

The Molecular Mechanisms of Anti-Obesity Medicinal Plants

Subjects: Cardiac & Cardiovascular Systems

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Inflammation is a crucial factor in the development and progression of cardiovascular diseases (CVD). Cardiac remodeling in the presence of persistent inflammation leads to myocardial fibrosis and extracellular matrix changes, which reduce cardiac function, induce arrhythmias, and finally, cause heart failure. Medicinal plants and phytochemicals can cure and prevent obesity and inflammation. In comparison to conventional therapies, the synergistic effects of several phytochemicals boost their bioavailability and impact numerous cellular and molecular targets.

Keywords: inflammation ; obesity ; diabetes ; CVDs

1. Introduction

Inflammation is a physiological response of the body to injury or infection, representing a universal reaction to various local tissue changes [1][2]. It is characterized by a set of standard vascular changes that result in swelling, followed by the movement of white blood cells to the affected area, forming an inflammatory focus [3]. The primary goal of inflammation is to identify the damaging element, remove it, and then regenerate or repair the affected tissue [4].

Cytokines are important signaling proteins involved in the inflammatory host response to inflammatory stimuli. They are classified as either pro-inflammatory (e.g., tumor necrosis factor-alpha (TNF- α), interleukine (IL)-1 (IL-1), IL-6, IL-15, IL-17, and IL-23), or anti-inflammatory (e.g., transforming growth factor beta(TGF β), and interferon (IFN), IL-4, IL-10, and IL-13) [5]. Chronic and persistent inflammation, as well as auto-immune response, have been linked to atherosclerosis, myocardial infarction, asthma, diabetes, psoriasis, osteoporosis, angiotensin II-derived hypertension, tumor progression, and cardiovascular disease (CVD) [1][2][6][7]. The latter, the world's largest cause of morbidity and mortality, includes hypertension, heart diseases, peripheral vascular disease, heart failure, and cardiomyopathies [8][7].

Because the number and kinds of secondary metabolites in a single herb vary [9], the pharmacological effects of herbs are specific to certain plant species or groups of plants. Secondary metabolites do not play a part in normal cell/tissue growth, development, and reproduction; rather, they serve as a defensive factor to protect a plant from potential environmental and interspecies injury. As a result, secondary metabolites are often produced by plants to regulate their metabolism in response to the local presence of herbivores, pollinators, and microorganisms. These metabolites are often derived from primary metabolites or share substrates with them and are produced to meet specific needs. Thousands of these secondary metabolites have been found, and the list is growing. Secondary metabolites are broadly classed as alkaloids, terpenoids, and phenolics [9][9][10] (**Figure 1**).

