous naturally-occurring compounds have been proposed for enhancement of weight loss *via* increased energy expenditure, mainly due to their thermogenic capacities. These include the alkaloids caffeine [136, 152], ephedrine [136] and capsaicin [52, 153]. Caffeine increases energy expenditure by inhibiting the phosphodiesterase (PDE)-induced degradation of intracellular cyclic adenosine monophosphate (cAMP) [146] and decreases energy intake through reduction of food intake [152]. Although, the effect of ephedrine was shown to be markedly potentiated by caffeine [132] owing to adverse cardiovascular side effects, the FDA has prohibited the sale of ephedra-containing dietary supplements [154].

The most reputed thermogenics are green tea, its extract and component catechins *viz.*, epigallocatechin (EGC) and epigallocatechin gallate (EGCG) [109, 110]. EGCG was also reported to stimulate thermogenesis through inhibition of the catechol-*O*-methyltransferase involved in degradation of norepinephrine [52, 75, 97, 155, 156]. Other extracts such as those of *Pinellia ternata* (Thunb.) Makino [157] and *Panax ginseng* (berry) [158] also boosted energy expenditure.

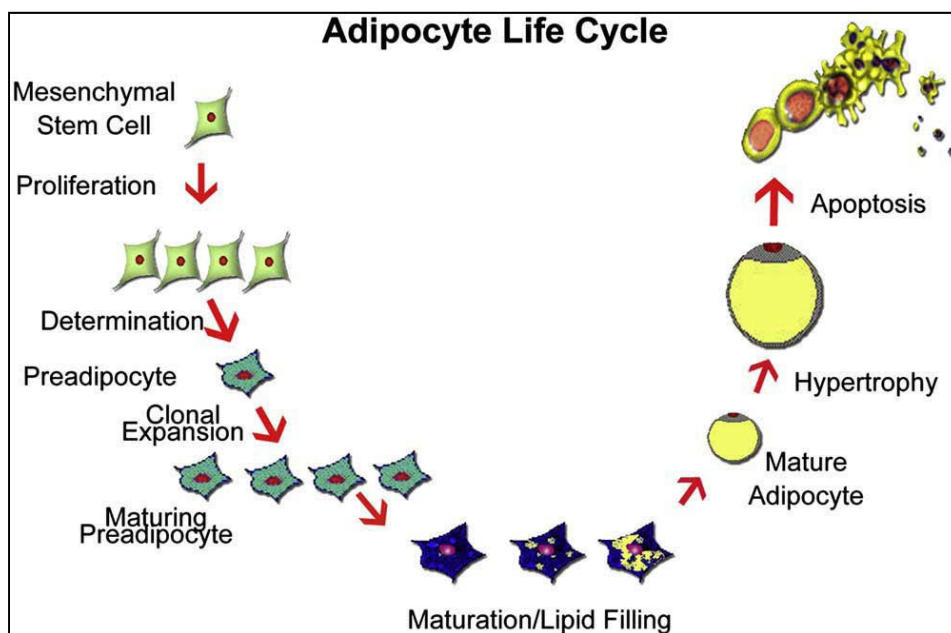
Moreover, the ethanol extract of *Ilex paraguariensis* A. St-Hil improved high fat diet-induced obesity through enhancing  $\beta$ -oxidation of fatty acids, increasing adenosine monophosphate protein kinase (AMPK) activation in visceral adipose tissue, and reducing Acetyl-CoA carboxylase (ACC) activity [159]. Activated AMPK phosphorylates (inactivates) ACC and lowers levels of intracellular malonyl-CoA, which is the fatty acid synthesis substrate. Simultaneously, malonyl-CoA inhibits Carnitine palmitoyltransferase 1 (CPT-1), the rate-limiting enzyme in mitochondrial fatty acid oxidation and metabolism. Hence, these combined processes lead to promotion of fatty acid oxidation [159].

### **Modulators of Adipocyte Life-Cycle**

The adipocyte life cycle (Fig. 2) includes alteration of cell shape and growth arrest, clonal expansion and a complex sequence of changes in gene expression leading to storage of lipid and finally cell death [52, 160].

Adipocytes play a central role in the maintenance of lipid homeostasis and energy balance, by storing triglycerides and releasing free fatty acids in response to

changing energy demands [142]. Since the growth of adipose tissue involves both hyperplasia (proliferation) and hypertrophy (enlargement) of adipocytes, the search for anti-obesity materials largely focused on their modulating behavior towards the processes of adipocyte proliferation and differentiation [161]. Adipose tissue mass can thus be reduced by both inhibiting adipogenesis and inducing apoptosis of adipocytes and natural products that specifically target both these pathways will, therefore, have better potential for treatment and prevention of obesity.



**Figure 2:** Adipocyte life-cycle: Mesenchymal stem cells are the precursors of several different types of cells, including myoblasts, chondroblasts, osteoblasts and preadipocytes. Once preadipocytes are triggered to mature, they begin to change shape and undergo a round of cell division known as clonal expansion, followed by initiation of the genetic program that allows them to synthesize and store triglycerides. Mature adipocytes can continue storing lipid when energy intake exceeds output, and they can mobilize and oxidize lipid when energy output exceeds input. Mature adipocytes can also undergo apoptotic cell death under certain conditions (Through reference [8]).

Usually, 3T3-L1 pre-adipocytes cells are used as an *in vitro* cell-culture model to elucidate the molecular mechanisms involved in modulation of adipogenesis, because they accumulate triglycerides upon differentiation [162, 163] due to the expression of adipocyte specific genes, such as the transcription factor

peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) and the CCAAT/enhancer-binding protein (C/EBP $\alpha$ ) [164, 165]. Consequently, natural products that target adipogenesis inhibition, in particular, could be effective in management of overweight and obesity [166]. Still, the inhibition of adipogenesis or adipose tissue expansion was reported to be unhealthy, inducing a number of metabolic diseases, such as type-2 diabetes and atherosclerosis [165].

Fatty acids, particularly polyunsaturated fatty acids (PUFA), act as signal transducing molecules in adipocyte differentiation. In adipocyte tissue, saturated and monounsaturated fatty acids are more readily acylated into triglycerides than PUFA are [167-169]. Thus, PUFA play a central role in suppressing fatty acid synthesis and regulating adipocyte differentiation through suppression of late-phase adipocyte differentiation [20, 167]. Recent reports have demonstrated another interesting mechanism, in the extract of the mycelia of the macrofungus *Cordyceps militaris* (L.: Fr.) Link., which suppressed 3T3-L1 adipocyte differentiation through activation of the aryl hydrocarbon receptor [170].

On the other hand, numerous natural compounds have demonstrated apoptotic activities on maturing pre-adipocytes and could thus be considered as suitable candidates for treatment of obesity [142]. These include phenolics such as: esculetin, resveratrol, quercetin, genistein and EGCG; capsaicin alkaloid; as well as conjugated linoleic acids. These compounds were found to induce apoptosis of maturing 3T3-L1 pre-adipocytes through a number of mechanisms including suppressing the phosphorylation of the extracellular-signal-regulated kinase ERK1/2, activation of the mitochondrial pathway, AMPK activation, or antioxidant activity [171-175].

Other herbal and dietary inhibitors of adipose differentiation identified include isorhamnetin [166], (-)-epigallocatechin-3-gallate (EGCG) [176], silibinin [177] retinoic acid [178] and 1, 25(OH) 2D3 (1, 25-dihydroxy vitamin D3, calcitriol) [179].

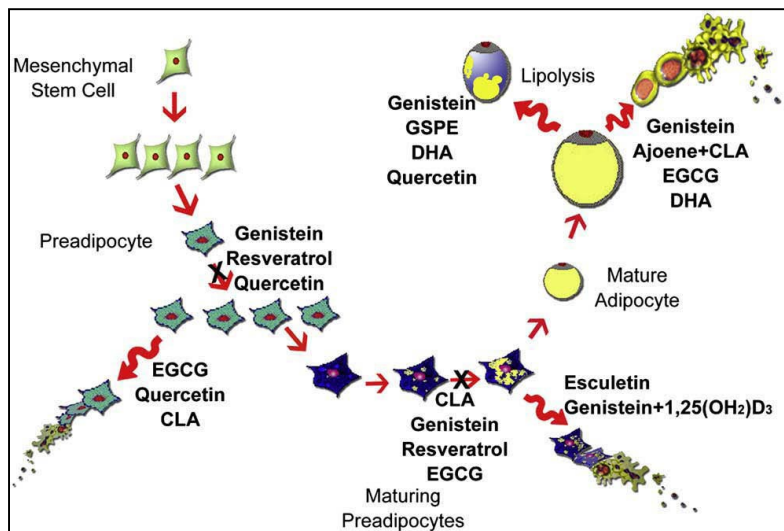
A number of phenolics were found to interfere with 3T3-L1 adipocyte differentiation by arresting the adipocyte cell cycle at the G1 phase [180]. Meanwhile, others efficiently induce apoptosis in 3T3-L1 adipocytes through



AMPK activation [181, 182]. Piceatannol, a natural polyphenolic stilbene, inhibits adipogenesis *via* modulation of mitotic clonal expansion and insulin receptor-dependent insulin signaling in early phase of differentiation [183].

A combination of ajoene, the unsaturated sulfide of *Allium sativum* L. (garlic), with conjugated linoleic acid, has significantly enhanced apoptosis in mature 3T3-L1 adipocytes through a synergistic increase of expression in several proapoptotic factors [52].

The NAD-dependent deacetylase, Sirtuin 1 (SIRT1), is an enzyme that deacylates proteins; it contributes to cellular regulation and could be targeted in anti-obesity management. Resveratrol, a phenolic stilbenoid, was found to decrease adipogenesis; its effect was indicated to be associated with increased expression of SIRT1, which promotes fat mobilization by repressing the peroxisome proliferator-activated receptor c (PPARc) [52, 184].



**Figure 3:** Effect of selected natural compounds on the different stages of the adipocyte life-cycle: Genistein inhibits preadipocyte proliferation and suppresses lipid accumulation in maturing preadipocytes. It also triggers lipolysis and induces apoptosis in mature adipocytes, and in combination with 1, 25(OH)<sub>2</sub>D<sub>3</sub>, it can induce apoptosis in maturing preadipocytes. EGCG induces apoptosis in both preadipocytes and mature adipocytes, and it can inhibit lipid accumulation in maturing preadipocytes. Quercetin also has multiple effects: it can inhibit preadipocyte proliferation, induce preadipocyte apoptosis and stimulate lipolysis in mature adipocytes. Ajoene+CLA are especially potent in inducing apoptosis in mature adipocytes (Through reference [52]).

The modulator effects of selected natural compounds, used single or in combination, on the adipocyte life-cycle are illustrated in Fig. 3 [52].

