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Review Article

Effects of Phytoconstituents on Adipocytes in the Management of Obesity and Hyperinsulinemia

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ABSTRACT

Obesity and overweight are the risk factors for Type 2 diabetes. Obesity is also linked to non-communicable diseases like dyslipidemia, hypertension, and cardiovascular diseases. Adipocyte precursor cells are multiplied and differentiated into mature adipocytes throughout the process of adipogenesis. Obesity is also linked to high levels of oxidative stress and dysfunctional antioxidant systems. White adipose tissue encourages the pathogenesis of insulin resistance, regulates metabolic inflammation, and stimulates the immune system through persistent low-grade inflammation, which further causes insulin resistance and type II diabetes mellitus. Adiponectin is the main peptide produced by adipocytes and its depletion is a major factor in obesity-related illnesses such type 2 diabetes, insulin resistance, and cardiovascular disease. Adiponectin's effects are mediated by adiponectin receptors that exist in two isoforms (AdipoR1 and AdipoR2). Numerous researches have recently looked into how natural ingredients affect adipocyte development and lipid accumulation. Natural products' potential anti-obesity actions include inducing apoptosis, stopping or delaying cell cycle development, and disruption of transcription factor cascades or intracellular signaling pathways at the initial stages of adipogenesis. Some of the phytoconstituents including curcumin, limonene, cinnamaldehyde, crocin, berberine, sulforaphane, piperonal, 6-gingerol and Ajoene are discussed for the management of obesity and hyperinsulinemia in this review.

Keywords: Antiobesity, Adiponectin, Adipocytes, Insulin resistance, Oxidative stress.

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INTRODUCTION

Worldwide, 39% of adults are overweight, with an extra 13% being obese, according to the World Health Organisation. Additionally, there are more than 370 million overweight or obese children worldwide (World Health Organization, 2020).

There are two types of adipose tissue brown and white. Brown adipose tissue is primarily involved in non-shivering thermogenesis in response to cold stress and β-adrenergic stimulation, whereas white adipose fat plays an important role in maintaining lipid homeostasis and energy balance. Increased white adipocytes, macrophage infiltration, and fibrosis cause hypertrophic white adipose tissue expansion which further disrupt hormonal balance. The release of proinflammatory cytokines and adipokines alters normal energy homeostasis, leading to metabolic syndrome (Jakab, 2021).

Obesity causes low-grade chronic inflammation, which causes oxidative stress. Chronic low-grade inflammation is brought on by erroneously high adipocytokine production and the activation of inflammatory signalling pathways, specifically Jun N-terminal Kinase (JNK) and inhibitor of NF-κB Kinase (IKK). Leptin, resistin, and adiponectin are secreted by white adipose tissue, together with other pro-inflammatory (IL-1, IL-6, IL-10, and TNF-) and anti-inflammatory (IL-4 and IL-10) cytokines.

Adiponectin administration in people and rodents has been proven to have insulin-sensitizing, anti-atherogenic, and anti-inflammatory properties. In some circumstances, it has also been demonstrated to reduce body weight (Trayhurn 2007, Katagiri 2007, Bartness 2007, Achari 2017).

Increased Reactive Oxygen Species (ROS) levels may be a significant initiator of insulin resistance, according to gene expression studies. In cell culture, the hypothesis is that ROS is linked to insulin resistance which was evaluated using six treatments intended to change ROS levels, including two small compounds and four transgenes. All of these treatments reduced insulin resistance to varied degrees. One of these treatments improved insulin sensitivity and glucose homeostasis when tested on obese, insulin-resistant animals (Houstis, 2006).

Phytochemicals play a crucial role in managing obesity and hyperinsulinemia by targeting adipocytes through different

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mechanisms. Phytoconstituents like flavonoids, polyphenols, and terpenoids inhibit adipocyte differentiation by downregulating adipogenic transcription factors such as PPAR-γ and C/EBP-α. Catechins and capsaicin may stimulate lipolysis by activating β-adrenergic pathways. Quercetin and genistein improve adiponectin levels and suppress pro-inflammatory adipokines such as TNF-α, reducing systemic inflammation and improving insulin sensitivity. Berberine and Epigallocatechin Gallate (EGCG) are potent inhibitors of lipogenic pathways. Curcumin and resveratrol enhance insulin receptor signaling in adipocytes, improving glucose uptake and reducing hyperinsulinemia (Figure 1).