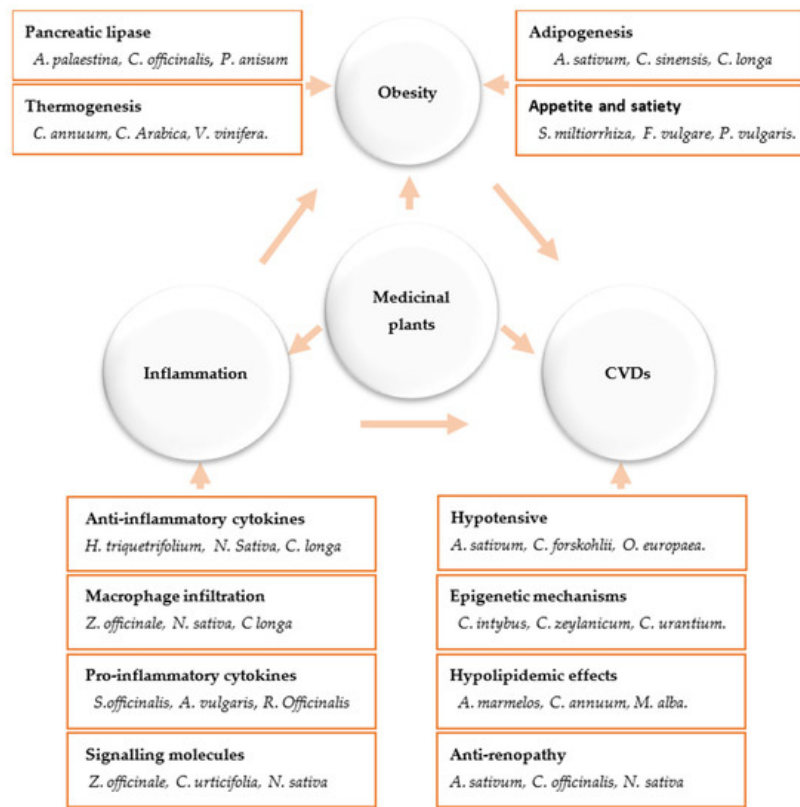


Figure 1. Anti-obesity and anti-inflammatory action mechanisms of medicinal plants and their impact on cardiovascular diseases.

2. Anti-Obesity Medicinal Plants and the Molecular Mechanisms Underlying Their Activities

Currently, medicinal plants, unprocessed extracts, and phytochemicals that aim to regulate weight are becoming more widespread. Significant decrease in body weight was seen by *Nigella sativa* (black seeds), *Curcuma longa* (curcumin), *Cinnamomum verum* (cinnamon), *Panax ginseng* (ginseng), *Foeniculum vulgare*, *Phaseolus vulgaris*, *Camellia sinensis* (green tea), *Allium sativum* (garlic), *Crocus sativus*, and virgin olive oil. These plants have been used in various traditional medical systems for a long time, and their anti-obesity and antidiabetic effects have been confirmed in numerous in vitro animal and clinical testing [11][12][13][14][15].

There has been a lot of progress in understanding how phytochemicals can reduce weight, according to a number of lines of evidence. One of the main categories of plant secondary metabolites is polyphenols, which are abundantly present in medicinal plants as well as in fruits, vegetables, grains, and legumes [16]. Their anti-obesity abilities have been repeatedly demonstrated in cell culture, animal, and clinical research. Examples of substances that have been shown to have weight-reducing properties include genistein and diadzein, cyanidin, grape seed proanthocyanidin extract, xanthohumol, apigenin and luteolin, kaempferol, myricetin and quercetin, and (-)-Epigallo-cathechin gallate (EGCG). Likewise, phytosterols, polyunsaturated fatty acids (PUFA), and organosulfur compounds are other bioactive dietary ingredients having anti-obesity characteristics [17][18][19][20][21][22][23][24][25][26][27][28][29][30][31]. The primary goals of medicinal plants and the products generated from them include inhibition of pancreatic lipase activity, suppression of hunger, stimulation of thermogenesis and lipid metabolism, prevention of lipolysis, and promotion of adipogenesis (**Figure 2**). A better treatment method for treating obesity is to target adipogenesis in adipose tissue. With weight reduction, mature adipocytes undergo apoptosis and/or lipolysis, which results in a decrease in adipose tissue mass [17][18] (**Figure 2**).