### **Regulators of Lipid Metabolism**

Lipolysis could be achieved by stimulating triglyceride hydrolysis in order to diminish fat stores and thereby controlling overweight and obesity. This alternative mechanism of action is associated with oxidation of the recently released fatty acids and led to the development of the  $\beta_3$ -adrenergic agonists [185]. Yet, extreme lipolysis results in high circulating fatty acid levels and development of dyslipidemia; therefore, blocking of fatty acid release may be of therapeutic interest [185]. Among, natural products involved in  $\beta$ -adrenergic receptor activation are the flavonoid constituents of the extract of the leaves of *Nelumbo nucifera* Gaertn. (Lotus leaves) [186].

Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), the transcription factor chiefly expressed in adipose tissue activates adipocyte differentiation both *in vivo* and *in vitro* [187]; when this factor is overexpressed, 3T3-L1 pre-adipocyte induction starts. This suggests that PPAR $\gamma$  suppression blocks adipogenesis and lipogenesis [165]. As a matter of fact, PPAR $\gamma$  agonists were found to improve dyslipidemia and insulin resistance. Beside, PPAR $\gamma$  agonists prevented increased adiposity and body weight without any reduction in food intake [188]. PPAR $\alpha$  is another enzyme responsible for fatty acid  $\beta$ -oxidation.

The aqueous extract of the root of *Salacia oblonga* Wall., having the phenolic xanthonoid magniferin as major component, has demonstrated PPAR $\alpha$  activator effect. This extract improved postprandial (after meal) hyperlipidemic and hepatic steatosis (fatty degeneration) in animal model [181].

Caffeine, a major component of oolong tea, helps in obesity control through a different structure-related mechanism. Caffeine molecule, similar to adrenaline, possesses both a positive charge and a hydrophobic moiety. Its lipolytic effect might be exerted through binding to the phospholipid phosphate groups and subsequent interactions between the lipase and triglyceride portions of lipid droplets, thus eliciting lipolysis [72].

A number of lipid metabolism inhibitors were discovered from microbial sources [86]. These mainly affect fatty acid and cholesterol metabolic pathways by acting as fatty acid synthase inhibitors (e.g. cerulenin), acyl-CoA synthetase inhibitors (e.g. triacsin C) or HMG-CoA synthase inhibitors (e.g. hymeglusin). Others comprise thiotetromycin, chlorogentisylquinone, as well as the beauverolides, pyripyropenes, terpendoles, and ferroverdins [86].

### **Natural Products with Multi-Functional Anti-Obesity Activity**

The previous survey reveals that a large number of natural products manage overweight and anti-obesity through variable mechanisms. A promising approach to efficiently fulfill this purpose is to use single products having multiple activities or to combine the synergistic effects of several products [52].

The most reputed natural products with possible multi-functional anti-obesity activity are green tea (*Camellia sinensis*) [72] and *Garcinia cambogia* [189]. Although other examples such as roselle (*Hibiscus sabdariffa*) [190], pomegranate (*Punica granatum*) [191], peanut (*Arachis hypogaea*) [70] and lotus (*Nelumbo nucifera*) [65] can be also cited.

Green tea was reported to possess a more pronounced anti-oxidant than anti-obesity activity, this due to its high catechin content, namely epicatechin, ECG, and EGCG. Later on, catechins were found to exert an antiobesity activity through a complex pharmacological action including: appetite suppression, increased lipolysis and energy expenditure, and decreased lipogenesis and adipocyte differentiation [74, 75, 97, 107-109, 156, 173, 176,192]. Thus, green tea extracts exert anti-obesity activities mainly through lipase inhibition and thermogenesis stimulation [97].

The commercially-available dried fruit extract of *Garcinia cambogia* tree is widely used to control obesity owing to its main active constituent, (-)-hydroxycitric acid [193]. *Garcinia cambogia* reduces lipogenesis by preventing the metabolism of carbohydrates into fats; moreover, it enhances excess fats burning, and suppresses appetite [193]. Its ability to inhibit adipocyte differentiation and to reduce fatty acid synthesis, lipogenesis as well as epididymal fat accumulation was established to be *via* reduction of ATP-citrate lyase activity [193, 194].

The aqueous extract of *Hibiscus sabdariffa* calyx and epicalyx (major constituents, anthocyanins) exert a potential anti-obesity effect through a number of mechanisms including anti-hyperglycemic activity, reduction of plasma cholesterol level, inhibition of gastric and pancreatic lipases, stimulation of thermogenesis, inhibition of lipid droplet accumulation in adipocytes, and inhibition of fatty acid synthase [190].

Pomegranate leaf extract (major components, ellagic and tannic acids) acts through a dual anti-obesity mechanism; it was reported as PL inhibitor, in addition to energy intake suppressant closely resembling sibutramine in this respect but acting through a different mechanism [191].

Extracts of peanut (*Arachis hypogaea*) shell were also reported to aid in obesity control by inhibiting fat absorption in the digestive tract, activating lipid metabolism in the liver, and reducing adipocyte lipolysis [70].

The lotus (*Nelumbo nucifera*) leaf extract possesses multiple anti-obesity activities, including inhibition of lipid and carbohydrate absorption and acceleration of lipid metabolism and energy expenditure [65].

*Salacia reticulata* stem extract met multiple obesity-reduction targets by both inhibition of  $\alpha$ -glucosidase and PL and modulation of PPAR $\alpha$ -mediated lipogenic gene transcription and angiotensin II type 1 receptor signaling [195].

Among isolated metabolites, raspberry ketone (rheosmin, a natural phenolic isolated from *Rubus* spp.) and numerous polyunsaturated fatty acids aid in obesity control *via* combined mechanisms of action. Raspberry ketone increases norepinephrine-induced lipolysis in WAT and enhances thermogenesis in BAT [196, 197]. Polyunsaturated fatty acids upregulate mitochondrial biogenesis and suppress adipocyte lipogenesis [150].

Taken together, combination therapies employing natural products that target different obesity genes and/or different stages of the adipocyte life cycle might prove beneficial in treating obesity.

## PLANT AND MICROBIAL SOURCES WITH MULTI-FUNCTIONAL ANTI-OBESITY ACTIVITY

### Higher Plants

#### *Aesculus turbinata*



**Name:** *Aesculus turbinata* Blume, Sapindaceae (Hippocastanaceae).

**Common name:** Japanese horse chest nut.

**Part used:** Seeds.

**Main active constituents:** Saponins; escins.

**Pharmacological action:** The total escins (1 mg/ml) inhibit pancreatic lipase (PL) activity. *In vivo*, total escins suppress the increase in body weight, parametrial adipose tissue weight, TG (triglyceride) and TC (total cholesterol) contents in mice's liver, with an increase TG level in the feces [198]. Also, anti-obesity effects of the polymerized proanthocyanidins from seed shells in mice are reported. Highly polymerized proanthocyanidins suppress the elevation of blood glucose, by preferential inhibition of the digestive enzymes of carbohydrates. Their anti-obesity effects is more evident after 9 weeks by the attenuation of the elevation in body weight, the mass of peritoneal adipose tissues, and the plasma levels of total cholesterol and leptin. Furthermore, a dietary supplement of the total proanthocyanidin fraction normalizes the increased size of hepatocytes and the generation of steatosis with micro- and macrovesicles in liver [199].

***Allium victoralis***



**Name:** *Allium victoralis* var. *platyphyllum* Makino, Alliaceae (Liliaceae).

**Common name:** Korean long-rooted garlic.

**Part used:** Leaves.

**Main active constituents:** Polyphenols.

**Pharmacological action:** The ethanolic extract decreases body weight gain, liver triglyceride content and liver size in association with an increase fecal lipid excretion, suggesting an inhibitory mechanism on lipid absorption [200]. The extract also causes considerable reduction of retroperitoneal, epididymal and total abdominal fat weight [29].

***Arachis hypogea***



**Name:** *Arachis hypogea* L., Fabaceae.

**Common name:** Peanut, Groundnut.

**Part used:** Seed shell, nut shell.

**Main active constituents:** Phytoalexins, stilbenoids.

**Pharmacological action:** An ethanolic extract of peanut shell PS (peanut shell extract) inhibits a number of lipases, including PL, LPL and, possibly, hormone sensitive lipase (HSL) [70]. Body weight and body weight gain, and liver size are decreased in rats fed the high-fat diet and 1% of PSE (w:w diet). Also, TG content in the liver, as well as the serum glucose and insulin are lowered. It also reduces intracellular lipolytic activity of cultured adipocytes which may reduce the levels of circulating free fatty acids. These effects are likely induced by more than one bioactive component of PSE. The PSE actions may, at least in part, be attributed to the inhibition of fat absorption in the digestive tract and the reduction of the adipocyte lipolysis [70].

### *Aralia elata*



**Name:** *Aralia mandshurica*, *Aralia elata* Miq. var. *mandshurica*, Araliaceae.

**Common name:** Japanese Angelica tree and Manchurian thorn.

**Part used:** Root and stem barks.

**Main active constituents:** Triterpenoid saponins, aralosides. Root and stem barks contain oleanolic acid, oleanolic acid derivatives and glucopyranoside, araloside A, C, and G. Tarasaponin I-VIII; stigmasterol; sitosterol.

**Pharmacological action:** Stimulation of hormone-sensitive lipase [201].

***Asparagus officinalis***



**Name:** *Asparagus officinalis* L. (DC), Asparagaceae.

**Common name:** Asparagus or garden asparagus.

**Part used:** Stems.

**Main active constituents:** Steroidal saponins; sarsasapogenin.

**Pharmacological action:** Ethanolic and aqueous extracts of asparagus significantly decrease the levels of body weight gain; serum total cholesterol and serum low-density lipoprotein cholesterol in hyperlipidaemic mice when administered at a daily dose of  $200 \text{ mg kg}^{-1}$  for 8 weeks. Also, serum high-density lipoprotein cholesterol levels are evidently increased. Moreover, both extracts dramatically decrease the activities of alanine and aspartate transaminases in serum [202]. Clinical studies revealed improvement of blood pressure, physical and emotional well-being and quality of life [203].

***Camellia sinensis***

**Name:** *Camellia sinensis* L. (Kuntze), Theaceae.

**Common name:** White tea, green tea, oolong and black tea.

**Part used:** Leaves.





**Main active constituents:** Polyphenols, caffeine, acylated oleanane triterpene saponins, floratheasaponins.

**Pharmacological action:** *In vitro*, green tea extract (hydro-alcoholic extract) exerts a direct inhibition of gastric and pancreatic lipases, inhibition of triglycerides lipolysis and a stimulation of thermogenesis [97]. The extract significantly, decreases hepatic steatosis and serum ALT and AST activities are lowered [204]. **Oolong tea** (Black dragon tea) extract enhances noradrenaline induced lipolysis and inhibits pancreatic lipase activity [72].

***Caralluma fimbriata***



**Name:** *Caralluma fimbriata* Wall., Asclepiadiaceae (Apocyanaceae).

**Common name:** Cactus, Kalli Mooliyan, Kallimudayan (Tamil), Karallamu (Telugu) (Sanskrit), Ranshabar, Makad Shenguli, Shindala Makadi.