Curcumin in insulin resistance and obesity

Study was carried out on the effects of curcumin on High Fat Diet (HFD)-induced insulin resistance and obesity, it was found that curcumin enhances insulin signalling, glucose disposal, and prevents obesity via reducing lipogenesis in the liver and the inflammatory pathway in adipocytes. Data showed that curcumin's effects are achieved through improving animal resistance to oxidative stress and reducing the inflammatory response in adipocytes.

Curcumin's beneficial effects were related to a drop in macrophage infiltration of the adipose tissue, an increase in adiponectin synthesis, and a reduction in hepatic NF-κB activity. Curcumin plays the role in improving the insulin stimulated PKB phosphorylation in adipose tissue and liver and glucose disposal. It did this by inhibiting the effect of HFD on macrophage infiltration in adipose tissue, which is linked to the suppression of NF- κB level and JNK activity (Shao, 2012).

Immunomodulation via herbal formulation in obese and prediabetics

Large levels of the macrophage chemoattractant MCP-1 are secreted by hypertrophied adipocytes in obese individuals, which aids in the infiltration of macrophages into adipose tissue.

In the study, serum obtained from mice on high-fat, high-sugar diet supplemented with herbal formulation with 20 μL showed that leptin levels came back to normal compared with the levels seen in the of low-fat diet group. By decreasing levels of IL-1α, IL-1β, IL-6, TNF-α, and MCP-1 and increasing levels of anti-inflammatory IL-4 and IL-10 at week 15, the herbal formulation lowers obesity and associated pro-inflammatory responses. Mice with diabetes and obesity who were supplemented with herbal formulation demonstrated significant reductions in body weight, fat pads, insulin levels, fasting blood glucose levels, metabolic parameters, immunological parameters, and a variety

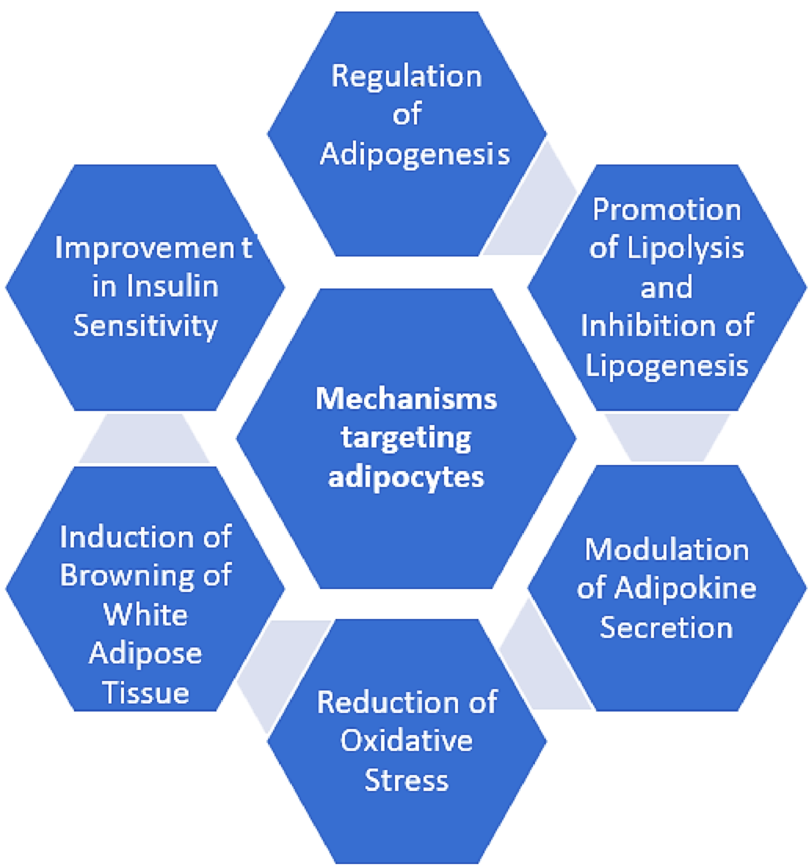
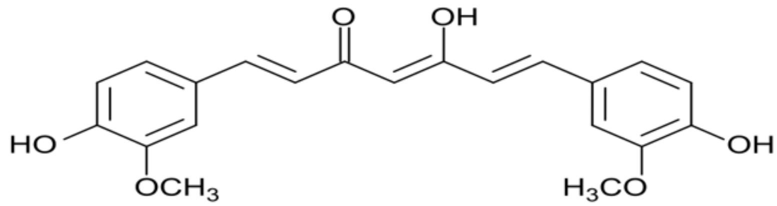
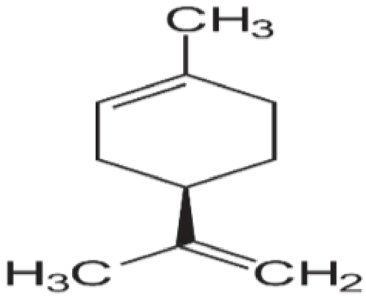


Figure 1: Mechanisms targeting adipocytes for managing obesity and hyperinsulinemia.