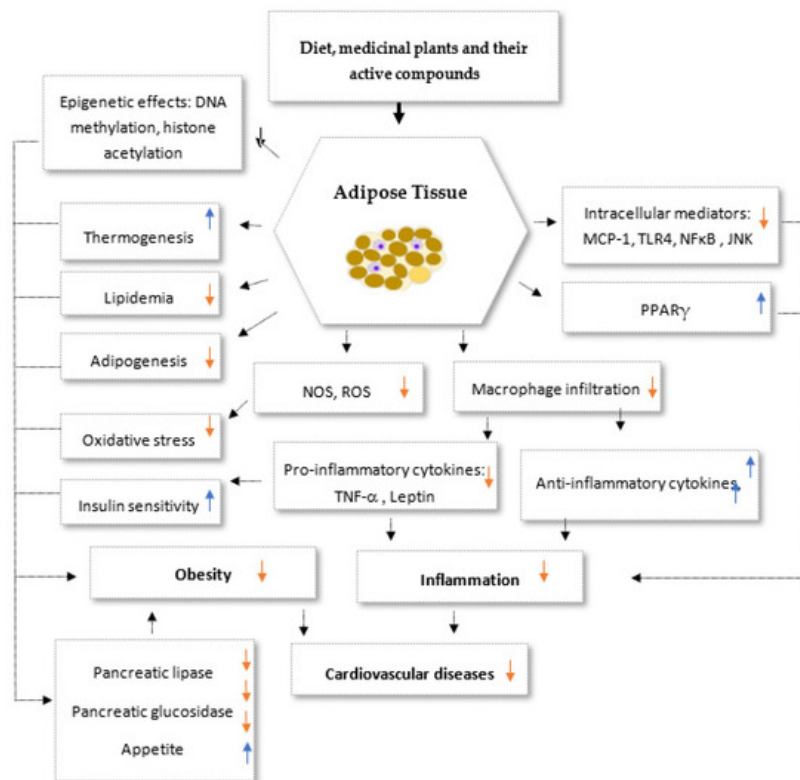


Figure 2. Potential synergistic anti-obesity molecular multi-target of medicinal plants and their secondary metabolites. PPAR γ : Peroxisome proliferator-activated receptors gamma, NOS: nitric oxide synthase, ROS: Reactive oxygen species, TNF- α : Tumor necrosis factor alpha, TLR4: Toll-like receptor 4, MCP-1: Monocyte Chemoattractant Protei-1, NF- κ B: Nuclear Factor- κ B. Up arrows: increased effects; down arrows: decreased effects.

2.1. Major Basic Anti-Obesity Mechanisms

Targeting appetite: Some anti-obesity phytochemicals that act through appetite reduction include thymoquinone from *Nigella sativa*, saponins from ginseng, HCA from *Garcinia cambogia*, EGCG from green tea, steroidal glycoside from *Hoodia gordonii* and *Hoodia Pylifera*, lectins from *Phaseolus vulgaris* (common bean), and ephedrine from Ephedra species [14][15][18][32]. Appetite and satiety are regulated by a coordinated action of anorexigenic and orexigenic hormones and neuropeptides produced in the hypothalamus as well as in the digestive tract, liver, and adipose tissue [32]. In the short term, neuronal and hormonal transmission from the gastrointestinal tract regulates hunger. The gastrointestinal tract is the biggest endocrine organ in the body and is thought to play a significant role in appetite control through the release of multiple peptide hormones. As a result, these hormones (e.g., ghrelin, melanin-concentrating hormone receptor) might be used to treat obesity. In addition, the inhibition of fatty acid synthase, an adipocyte enzyme, catalyzes the synthesis of fatty acids and represents a potential therapeutic target for appetite suppression. Indeed, many medicinal herbs and their extracts were reported to exert their weight-reducing effect through the inhibition of fatty acid synthase activity and, thus, reduce appetite [17][32].

Targeting pancreatic lipase: Inhibition of fat digestion and absorption is one of the currently used strategies to reduce energy intake through inhibition of the activity of the pancreatic lipase. It is responsible for the hydrolysis of 50–70% of total dietary fats to glycerol and free fatty acids. The latter are then incorporated into bile acid-phospholipid micelles, absorbed in the small intestine, and finally entered the peripheral circulation as chylomicrons [33]. Pancreatic lipase inhibitory effects of medicinal plants and phytochemicals have been extensively investigated. Hitherto, many herbs, as well as isolated phytochemicals, were found to attenuate pancreatic lipase activity. Some phytochemicals that can help reduce weight by inhibiting pancreatic lipase include saponins and catechins from green tea, polyphenols like mangiferin and catechins and condensed tannins from *Salacia reticulata*, punicalagin, ellagic acid, and anthocyanins from pomegranate, rosmarinic acid and carnosic acid from rosemary, and proteins and isoflavones from soybean [14][15][33][34].