**Part used:** Aerial parts (edible cactus).

**Main active constituents:** Flavonoids, tannins proanthocyanidins and pregnane glycosides.

**Pharmacological action:** Pregnane glycosides or its related molecules suppress appetite, by amplifying the signaling sensing function in the basal hypothalamus [101, 111]. Clinical studies evidence a significant decrease in waist circumference, hunger levels, body weight, BMI (body mass index), hip circumference and body fat in over weight volunteers fed with *Caralluma* extract [111].

### *Cissus quadrangularis*



**Name:** *Cissus quadrangularis* L. = *Vitis quadrangularis* L., Vitaceae.

**Common name:** Veldt Grape, Devil's Backbone.

**Part used:** Aerial parts.

**Main active constituents:** Flavonols, isoflavones, resveratrol and its stilbene glycosides.

**Pharmacological action:** A standardized extract of *C. quadrangularis* containing 2.5% keto-steroids and 15% soluble plant fiber significantly reduces plasma TBARS (Thiobarbituric acid reactive substance- byproduct of lipid peroxidation) and carbonyls, as well as body weight, body fat, total cholesterol, LDL-cholesterol, triglycerides, and fasting blood glucose levels. This decrease in serum

lipids improves cardiovascular risk factors. While the increase in plasma 5-HT and creatinine hypothesizes a mechanism of controlling appetite and promoting the increase of lean muscle mass by *Cissus quadrangularis*, thereby supporting the clinical data for weight loss and improving cardiovascular health [205].

### ***Citrus aurantium***



**Name:** *Citrus aurantium* L., Rutaceae.

**Common name:** Bitter orange, Seville orange.

**Part used:** Peels.

**Main active constituents:** Tyramine derivative; synephrine.

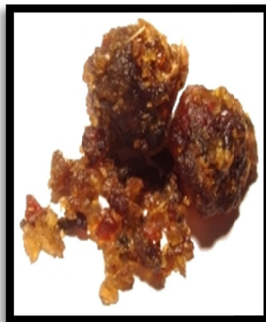
**Pharmacological action:** Bitter orange peel works in a similar way to ephedrine, stimulating the release of catecholamines. Bitter orange peel extract raises the metabolic rate. Synephrine, which has thermogenic properties, is structurally related to ephedrine. The extract of bitter orange peel contains tyramine and octopamine. Studies show that octopamine gives the feeling of fullness on fewer calories. This makes bitter orange peel very popular with dieters who struggle to control their food cravings [206, 207].

### ***Commiphora mukul***

**Name:** *Commiphora mukul* (Stocks) Hook. = *Commiphora wightii* (Arn.) Bhandari, Burseraceae.

**Common name:** Guggal, guggul or mukul, myrrh tree.

**Part used:** Gum, gummy resin.



**Main active constituents:** Extract of gugul gum (gugulipid), pregnane derivative, guggulsterone; 20(S), 21-epoxy-3-oxocholest 4-ene, 8 $\beta$ -hydroxy-3, 20-dioxopregn-4,6-diene, and 5-(13' Z-nonadecenyl) resorcinol.

**Pharmacological action:** The extract inhibits NO formation in lipopolysaccharide (LPS)-activated murine macrophages J774 [208]. Guggulsterone inhibits the differentiation of preadipocytes, induces apoptosis and promotes lipolysis of mature adipocytes [175].

### *Dimocarpus longan*



**Name:** *Dimocarpus longan* Lour. = *Euphoria longan* Steud., Sapindaceae.

**Common name:** Longan or dragon eye (as it resembles an eyeball when its fruit is shelled, the black seed shows through the translucent flesh-like a pupil/iris).

**Part used:** Flower and fruit.

**Main active constituents:** Polyphenolic compounds; phenolic acids and flavonoids.

**Pharmacological action:** Longan flower water extract inhibits pancreatic lipase activity, sterol regulatory element binding protein-1c (SREBP-1c) and fatty acid synthase (FAS) gene expressions, and increases fecal triglyceride excretion. This results in a decrease in, body weight, size of epididymal fat, serum triglyceride level and atherogenic index, and hepatic lipids [209].

### *Ephedra sinica*



**Name:** *Ephedra sinica* Stapf, Ephedraceae.

**Common name:** Ma Huang, Chinese ephedra.

**Part used:** Stems.

**Main active constituents:** Phenyl alkylamine alkaloids, ephedrine.

**Pharmacological action:** Ma Huang (*Ephedra sinica*) significantly decrease food intake and body weight in animals treated with the aqueous herb extract (25 and 50 mg/100 g bw/day). However, the fluid intake increases, even above the levels of control animals and tests, in Ma Huang treated groups, 100 mg/100 mg/100 g bw/day, indicating that Ma Huang effects on adipogenesis are dose-dependent [210]. Clinically, ephedra extract significantly decreases serum cholesterol,

triglycerides, glucose, fasting insulin and leptin levels in obese and over-weight women [211].

### *Garcinia cambogia*



**Name:** *Garcinia cambogia* L., *Garcinia gummi-gutta* (L.) N. Robson, *G. quaestia*, *Mangostana cambogia* (Gaern.) Clusiaceae (Guttiferae).

**Common name:** Gambooge, brindleberry, bitter cola, brindall berry, Malabar tamarind or Essam fruit. Commonly, the plants in this genus are called saptrees, mangosteens (which may refer specifically to the purple mangosteen, *G. mangostana*), garcinias or, ambiguously, "monkey fruit".

**Part used:** Fruits, rind and seed.

**Main active constituents:** Hydroxy-citric acid.

**Pharmacological action:** Administration of *Garcinia cambogia* (powder) containing HCA suppresses body fat accumulation in obese rats at different doses of HCA. The highest dose of HCA-containing *Garcinia cambogia* (154 mmol HCA/kg diet) causes significant suppression of epididymal fat accumulation in male obese rats. Fifty-one mmol HCA/kg diet (389 mg HCA/kg BW/d) is the chosen dose with no observed adverse effect level (NOAEL) [194]. *Garcinia cambogia* seed (220 and 400 mg/kg) fed for 5 weeks in rats decreases triglyceride pool of adipose tissue and liver, with a significant increase in HDL and decrease in LDL [189].



***Glycyrrhiza glabra***

**Name:** *Glycyrrhiza glabra* L., European licorice, *Glycyrrhiza uralensis*, Chinese licorice, *Glycyrrhiza lepidota* American licorice, Fabaceae

**Common name:** Liquorice or licorice.

**Part used:** Rhizomes and roots.



**Main active constituents:** Triterpenoidal saponins and flavonoids.

**Pharmacological action:** Licorice flavonoids decrease abdominal WAT and body weight gain (at concentrations of 1% and 2%) with a decrease in adipocyte size in obese mouse. Moreover, at concentration 2% it improves fatty degeneration of hepatocytes and changes in genes implicating regulation of lipid metabolism [212]. Clinical studies on obese women, with impaired glucose tolerance, taking an herbal medicine containing licorice, show a significant decrease in body weight and abdominal visceral fats with significant improvement in insulin resistance [213].

***Gymnema sylvestra***



**Name:** *Gymnema sylvestre* R. Br., Asclepiadaceae.

**Common name:** Gurmar (sugar destroyer), miracle fruit.

**Part used:** Leaves.

**Main active constituents:** Oleanane saponins, gymnemic acids (saponins), flavones and anthraquinones.

**Pharmacological action:** Gymnemic acids stimulate the pancreas and thus increase insulin release. These compounds have also been found to increase fecal excretion of cholesterol. There are some possible mechanisms by which the leaves extract of *G. sylvestre* or (gymnemic acid) exerts its hypoglycemic acid effects including: [214, 215].

- a. Promotion for the regeneration of islet cells.
- b. Enhancement of insulin secretion.
- c. Inhibition of glucose absorption from intestine.
- d. Enhancement of glucose utilization due to an increase in the enzyme activity responsible for utilization of glucose by insulin-dependent pathways, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase.

***Hibiscus sabdariffa***



**Name:** *Hibiscus sabdariffa* L., Malvaceae.



**Common name:** Roselle.

**Part used:** Calyx and epicalyx.

**Main active constituents:** Anthocyanins.

**Pharmacological action:** *Hibiscus sabdariffa* aqueous extract (33.64 mg of total anthocyanins/120 mg of extract) significantly reduces body weight gain in obese mice and increases liquid intake in healthy and obese mice. ALT levels are significantly increased in obese mice, but AST levels are not affected. Triglycerides and cholesterol levels are not affected as well [190].

### *Hoodia gordonii*



**Name:** *Hoodia gordonii* (Masson) Sweet ex Decne. *Opuntia dillenii* (Ker Gawl.) Haw., *Stapelia gordon* (Masson), Asclepiadaceae (Cactaceae).

**Common name:** Hoodia.

**Part used:** Stem.

**Main active constituents:** Pregnane glycosides (calogenin glycoside)

**Pharmacological action:** It acts as an appetite suppressant and reduces food intake [216]. Methylene chloride extract of *Hoodia gordonii* and two isolated pregnane glycosides (tested orally at doses 6.25-50 mg/kg) decrease food consumption and food intake [103].

***Hordeum vulgare***

**Name:** *Hordeum vulgare* L., Poaceae.

**Common name:** Barley.

**Part used:** Seeds.

**Main active constituents:** Polysaccharides and saponins.

**Pharmacological action:** Plasma lipid-lowering effects of barley have been attributed to its high content of  $\beta$ -glucan, a water-soluble fiber [217-219]. The  $\beta$ -glucan component of barley slows down the gastric emptying time, prolonging the feeling of fullness, and hence stabilizes blood sugars. Other contributory factors may be d- $\alpha$ -tocotrienol, which has the ability to affect lipid controlling enzymes and lower cholesterol. Barley contains fermentable carbohydrates; fermentation of undigested carbohydrate produces short chain fatty acids, some of which may reduce hepatic glucose production and affect postprandial glycemia. The  $\beta$ -glucan significantly decreases glycemic and insulinemic responses on food [220].

***Ilex paraguariensis***

**Name:** *Ilex paraguariensis* A. St. Hil., Aquifoliaceae.

**Common name:** Yerba mate.

**Part used:** Leaves.

**Main active constituents:** Polyphenols, caffeine and saponins.

**Pharmacological action:** The effect of mate on weight loss is due to both its caffeine content, contributing to lipolytic activity and saponin content, interfering with cholesterol metabolism and delaying intestinal absorption of dietary fat [221]. Mate tea also affects other aspects of lipid metabolism; it has the ability to inhibit atherosclerosis (in rabbits) when fed with a high cholesterol diet and an aqueous extract of Mate tea [222]. Giving Mate extracts to hypercholesterolemic-diet fed rats reduces serum concentrations of cholesterol and triglycerides [223]. Mate is a potential digestive aid due to a choleric effect and through increasing the rate of bile flow [224].