Structure 1: Curcumin.



Structure 2: Limonene.

of pro- and anti-cytokines compared to control (lean) mice fed a regular diet (Tikoo, 2013).

Grapefruit oil olfactory stimulation effects on lipolysis

According to the study, the sympathetic nerve that innervates the white adipose tissue in rats is stimulated by the Smell of Grapefruit Oil (SGFO), or olfactory stimulation.

Researchers conducted additional experiments using SGFO, which stimulated the sympathetic nerves that innervate the brown adipose tissue and the adrenal gland while inhibiting the parasympathetic gastric nerve. A grapefruit oil ingredient called limonene generated reactions resembling those brought on by the aroma of grapefruit oil, and diphenhydramine eliminated the glycerol response to limonene. As a result, the aroma of grapefruit oil, especially its main compound limonene, has an impact on autonomic nerves, promotes lipolysis through a histaminergic reaction, and decreases hunger and body weight (Shen, 2005).

Anti-obesity and anti-hyperglycemic effects of phytochemicals

The effectiveness of the ayurvedic Mohana Choorna on T2D-related parameters in patients with impaired glucose tolerance was investigated. In comparison to the placebo, the herbal intervention was associated with an increase in the expression of gene sets related to inflammation in adipose tissue and a tendency towards higher levels of insulin, HOMA-IR, and postprandial insulin (Esser, 2021).

Mice were given a diet containing cinnamonaldehyde (250 mg/kg/day) for a period of five weeks. Measurements included fat mass, lean mass, blood sugar and insulin levels, cholesterol, triglycerides, adiponectin, and leptin. The results of the study showed that cinnamaldehyde is a natural ghrelin suppressor that can be utilised to lower blood sugar and improve insulin sensitivity (Camacho, 2015).

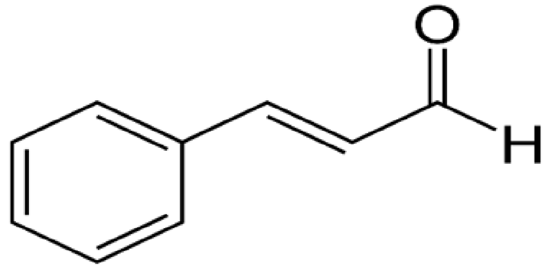
A daily dose of 176.5 mg of saffron-ethanol was given to 60 overweight women in capsule form. According to the study, all of the subjects lost weight and their need for unnecessary snacks decreased. The phytochemical crocin, a natural pancreatic lipase inhibitor, found in saffron aids in fat loss. With a dosage of 102 micrograms/kg, it decreases fat absorption at a rate of 12%. TNF-alpha, adiponectin, and leptin's mRNA expression is dysregulated by crocin (Thushara, 2013).

Conjugated Linoleic Acid (CLA), green tea, and compounds from garlic have all been proven to either have antidiabetic effects or to directly affect adipose tissue. Polyphenols such as apigenin, luteolin, kaempferol, myricetin, quercetin, genistein, diadzein, cyanidin, grape seed proanthocyanidin, xanthohumol, and epigallocatechin gallate have all been the subject of several investigations examining their antiobesity qualities. Studies are conducted to investigate the effects fucoxanthin, coumarin derivatives like esculetin, and phytoalexins like resveratrol on lipid metabolism (Saad, 2022).