Stimulators of thermogenesis: Thermogenesis is literally defined as heat production. It takes place in the mitochondria of the brown adipose tissue through uncoupling of the mitochondrial electron transport chain by uncoupling protein 1 (UCP1). The “adaptive thermogenesis” that maintains an ideal environment for weight recovery and is active in both lean and obese persons attempting to sustain reduced body weights is what causes the over 80% weight regain to pre-weight loss following a successful weight loss. The adipocyte-derived hormone leptin has a significant role in mediating this resistance to long-term weight loss. Thermogenesis is influenced by phytochemicals and macromolecules in food as well

as dietary carbohydrates. Numerous animal and human studies have demonstrated the ability of several phytochemicals to reduce body weight, including oleuropein, capsaicin, resveratrol, epigallocatechin gallate, gingerol, caffeine, and ephedrine [14][15][18][34][35]. Capsaicin, for example, increases catecholamine release from the adrenal medulla to exert its thermogenic action, whereas EGCG promotes thermogenesis by inhibiting catechol methyl-transferase, an enzyme that destroys norepinephrine. Caffeine mediates thermogenic effects by inhibiting the phosphodiesterase-induced degradation of intracellular cAMP, and it decreases energy intake by reducing food intake [14][15][18][34][35].

Increase satiety: Long-term studies have established the favorable weight-loss effects of dietary fiber [36] in obese people, and they are related to a lower BMI. Many entire plant meals include substantial levels of dietary fiber, including pectin, gum, mucilage, cellulose, hemicellulose, lignin, and soluble fibers. Supplementing regular meals with gel-forming fibers, such as guar gum, increases satiation, most likely owing to delayed stomach emptying. Dietary fibers are normally indigestible by humans; however, they may be fermented by gut microorganisms. Soluble or fermentable fibers and insoluble fibers can both be fermented by gut microorganisms to give bulk. Natural hydrogel-forming fibers such as pectin, gum, and mucilage are examples of soluble fibers, whereas structural fibers such as cellulose and lignin are examples of insoluble fibers. Through the hydrogel effect, which slows the absorption of energy-rich macromolecules, insoluble fibers are known to reduce hunger and, thereby, meal intake [14][35][36]. A high-fiber diet decreases both food intake during meals and food intake at the next meal, according to a number of clinical studies. Foods high in pectin cause the stomach to take longer to empty and make you feel fuller [14][35][36]. Recent studies have found a connection between satiation and changes in the hormones orexigenic and anorexigenic. People believe that systematic analyses of the key gut hormone responses to diverse fiber types and formulations will significantly advance our knowledge of this subject. While leaving the HDL fraction alone, hydrogel-forming fibers are particularly effective at lowering high LDL cholesterol. Additionally, they support those with diabetes or impaired glucose tolerance. These effects are most likely connected to the fiber's gelling characteristic, which slows the absorption process [17].

2.2. Targeting Adipocyte Apoptosis

Antiobesity medicinal plants and phytochemicals can reduce the mass of adipose tissue by apoptosis. At the cellular level, obesity is characterized by an increase in the number or size or both of the adipocytes. The adipocyte life cycle consists of alteration of cell shape and growth arrest, clonal expansion, and a complex sequence of changes in gene expression leading to storage of lipids and finally to apoptosis [14][17][37]. During the terminal phase of adipocyte maturation, mRNA levels for enzymes involved in triacylglycerol metabolism (e.g., glyceraldehyde-3-phosphate dehydrogenase, fatty acid synthase, and glycerol-3-phosphate dehydrogenase) rise significantly. While it was previously thought that the number of fat cells in the body stays the same throughout a person's life, recent evidence suggests that new fat cells can be created and old ones can be removed through a process called apoptosis [17][37].