### *Irvingia gabonensis*



**Name:** *Irvingia gabonensis*, (Aubry-Lecomte ex O'Rorke) Baill., Irvingiaceae.

**Common name:** African mango.

**Part used:** Seeds.

**Main active constituents:** Ascorbic acid, polyphenols and carotenoids.

**Pharmacological action:** *Irvingia gabonensis* seed extract decreases body weight. The obese patients under *Irvingia gabonensis* treatment show a significant

decrease of total cholesterol, LDL-cholesterol, triglycerides, and an increase of HDL-cholesterol [225]. The soluble fibre of the seed of *I. gabonensis* like other forms of water-soluble dietary fibres, are "bulk-forming" laxatives. *Irvingia gabonensis* seeds delay stomach emptying, leading to a more gradual absorption of dietary sugar. This effect can reduce the elevation of blood sugar levels that is typical after a meal [226]. The soluble fibers of *I. gabonensis* seed can bind to bile acids in the gut and carry them out of the body in the feces, which requires the body to convert more cholesterol into bile acids. This can result in lowering blood cholesterol as well as other blood lipids [227].

### *Kochia scoparia*



**Name:** *Kochia scoparia* (L.) Schrad. = *Bassia scoparia*, (L.) A.J. Scott, *Chenopodium scoparia* L., Chenopodiaceae.

**Common name:** Mock cypress, kochia, fireweed, summer cypress.

**Part used:** Fruits.

**Main active constituents:** Saponins; scopariosides, momordin Ic, IIc and its 2'-O-β-D- glucopyranoside.

**Pharmacological action:** Momordin and its 2'-O-β-D-glucopyranoside (principal saponin constituents) potently inhibit glucose and ethanol absorption [228]. The ethanol extract of *K. scoparia* fruit prevents the increase in body weight and parametrial adipose tissue weight induced by the high-fat diet. Furthermore, consumption of a high-fat diet containing 1% or 3% *K. scoparia* extract significantly increase the fecal content and the fecal triacylglycerol level. The ethanol extract (250 mg/kg) and total saponins (100 mg/kg) of *K. scoparia* inhibit the elevation of the

plasma triacylglycerol level. Total saponins and momordin isolated from *K. scoparia* fruit inhibit the PL activity (*in vitro*). Therefore, the anti-obesity actions of *K. scoparia* extract in a high-fat diet may be partly mediated through delaying the intestinal absorption of dietary fat by inhibiting PL activity [229].

### *Ligusticum sinense*



**Name:** *Ligusticum sinense* (Lour.) Oliv. (= *Ligusticum chuanxiong* S. H.), Oleaceae.

**Common name:** Chinese privet, gaoben, lovage root.

**Part used:** Roots.

**Main active constituents:** Volatile oil and phenolic acids.

**Pharmacological action:** An herbal preparation (Slimax) containing *Ligusticum sinense* decreases body weight, waist and hip circumference and Body Mass Index (BMI). The basis of its anti-obesity effect is through modification of lipid metabolism, with significant impact on both the accumulation and the release of lipid from adipose tissue [230].

### *Lilium brownii*



**Name** *Lilium brownii* F. E. Brown var. *viridulum* Baker, Liliaceae.

**Common name:** Lily bulb.

**Part used:** Dried fleshy scale leaf.

**Main active constituents:** Steroidal saponins, phenolic compounds and alkaloids.

**Pharmacological action:** An herbal preparation (Slimax) containing Lilly bulb extract decreases body weight, waist and hip circumference and body mass index (BMI), by modification of lipid metabolism affecting accumulation and release of lipid from adipose tissue [230].

***Momordica charantia***



**Name:** *Momordica charantia* L., Cucurbitaceae,

**Common name:** Bitter melon, bitter gourd or bitter squash.

**Part used:** Fruit.

**Main active constituents:** Terpenoid compounds; momordicin I and II, and cucurbitacin.

**Pharmacological action:** The fruit water extract significantly decreases the epididymal WAT weight and visceral fat weight. Also, it improves blood glucose level and leptin [231]. In other studies, the treatment of rats with high fat diet (HFD) with the fruit extract causes a significant decrease in the number of large adipocytes and also a decrease in adipose tissue mass with a decrease in weight gain without affecting food consumption [4].



***Panax ginseng***

**Name:** *Panax ginseng* C.A. Meyer (*P. schinseng* Nees) (the most widely used), Araliaceae. *Panax japonicum* C.A. Meyer (Japanese ginseng).

**Common name:** Panax, Korean ginseng, Asian ginseng, Chinese ginseng, Oriental ginseng, true ginseng, Racine de ginseng.

**Part used:** Root and berries.

**Main active constituents:** Dammarane-type saponins; ginsenosides (panaxosides), steroidal and pentacyclic triterpenoid saponins.

**Pharmacological action:** The crude saponin of Korean red ginseng reduces body weight, food intake and fat content in (HFD) rats by reduction of hypothalamic NPY (Neuropeptide Y) expression and serum leptin [106]. On the other hand, wild ginseng ethanolic extracts exhibit significant inhibition of body weight gain (dose-dependent) with a decrease of white and brown adipocyte diameters. There is also significant inhibition of fasting blood glucose and triglyceride levels (dose-dependently) and improvement of insulin resistance [232]. Ginseng berries decrease body weight with significant increase in glucose tolerance but no significant decrease in FBG (fasting blood glucose) [233].

***Phaseolus vulgaris***

**Name:** *Phaseolus vulgaris* L., Fabaceae.

**Common name:** Kidney bean, the green bean, or common bean.

**Part used:** Seeds.

**Main active constituents:** Carbohydrates and lipids.

**Pharmacological action:** Reduction of body weight, BMI, fat mass, adipose tissue thickness, and waist/hip/thigh circumferences [95]. Seeds of *P. vulgaris* (300 g/kg bw) show maximal blood glucose lowering effect in diabetic rats. The combination of seeds (300 mg/kg bw) and glibenclamide (0.20 g/kg bw) are safer and potent hypoglycemics as well as antihyperglycemics, without creating severe hypoglycemia in normal rats [234]. *P. vulgaris* extract acts as  $\alpha$ -amylase inhibitor starch blockers. Consumption of the  $\alpha$ -amylase inhibitor causes marginal intraluminal  $\alpha$ -amylase activity facilitated by the inhibitor's appropriate structural, physico-chemical and functional properties. As a result there is decrease in postprandial plasma hyperglycaemia and insulin levels, increase resistance of starch to digestion and an increase in the activity of colorectal bacteria. The extracts are potential ingredients in foods for increased carbohydrate tolerance in diabetics, decreased energy intake for reducing obesity and for increased resistant starch [235].

### ***Punica granatum***



**Name:** *Punica granatum* L., Punicaceae

**Common name:** Pomegranate, Anar.

**Part used:** Seeds and flowers.



**Main active constituents:** Phenolic constituents; hydrolyzable tannins: pomegranate ellagitannins (punicalagins).

**Pharmacological action:** The aqueous extract of pomegranate leaves (AEP) and its isolated compounds (ellagic and tannic acid) show a significant decrease in body weight, energy intake and various adipose pad weight percent and serum, TC (total cholesterol), TG (triglycerides), glucose levels and TC/HDL-C ratio on mice fed with high fat diet (obese). Moreover, AEP significantly attenuates the raising of the serum TG level and inhibits the intestinal fat absorption, in addition to, a significant difference in decreasing the appetite of obese mice. These effects are partly mediated by inhibiting PL activity and suppressing energy intake [191].

***Platycodon grandiflorum***



**Name:** *Platycodon grandiflorum* (Jacq.) A. DC., Campanulaceae.

**Common name:** Japanese bellflower, common balloon flower, or balloon flower.

**Part used:** Root.

**Main active constituents:** Triterpenoid saponins: sapogenins platycodigenin and polygalacic acid; platycodins A-I and polygalacins D and D2.

**Pharmacological action:** The aqueous *Platycodon grandiflorum* extract (150 mg/kg), when fed to obese rats, decreases significantly body weight with adipose tissues being converted to NLD (Necrobiosis lipoidica diabetorum). In addition, it significantly decreases fat cells number and size and FABP (fatty acid binding protein) expression [236].

***Rheum palmatum***



**Name:** *Rheum palmatum* L., Polygonaceae.

**Common name:** Rhubarb.

**Part used:** Rhizome and root.

**Main Active Constituents:** Anthraquinones, flavonoids; free and combined.

**Pharmacological action:** Methanolic extracts from *Rheum palmatum* L., at a concentration of 200 mg/mL, significantly inhibit PPL. Emodin, one of the main effective components in *R. palmatum* promotes proliferation of 3T3-L1 preadipocyte at low concentration and inhibits the proliferation at high concentration in a dose-related manner. In contrast, it inhibits cell differentiation into adipocyte at low concentration in a dose-related manner. Emodin exerts anti-lipase activity which suggests that it can be used as an anti-obesity drug [237].

***Rubus coreanus***



**Name:** *Rubus coreanus* Miq., Rosaceae.

**Common name:** Korean blackberry.

**Part used:** Berries.

**Main active constituents:** Anthocyanins, dimeric triterpene glucosyl ester; 23-Hydroxytormentonic acid.

**Pharmacological action:** *Rubus coreanus* significantly reduces intracellular lipid accumulation by regulating PPAR $\gamma$  and C/EBP $\alpha$  (PPAR $\gamma$  and C/EBP $\alpha$  are critical transcription factors in adipogenesis) [238]. High content of anthocyanins attenuates the adipogenesis by inhibition of the Nrf2 binding with regions of PPAR $\gamma$  promoter (PPAR $\gamma$  is a nuclear receptor that controls lipid and glucose metabolism and exerts anti-inflammatory activities). Anthocyanins play an important role in anti-adipogenic activity by regulation of Nrf2 activation (a powerful protein that is dormant within each cell in the body, unable to move or perform until it is released by an Nrf2 activator. Once released it migrates into the cell nucleus and bonds to the DNA at the location of the Antioxidant Response Element (ARE) or also called hARE (Human Antioxidant Response Element) which is the master regulator of the entire antioxidant system that is present in all human cells) [238].

### *Rubus idaeus*



**Name:** *Rubus idaeus* L, Rosaceae.

**Common name:** Red raspberry.

**Part used:** Berries.

**Main active constituents:** Polyphenols and raspberry ketone.

**Pharmacological action:** RK (Raspberry ketone), administered to mice either admixed in concentrations 0.5-2% to a high-fat diet for 10 weeks or to mice fed a high-fat diet for 6 weeks and subsequently fed the same diet containing 1% RK for the next 5 weeks, reveals anti-obesity activity. RK (Raspberry ketone) prevents the high-fat-diet-induced elevations in body weight and the weights of the liver and visceral adipose tissues (epididymal, retroperitoneal, and mesenteric) in mice. RK also decreases these weights and hepatic triacylglycerol content after being increased by a high-fat diet. RK significantly increases norepinephrine-induced lipolysis associated with the translocation of hormone-sensitive lipase from the cytosol to lipid droplets in rat epididymal fat cells. In conclusion, RK prevents and improves obesity and fatty liver [196].

### ***Salacia reticulata***



**Name:** *Salacia reticulata* Wight., Hippocrateaceae.

**Common name:** Sinhala: Kothalahimbatu.

**Part used:** Root bark.

**Main active constituents:** Polyphenols; salacinol, kotalanol, and mangiferin.

**Pharmacological action:** The aqueous extract of *Salacia reticulata* root (125 mg/kg) suppresses body weight and periuterine fat storage in female obese rats. Polyphenolic compounds, isolated from *Salacia reticulata*, are involved in its anti-obesity effects through inhibition of fat metabolizing enzymes (PL, LPL and GPDH (Glycerol-3-phosphate dehydrogenase; an enzyme maintaining lipid metabolism)) and enhance lipolysis [239].

***Sambucus nigra***



**Name:** *Sambucus nigra* L., Adoxaceae.

**Common name:** Elder, elderberry, black elder, European elder, European elderberry, European black elderberry, common elder, or elder bush.

**Part used:** Flower heads and berries.

**Main Active Constituents:** Phenolic compounds; flavonoids and anthocyanins.

**Pharmacological action:** The juice directly stimulates insulin secretion and glucose metabolism [240]. Powdered elder juice decreases total cholesterol and induces slight reductions in triglycerides, and HDL- and LDL-cholesterol [241]. Also, food supplements containing elderberry cause significant decrease in plasma and hepatic lipids [242].

***Terminalia arjuna***



**Name:** *Terminalia arjuna* (Roxb.) Wight & Arn. Combretaceae.

**Common name:** Whitem, arjun or Koha.

**Part used:** Herb and bark.

**Main Active Constituents:** Tannins, and saponin glycosides.

**Pharmacological action:** The petroleum ether extract of *Terminalia arjuna* causes a significant decrease in body weight in hyperlipidemic humans, accompanied by significant decrease in serum total lipid levels [243].

### *Zingiber officinale*



**Name:** *Zingiber officinale* L., Zingiberaceae.

**Common name:** Ginger Root.

**Part used:** Dried, peeled rhizome, chopped.

**Main active constituents:** Gingerol and shogaol (oleoresins).

**Pharmacological action:** Aqueous extract of *Z.officinale* at 0.4 ml/kg body weight causes significant decrease in plasma glucose and cholesterol in rats [244]. Ethanolic extract of ginger (200 mg/kg) lowers: serum triglycerides, lipoproteins, phospholipids, as well as serum and tissue cholesterol. Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice [245].



## Lower Plants and Micro-Organisms

### Algae

#### *Brown algae*

Phaeophyta, Phylum Heterokontophyta and Class Phaeophyceae; about 1800 species; examples of brown algae are the seaweeds of genus *Fucus* commonly called "rockweed," or "wracks," and members of genus *Sargassum*, which form floating mats.



**Name:** *Undaria pinnatifida* (Harvey) Suringar = *Alaria pinnatifida* Harvey, Alariaceae.

**Common name:** Brown algae, wakame, kelp and seaweeds.

**Part used:** Thallus.

**Main active constituents:** Fucoidan (sulfated fucose containing polysaccharide, found in the fibrillar cell walls and intercellular spaces of brown seaweeds of the class Phaeophyceae) and fucoxanthin (carotenoid).

**Pharmacological action:** PL inhibitors; Fucoidan reduces lipid accumulation by stimulating lipolysis. Treatment with fucoidan reduces lipid accumulation in cells in a dose-dependent manner suggesting that it can be useful for prevention or treatment of obesity [246]. Fucoxanthin, isolated from wakame significantly suppresses body weight and white adipose tissues (WAT). A dietary of wakame

may ameliorate alterations in lipid metabolism and insulin resistance induced by a HFD (high fat diet) [247]. The anti-obesity effect of fucoxanthin is likely linked to its structural characteristic- an allene bond and an additional hydroxyl substituent on the side group of the fucoxanthin metabolites, fucoxanthinol and amarouciaxanthin A [248].

### ***Green algae***

Phylum chlorophyta includes about 4300 species of green algae.



**Name:** *Caulerpa lentillifera* J. Agardh, class: Bryopsidophyceae, order: Bryopsidales F. Caulerpaceae; and *Codium fragile* (suringar) Hariot, class: Bryopsidophyceae, order: Bryopsidales F. Codiaceae.

**Common name:** *Caulerpa lentillifera* is known as sea grapes, green caviar and *Codium fragile* as Green sea fingers, Dead man's fingers, felty fingers, felt-alga, green fleece.

**Part used:** Thallus.

**Main active constituents:** Siphonaxanthin (carotenoid).

**Pharmacological action:** PL inhibitor; siphonaxanthin (isolated from green algae as *Caulerpa lentillifera* and *Codium fragile*) significantly reduces lipid accumulation during differentiation to adipocytes. This suppressive effect is stronger than that of fucoxanthin [249].



## Fungi

### *Ganoderma lucidum*



**Name:** *Ganoderma lucidum* (Curtis) P. Karst, Ganodermataceae.

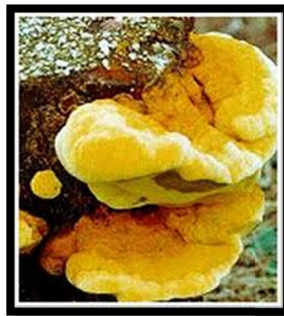
**Common name:** Mushroom of immortality, lingzhi mushroom or reishi mushroom, supernatural mushroom.

**Part used:** Whole mushroom.

**Main active constituents:** Lanostane triterpenes.

**Pharmacological action:** Extracts from *Ganoderma* reduce glucose levels [193] Lanostane triterpenes reduce TG accumulation [250]. This suggests that *G. lucidum* may serve as a new potential natural product for the prevention of obesity.

### *Phellinus linteus*



**Name:** *Phellinus linteus* (Berkeley & M. A. Curtis), class: Basidiomycetes, Hymenochaetaceae.

**Common name:** Medicinal mushroom, black hoof fungus (Japanese, "meshimakobu"; Chinese, "song gen"; Korean "sanghwang").

**Part used:** Whole mushroom.

**Main active constituents:** Polyphenolic compounds, polysaccharides [251].

**Pharmacological action:** Lipase inhibitor. Methanolic extract of the fruiting bodies of *Phellinus linteus* reveals anti-obesity activity by inhibition of lipase enzyme (a key enzyme for dietary fat adsorption, hydrolyzing triacylglycerols to 2-monoacylglycerols and fatty acids). A potent lipase inhibitor which could be very useful as an anti-obesity compound [252].

### *Sparassis crispa*

**Name:** *Sparassis crispa* Fr., *Sparassis radicata* Weir, Sparassidaceae.

**Common name:** Cauliflower mushroom of immortality, lingzhi mushroom, reishi mushroom, supernatural mushroom.

**Part used:** Whole mushroom.



**Main active constituents:** Diterpenes, triterpenes and fatty acids [253].

**Pharmacological action:** Water-soluble extract of Cauliflower mushroom reduces weight gain of the mice. Additionally, serum level of total cholesterol, triglyceride and glucose are decreased in mice fed with CM (cauliflower mushroom). Moreover, hepatic triglyceride and total cholesterol level are also

lowered. These results demonstrate that the water extract of CM improves serum and hepatic lipids and body weight reduction [254].

### Micro-Organisms

#### *Streptomyces species*

(Phylum, Actinobacteria; Order, Actinomycetales; F. Streptomycetaceae).

**Name:** *Streptomyces toxytricini*.

**Active constituent:** Lipstatin, a PL inhibitor was first isolated from this *Streptomyces* sp. [89], its saturated derivative is the popular antiobesity drug, Orlistat. The lipstatin molecule has an unusual  $\beta$ -lactone structure incorporated into a hydrocarbon backbone.

**Pharmacological action:** Lipstatin is a potent, irreversible inhibitor of pancreatic lipase. The  $\beta$ -lactone structure probably accounts for the irreversible lipase inhibition [89].

**Name:** *Streptomyces* sp. MTCC 5219.

**Source:** Isolated from a soil sample of a cow barnyard in India.

**Pharmacological action:** PL inhibitor. A low molecular weight molecule, (E)-4-aminostyryl acetate (belonging to the class of enol acetate of *p*-amino phenyl acetaldehyde), isolated from this *Streptomyces* sp., has shown *in vitro* lipid lowering activity in mammalian lipase inhibition assay. The small size along with the good solubility property would give this molecule a better druggability character [255].

**Name:** *Streptomyces* sp.

**Source:** Isolated from the western ghat soil samples of Agumbe, Karnataka, India.

**Pharmacological action:** PL inhibitor. The activity of lipase enzyme is drastically inhibited by the *n*-butanol extract of the culture broth in dose-dependent manner [256].

***Bifidobacterium species***

(Phyllum, Actinobacteria; Order, Bifidobacteriales; Family, Bifidobacteriaceae).

**Name:** *Bifidobacterium pseudocatenulatum* SPM 120, *B. longum* SPM 1205, and *B. longum* SPM 1207.

**Pharmacological action:**  $\alpha$ -amylase and PL inhibitors. They significantly decrease activities of  $\beta$ -glucosidase,  $\beta$ -glucuronidase, and tryptophanase [257].

They act through the following [257-259]:

- a. Inhibition of cholesterol synthesizing enzymes and thus reducing cholesterol production.
- b. Enhancement of cholesterol elimination in feces.
- c. Inhibition of back absorption of cholesterol into the body by binding with it.
- d. Interference with recycling of bile salt (a metabolic product of cholesterol) and enhancement of its elimination, which raises the demand for bile salt produced from cholesterol and thus results in body cholesterol consumption.
- e. Reduction of levels of triglyceride, glucose, AST, and ALT in serum.