Targeting preadipocyte apoptosis: Natural compounds that control the adipocyte life cycle have as their main target preadipocyte maturation [38]. It has been demonstrated that several phytochemicals can increase apoptosis and reduce preadipocyte growth. For instance, it has been discovered that the antioxidant activity of flavonoids is related to the triggering of apoptosis in preadipocytes. It has been demonstrated that a number of flavonoids, including naringenin, rutin, hesperidin, resveratrol, naringin, and genistein, have cytostatic effects on preadipocytes. One of the most current flavonoids, quercetin is present in a variety of fruits and vegetables; the green tea polyphenol EGCG, and capsaicin from paprika have been shown to induce preadipocyte apoptosis. Induction of apoptosis in preadipocytes is intermediated by the activation of caspase-3, Bax, and Bak, followed by fractionalization of PARP and downregulation of Bcl-2. Likewise, treatment of preadipocytes with phenolic acids similar to o- coumaric acid, m- coumaric acid, and chlorogenic acid redounded in cell cycle arrest in the G1 phase in a time- and cure-dependent manner. CLA has recently been found to induce apoptosis in human preadipocytes. During insulin therapy, EGCG also promotes apoptosis in post-confluent premature preadipocytes, although the molecular pathways involved remain unclear. Induction of apoptosis in post-confluent differentiated cells leads to a decrease in the number of adipocytes, as preadipocytes undergo multiple rounds of replication during the first two days of differentiation [17][38][39][40][41][42][43][44][45][46][47][48][49]. The effect of curcumin on the cell cycle was recently determined. It significantly decreased the viability of preadipocytes at a concentration that caused apoptosis in preadipocytes and induced activation of caspases 8, 9, and 3. A non-cytotoxic dose of curcumin (15 μ M) inhibited MCE, attenuated the expression of PPAR γ and C/EBP α , prevented differentiation medium-induced β -catenin downregulation, and decreased the lipid accumulation in 3T3-L1 adipocytes. These data show that curcumin can induce preadipocyte apoptosis and attenuate adipocyte differentiation, leading to inhibition of adipogenesis [17][38].

Targeting adipocyte apoptosis: Animal studies have shown that EGCG, genistein, capsaicin, soy isoflavones, and CLA reduce body fat. However, the mechanism by which they exert their apoptosis-inducing effects on adipocytes has only recently been investigated. EGCG-induced apoptosis is thought to be mediated by protein 1, nuclear factor kappa B (NF-

kB), p53, and caspase-3 activity. Although the effects of conjugated linoleic acid (CLA) on body fat are not fully understood, the marked increase in TNF- α mRNA observed after treatment of adipocytes with uncoupling protein 2 (UCP2) suggests that CLA-induced apoptosis is suspected to be responsible for apoptosis [17][45][46][47][48][49]. Genistein, ajoene, EGCG, and capsaicin exert apoptotic effects by stimulating the release of reactive oxygen species (ROS), thereby activating AMP-activated protein kinase (AMPK), an important target for anti-obesity therapy. Ajoene also induces apoptosis in leukemia cells through the formation of ROS, and more recently, it was shown that ajoene also induces ROS-mediated apoptosis in adipocytes [17][46][47][48][49][50][51][52][53].

Synergistic apoptosis-inducing effects of phytochemicals: The apoptosis regulator Bcl-2 and its homologs, which control the outer mitochondrial membrane, are members of the Bcl-2 family. They are either anti-apoptotic (Bcl-2, Bcl-xL, Bcl-w, etc.) or pro-apoptotic (particularly Bax, Bak, Bok, etc.). The Bcl-2 family of proteins induces the release of cytochrome c and translocates from the cytosol to the mitochondria, where it displays pro-apoptotic action. In 3T3-L1 adipocytes, CLA promotes apoptosis brought on by ajoene. Individually, neither CLA nor ajoene had an impact on cytochrome c, whereas ajoene enhanced and CLA had no impact on the expression of the Bax protein [15][54][55]. However, the expression of cytochrome c and Bax was enhanced when ajoene and CLA were combined. Similarly to this, vitamin D3 increases genistein's ability to induce apoptosis and prevent adipogenesis in mature 3T3-L1 preadipocytes. Vitamin D3 alone boosted VDR protein levels in 3T3-L1 adipocytes by only 40%, while genistein alone did not enhance these levels at the dosages studied. In contrast, the combination of genistein and vitamin D3 elevated VDR protein levels by more than 100%. With combination therapy, this impact on VDR was associated with a roughly 200% increase in apoptosis. The results of such synergy point to the possibility of reducing the harmful effects of two or more chemicals while still producing desired effects on adipocytes. Despite the fact that outcomes from in vitro and animal experiments cannot be directly extrapolated to clinical efficacy, such studies indicate that selected phytochemicals, alone or in combination, are widely used to treat obesity through adipocyte apoptosis contribute to our understanding of important molecular and cellular pathways. It may be effective in inhibiting adipogenesis [17][54][55][56].