**TYPES OF SECONDARY PLANT AND MICROBIAL METABOLITES WITH ANTI-OBESITY ACTIVITY**

Natural products, particularly medicinal plants, are believed to harbor potential antiobesity agents that can act through various mechanisms either by preventing weight gain or promoting weight loss amongst others. New technologies such as metabolomics, which deals with the study of the whole metabolome has been identified to be a promising technique to probe the progression of diseases, elucidate their pathologies and assess the effects of natural health products on certain pathological conditions. The inhibition of key lipid and carbohydrate

hydrolyzing and metabolizing enzymes, disruption of adipogenesis and modulation of its factors or appetite suppression are some approaches to probe the anti-obesity potential of medicinal plants [56]. The potential and relevance of metabolomics in obesity are discussed below:

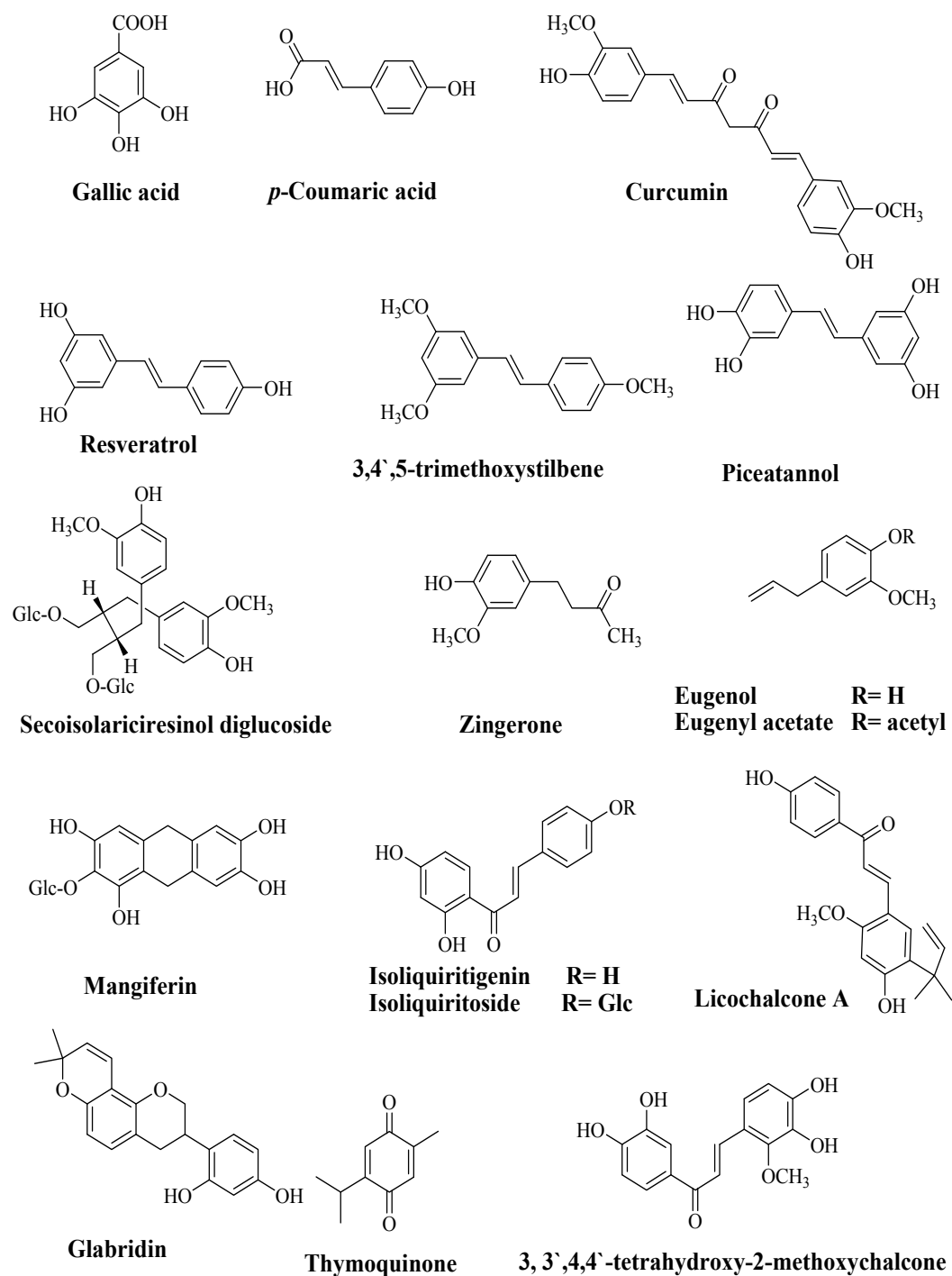
### **Phenolics**

Phenolics in particular polyphenols are a group of antioxidants characterized by the presence of several hydroxyl groups on an aromatic ring. Over the last decade, polyphenols have been implicated in the prevention of a number of oxidative-related diseases including cardiovascular diseases, hypertension and diabetes. They are often categorized into 4 groups depending on the number of phenol rings embodied in their structure and the elements that bind these rings together [260]. Distinction is hence made between phenolic acids, flavonoids, stilbenes and lignans [260, 261].

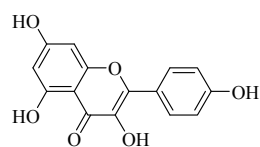
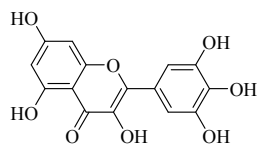
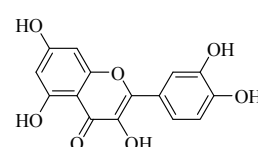
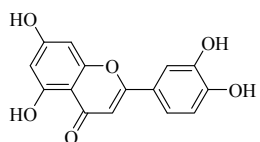
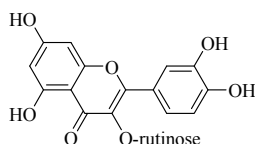
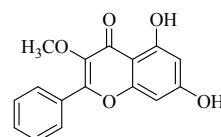
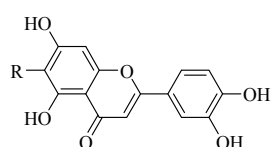
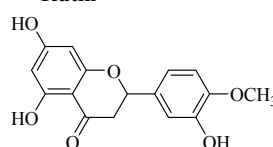
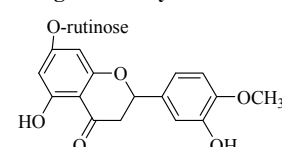
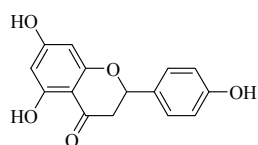
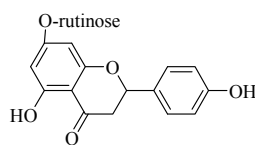
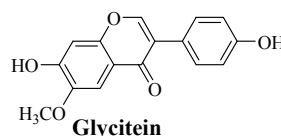
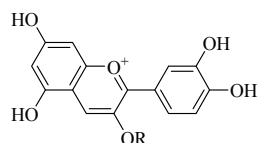
- a. Phenolic acids.
- b. Flavonoids.
- c. Stilbenes.
- d. Lignans.

### **Pharmacological Action:**

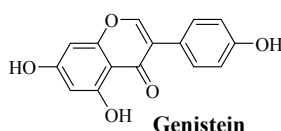
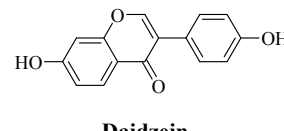
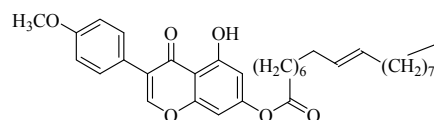
- Phenolics are PL inhibitors [56, 70, 228].
- Phenolic extracts are able to decrease the blood levels of glucose, triglycerides and LDL cholesterol, increase energy expenditure and fat oxidation, and reduce body weight and adiposity [ 262, 263].
- Catechin acts as anti-obesic through its anti-lipase activity and by increasing thermogenesis [97].
- Epigallocatechingallate suppresses the number of adipocytes and triacylglycerols uptake [264].
- Selected examples of phenolics with reported anti-obesity activity are represented in Figs. 4, 5 and 6.

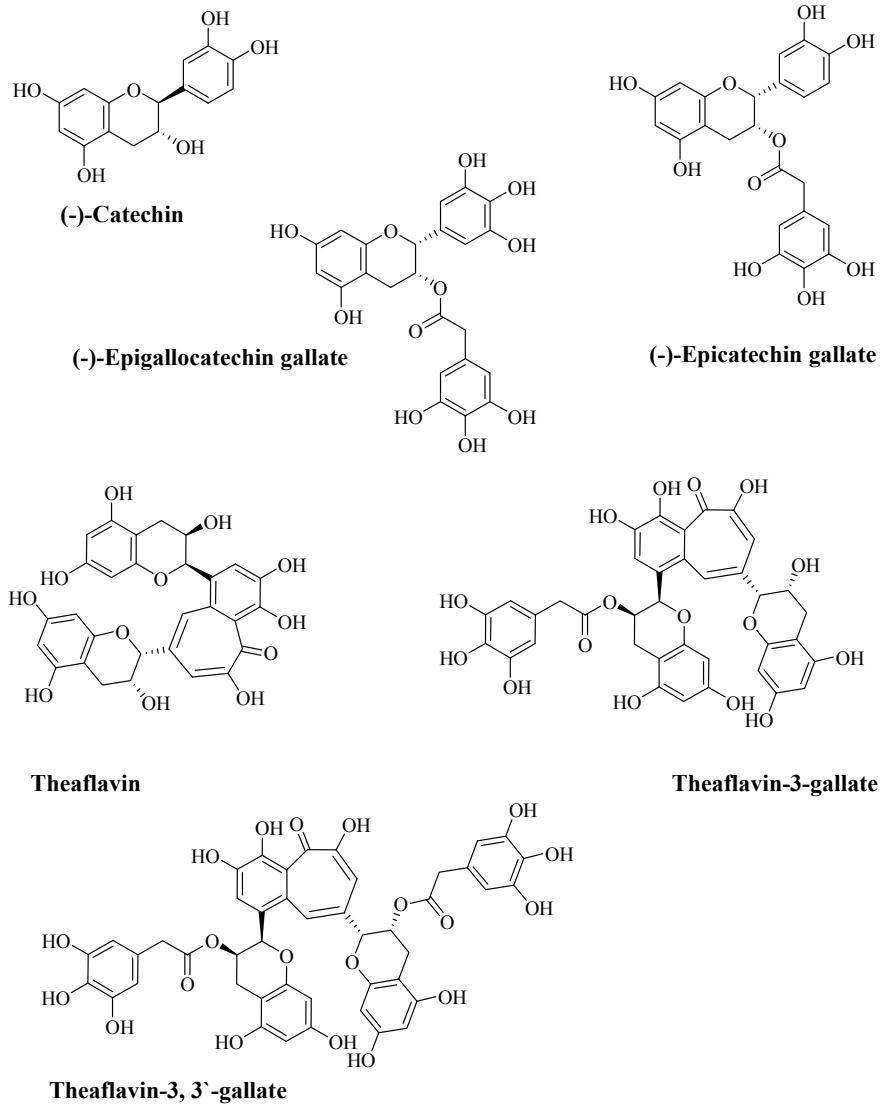


**Figure 4:** Phenolic compounds.

**Kaempferol****Myricetin****Quercetin****Luteolin****Rutin****Galangin 3-methylether****Derhamnosylmaysin R= Rh****Hesperetin****Hesperidin****Naringenin****Naringin****Glycitein**

**Cyanidin** (R= H)  
**Cyanidin-3-glucoside** (R= Glc)  
**Cyanidin-3-galactoside** (R= Gal)  
**Cyanidin-3-rutinoside** (R= Rutinose)

**Genistein****Daidzein****Isoflavone linoleic acid ester****Figure 5:** Flavonoidal compounds.



**Figure 6:** Catechins and theaflavins.

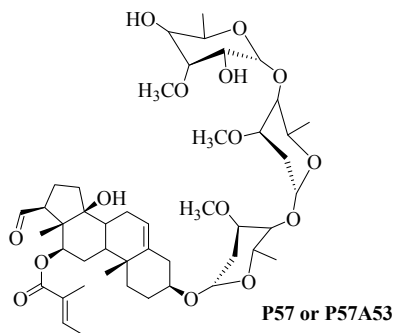
### **Pregnane Glycosides**

These are steroidal compounds mostly present in the Milkweed family; *e.g.* P57 or P57A53.



### Pharmacological Action

- Pregnane glycosides are reputed for their appetite suppressant property [103, 265].
- Pregnane glycosides act on two levels; by blocking the growth of pre-adipocytes and reducing the level of leptin. These immature cells (pre-adipocytes) are the source of adipocytes which absorb fat and produce leptin, a hormone involved in the long-term regulation of bodyweight. High levels of leptin are found in overweight and obese people. In human trials, there is a significant reduction in the feelings of hunger and body weight in overweight people [266].



### Saponins

Saponins are a major family of secondary metabolites that occur in a wide range of plants species [267]. These compounds have been isolated from different plant parts, including roots, rhizomes, stems, bark, leaves, seeds and fruits. Occasionally, the whole plant has been used [268].

Saponins are categorized into two major classes;

- a. Triterpenoidal saponins.
- b. Steroidal saponins.

Both are from the 30 carbon atoms-containing precursor oxidosqualene [268, 269].

**Pharmacological Action**

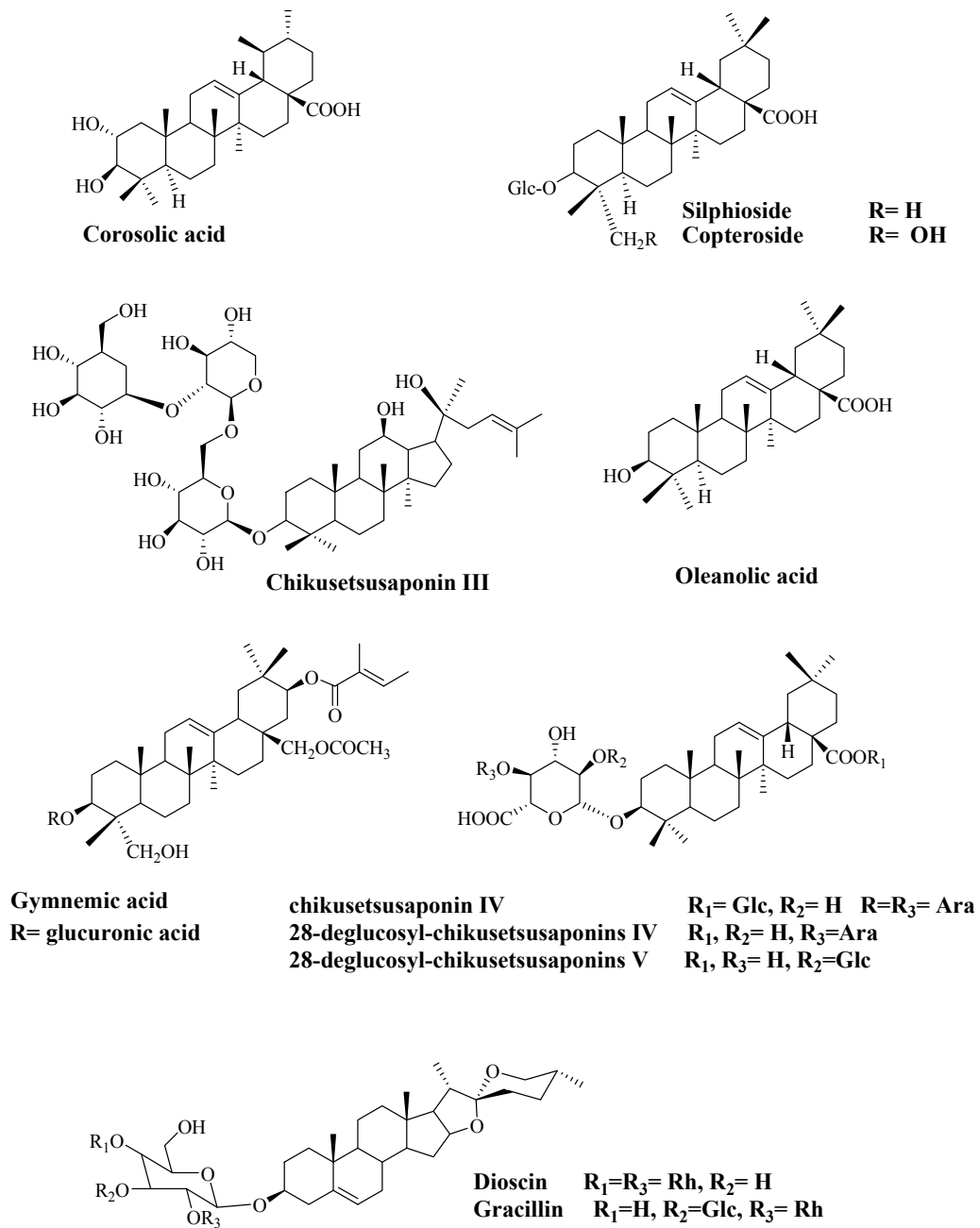
- Saponins inhibit P enzyme.
- Escins (triterpenoidal saponins) suppress the increase in body weight, adiposity and liver fat, and the increase in triglyceride level in the feces, also they decrease plasma triglycerides [270].
- Steroidal saponins *e.g.* Ginsenosides decrease plasma triacylglycerides and cause a delay in intestinal fat absorption due to inhibition of pancreatic lipase [62, 271, 272].
- Diosgenin (steroidal saponin) decreases the plasma and hepatic total cholesterol levels, and increases the plasma high-density lipoprotein (HDL) cholesterol level [273].
- Steroidal and triterpenoidal saponins of reported anti-obesity effect are represented in Fig. 7.

**Alkaloids**

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties. Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants, and animals.

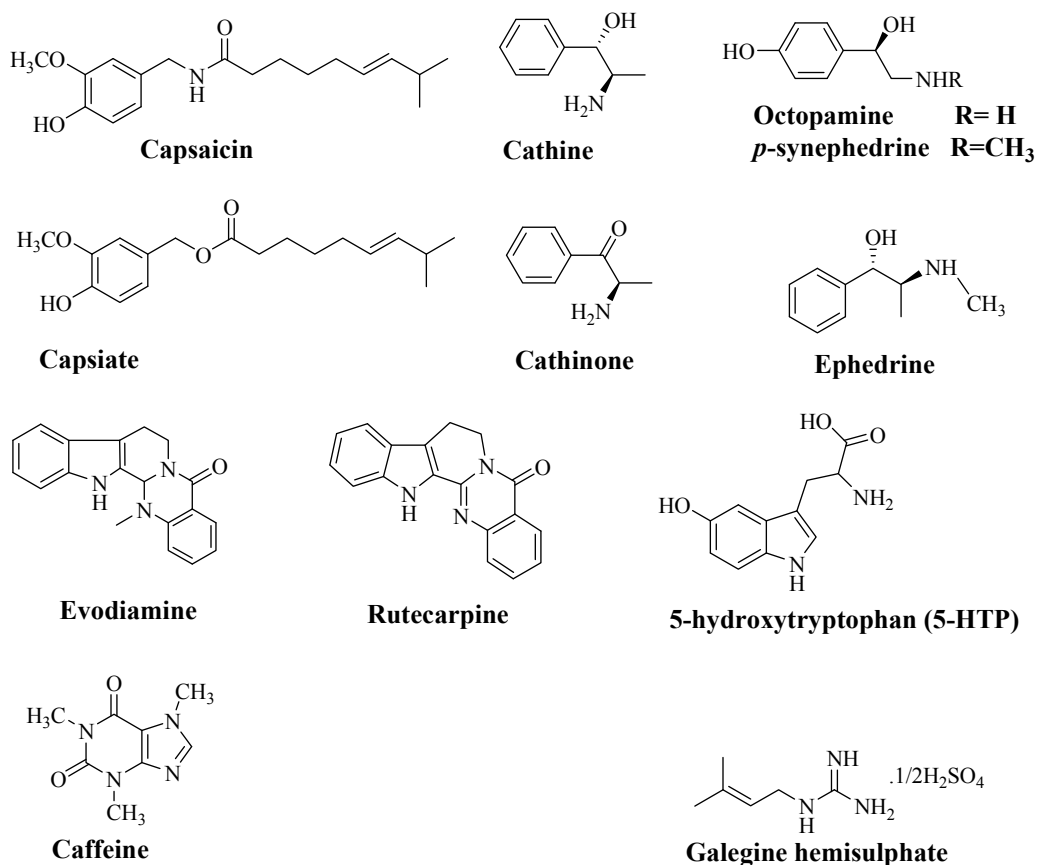
**Pharmacological Action**

- Berberine (isoquinoline alkaloid) reduces blood lipid levels (triglycerides and cholesterol levels) in human [274].
- Ephedrine (phenylalkylamine) and caffeine (methylxanthine alkaloid) exert their anti-obesity activity by thermogenesis (significant increase in energy expenditure) [131].
- Capsaicin (proto-alkaloid) increases thermogenesis through enhancement of catecholamine secretion from the adrenal medulla [274, 275].



**Figure 7:** Steroidal and triterpenoidal saponins.

- Alkaloids reported to play a role in management of obesity are represented in Fig. 8.



**Figure 8:** Alkaloids.

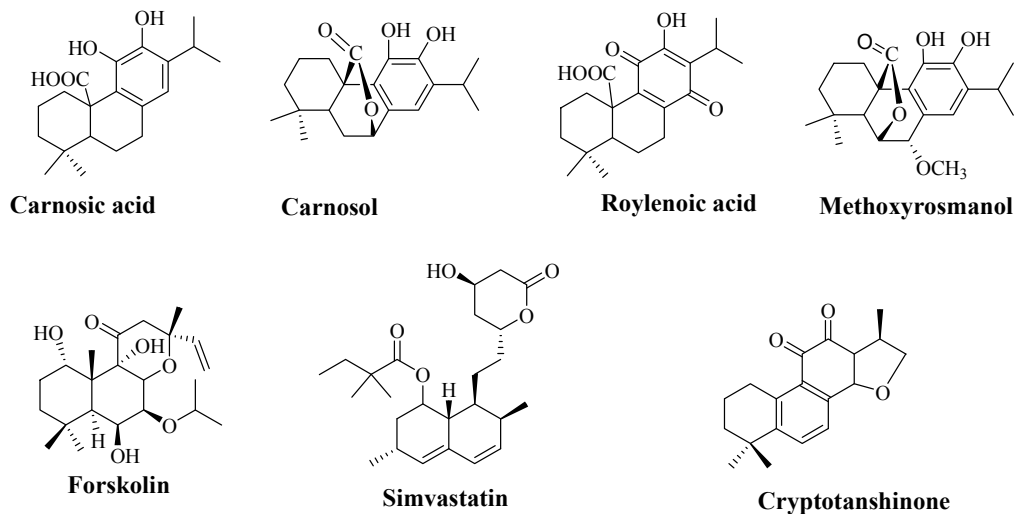
## Diterpenes

Diterpenes are a type of terpenoids composed of four isoprene units and have the molecular formula C<sub>20</sub>H<sub>32</sub>. They derive from geranylgeranyl pyrophosphate. Abietane is a diterpene skeleton that forms the structural basis for a variety of natural compounds such as abietic acid, carnosic acid, and ferruginol which are collectively known as abietanes or abietane diterpenes.