2.3. Targeting of Adipogenesis

Adipogenesis is reduced by medicinal herbs and phytochemicals such as resveratrol, guggulsterone, CLA, capsaicin, baicalin, EGCG, genistein, esculetin, DHA, berberine, and procyanidins. Capsaicin, genistein, berberine, and EGCG inhibited the synthesis of CCAAT/enhancer-binding protein (C/EBP) and peroxisome proliferator-activated receptor (PPAR). These transcription factors have been implicated in the suppression of preadipocyte proliferation, which is essential for adipocyte differentiation. Resveratrol, for example, has been found to decrease adipogenesis by enhancing the expression of the Sirt1 gene, which activates fat mobilization by suppressing PPAR γ . Capsaicin, genistein, and EGCG have been shown to inhibit adipocyte differentiation through activation of AMPK [17][37][57]. At the same time, PUFA has been shown to suppress adipogenesis by lowering the expression of sterol-regulatory element-binding proteins and slowing the late phases of adipocyte differentiation. Many cell lines have recently been proven in vitro to undergo lipogenic differentiation into adipocytes. The 3T3-L1 preadipocyte is a well-studied biological model for understanding the adipogenesis process [58][59][60]. To assess the effect of test plant extracts on 3T3-L1 cell adipogenesis, 3T3-L1 preadipocytes are differentiated into mature adipocytes in the presence of different concentrations of the test plants (0–2 days), and the treatment is maintained for a total of 10 days [15][61][62]. Grape seed, green tea, *Allium sativum*, *Camellia sinensis*, *Capsicum annuum*, *Curcuma longa*, *Ginkgo biloba*, *Olea europea*, *Mentha longifolia*, *Alchemilla vulgaris*, *Vitis vinifera*, and *Salvia officinalis* extracts [15][61][62] have been reported to reduce adipogenesis in the 3T3-L1 cell line. *Salvia officinalis* leaves act through synergistic mechanisms to reduce the weight of overweight and obese patients [13]. Further research is needed to determine if combining these extracts could create a more effective way to suppress the formation of fat cells. Adipogenesis, the process of creating new fat cells, is controlled by adipogenic signaling, which activates transcriptional activators, mainly from the PPAR and C/EBP families, to regulate fat cell differentiation and fat storage within cells [58][59]. During the final stages of preadipocyte development, PPAR and C/EBP coordinate the activation of various adipogenic gene products, including ADRP, aP2, CD36, and perilipin. These gene products work together to produce the adipocyte phenotype [58][59].

Lipolysis: Lipolysis in adipocytes and the release of free fatty acids play a major role in regulating energy homeostasis. Hormone-sensitive lipase is the key enzyme that catalyzes lipolysis in adipocytes. Several medicinal plants and phytochemicals can also affect lipolysis [63][64]. Flavonoids genistein, diadzein, coumestrol, and zearalenone stimulate lipolysis in a dose-dependent manner. Quercetin, luteolin, and fisetin increase lipolysis in rat adipocytes in a dosage and time-dependent manner that was synergistic with epinephrine [65][66]. It has also been observed that these flavonoids inhibit phosphodiesterase. Proanthocyanidins produced from grape seeds promote long-term lipolysis in 3T3-L1 adipocytes through elevating cAMP and protein kinase A. In human adipocytes and 3T3-L1 adipocytes, conjugated

linoleic acid was observed to increase basal lipolysis. When docosahexaenoic acid (an omega-3 fatty acid) is introduced to mature adipocytes, it also induces lipolysis [17][67][68][69][70].

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