## Pharmacological Action

Carnosic acid inhibits pancreatic lipase [276], activates peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) [277], and prevents the differentiation of pre-adipocytes into adipocytes [278].

Selected examples of diterpenes with reported anti-obesity activity are displayed in Fig. 9



**Figure 9:** Diterpenes.

### Carotenoids

Carotenoids are organic pigments that are found in chloroplasts of plants and some other photosynthetic organisms like algae, and certain bacteria and fungi. Carotenoids can be produced from fats and other basic organic metabolic building blocks by all these organisms. Carotenoids generally cannot be manufactured by species in the animal kingdom so animals obtain carotenoids in their diets, and may employ them in various ways in metabolism. All carotenoids are tetraterpenoids, *i.e.* that they are produced from 8 isoprene molecules and contain 40 carbon atoms.

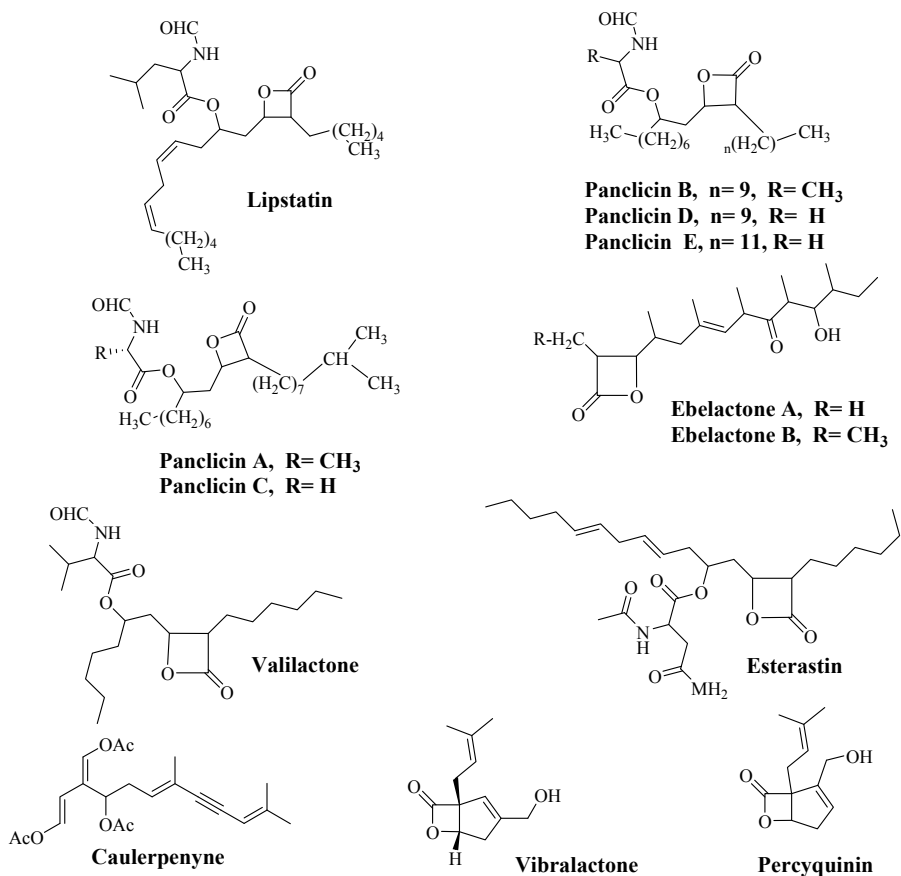
They are split into two classes:

- a. Xanthophylls (which contain oxygen).
- b. Carotenes (which are purely hydrocarbons, and contain no oxygen).

### Pharmacological Action

- Carotenoids containing an allene bond, such as fucoxanthin and fucoxanthinol, show anti-obesity effects by suppressing adipocyte





**Figure 11:** Secondary metabolites from microbial sources.

## ADVERSE EFFECTS OF NATURAL ANTI-OBESITY PRODUCTS

Synthetic drugs designed to suppress hunger have promoted weight loss, but are often accompanied by untoward side effects. Most anorectic drugs act by central mechanisms have many side effects on the central nervous system, the development of tolerance, abuse potential, and rebound hyperphagia (over-eating) on discontinuation of treatment.

Natural products used in management of obesity experience also a number of side effects which range from mild to seriously adverse.

According to the amount of administered doses, herbal supplements containing ephedra and/or caffeine were reported to produce greatly variable results in terms

of both effectiveness and experienced side effects. Minor adverse effects, such as dry mouth, insomnia, headache and nervousness, were reported at low doses and short term use. On the other hand, palpitation, increase in blood pressure and loose bowel movements were observed at higher doses and long term use. Ephedrine, a sympathomimetic alkaloid and major constituent of ephedra and stimulator of  $\alpha$ - and  $\beta$ -adrenergic receptors lead to increase blood pressure and vasoconstriction which may be taxing on the heart [29]. Adverse events reported to be attributable to ephedra or ephedrine consumption exposed five deaths, five myocardial infarctions, 11 cerebrovascular accidents, four seizures, and eight psychiatric cases of an idiopathic nature. In 2004, FDA banned the sale of dietary supplements containing ephedra alkaloids because such supplements present an unreasonable risk of illness or injury [281].

The administration of *Garcinia cambogia* extract to obese male Zucker rats resulted in suppression of epididymal fat accumulation at a dose of 154 mmol hydroxyl citric acid (HCA)/kg diet, but diets containing 102 mmol/kg HCA and more caused testicular toxicity, while the no-observed-adverse-effect-level was determined to be 51 mmol HCA/kg diet [194]. A few adverse events were reported, mostly related to GIT disturbances, headache and upper respiratory tract symptoms. Toxicity studies on CitriMax, which contains a calcium/potassium-HCA complex, revealed low oral acute toxicity with mild skin and eye irritation in rats. No significant toxic effects were found in a sub-chronic toxicity study and mutagenicity has not been demonstrated. Taking all of the clinical trials and other scientific studies into consideration, consumption of HCA at 2800 mg/day was proposed as safe [194, 282].

Data on the toxicity/safety of *H. gordonii* is very limited. Acute toxicity studies were described in a patent application [283]. A plant extract administered orally to mice in doses of 100-3028.5 mg/kg revealed no clinical signs of toxicity. In animal study, a dose-related reversible histopathological liver changes in the form of moderate cloudy swelling and hydropic degeneration of hepatocytes was recorded from a dose of 200 mg/kg, but further investigation is required. But, no adverse effects were reported for the clinical study performed in humans.

Reviewing most animal and human studies, only few studies mentioned adverse effects, it should be noted that many serious adverse events which would have



stopped a trial of a pharmaceutical agent would likely not have been identified by the authors' search methods. Moreover, important safety issues including significant adverse events or supplement-drug interactions relevant to many clinical populations may not be fully addressed. Therefore, the determination of a favorable risk-benefit ratio should always be kept in mind. It looks that most of the plants reported in this chapter has been not investigated comprehensively. In addition to safety, the quality and efficacy of these plants are also neglected to a large extent.

## CONCLUSIONS

Obesity is no longer considered a cosmetic problem. The incidence of obesity is recently increasing at an enormous rate, becoming a worldwide health burden which could be described as the pandemic of the 21<sup>st</sup> century. Moreover, its consequences are not only detrimental to human health but are expected to inflict unpredicted financial and social burdens on global society, unless effective measures are taken to control its prevalence.

Anti-obesity pharmacological treatment should be administered only when considered safe and effective for long-term use. Despite the large number of drugs proposed over the past three decades, few have been developed or approved, while others have been discarded from the market due to serious side-effects or abuse. The currently available drugs Sibutramine<sup>®</sup> and Orlistat<sup>®</sup> are commonly indicated in combination with dietary, behavioral, and exercise therapy to produce 10% weight loss utmost. This necessitates a continuous search for anti-obesity drugs which are better tolerated and at the same time more efficient.

The popularity of alternative medicine is tremendously rising as revealed by the boost in demand of natural health products. Extensive attention is focused on the use of naturally-derived remedies to alleviate obesity due to the failure of synthetic drugs to achieve the necessary long-term results. In this respect, various plant and microbial products have been explored either *in vitro* or *in vivo* animal models. They were found effective through various mechanisms such as gastric and PL inhibitors, central or peripheral appetite suppressants and enhancers of energy expenditure. The chief disadvantage is the uncertainty to extrapolate those effects to human subjects. Other drawbacks include the unclear risk of toxicity,

insufficient information on mechanisms of action, as well as poor quality control of natural herbal products.

Drugs that regulate energy balance overlap considerably with other physiological functions, and are influenced by social and psychological factors that limit their use. Drugs that target pathways in metabolic tissues, such as adipocytes, liver and skeletal muscles, were found effective in preclinical studies but none has yet reached clinical development. The prolong use of certain gut peptides seems to be rational, particularly, that the deficiency of these peptides in obese individuals has been documented. Certain treatments are designed to meet diverse molecular targets in the CNS and/or periphery and, others several targets simultaneously.

Successful discovery and development of potent and safe natural drugs for both prevention and long-term treatment of obesity will probably rely on polytherapeutic strategies and necessitate continuous improvement of the identification and characterization tools. Among the advantages of polytherapy are: the use of lower drug doses, improvement of weight loss through additive and possible synergistic effects, as well as reduction of incidence of adverse side effects and consequently of the possibility for counter-regulation and further withdrawal.

Finally, medicinal plants and other naturally-derived products are gaining more scientifically-based validity as antiobesity agents; some of the natural compounds have reached clinical trials such as the oxypregnane steroidal saponin, P57 from *H. gordonii*. However, there are still numerous unstudied plants around the world which have traditionally been used as slimming agents, thus justifying the need for deeper research in this field in view to reach a safer and more effective pharmacological treatment for obesity.

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#### **CONFLICT OF INTEREST**

The author confirms that this chapter contents have no conflict of interest.

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