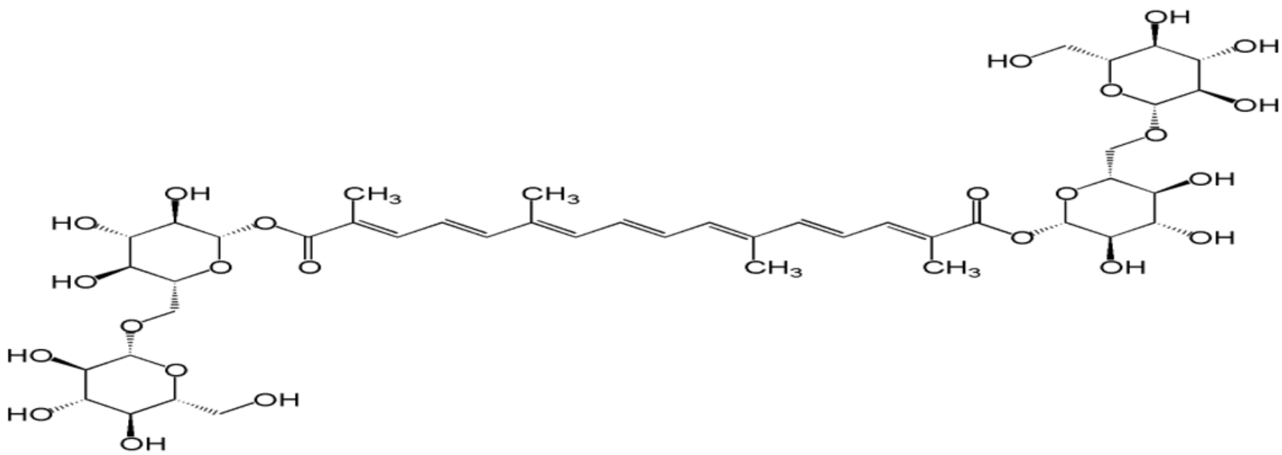
Obesity treatment by traditional Chinese medicine and leptin resistance Interrelation was studied. it shown to have the advantages of targeting multiple pathways including the leptin signaling pathways. According to the study's findings, TCM may effectively interfere with leptin resistance and its associated intervention mechanisms, giving new targets for the development of anti-obesity drugs (Shao, 2022).

Berberine effect on intestinal flora of obese mice was studied. The results showed that there was significant difference in body mass between the control group and the control model group on the 14^{th} day, which indicated successful molding. On the 28^{th} day, the body mass of mice administered berberine was significantly different from that of the control model group and it could significantly improve the lipid level and the number of Bifidobacteria and lactobacillus in the obese mice. The involved mechanism of berberine might be related to lipid metabolism, inflammatory response and changes in intestinal microenvironment (Huang, 2019).

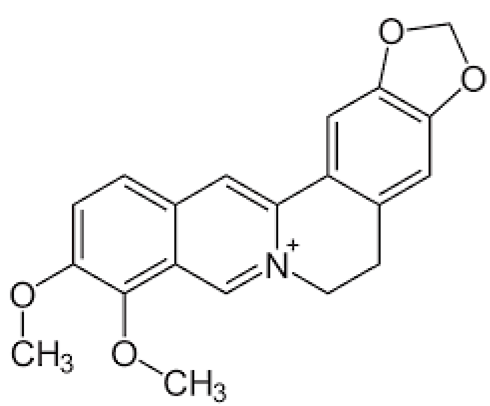
The herbal medicine Yijin (Erchen)-Tang (YJT), used in traditional Chinese and Korean medicine, has been investigated for the treatment of disorders associated with obesity. After being



Structure 3: Cinnamaldehyde.



Structure 4: Crocin.



Structure 5: Berberine.

given a diet high in fat and cholesterol (HFHC, 40% fat and 1% cholesterol) for eight weeks, C57BL/6 J mice were then given YJT for an additional six weeks. The study demonstrated the variations in adipocytes and adipokines brought about by YJT, confirmed that YJT reversed HFHC-induced changes in leptin and adiponectin levels in adipose tissue and plasma. Reduction in adipocyte inflammation and macrophage infiltration was also observed (Lee, 2020).

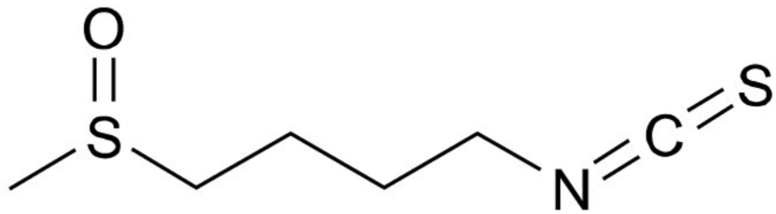
A naturally occurring isothiocyanate known as Sulforaphane (SFN) is produced by cruciferous vegetables like broccoli, cabbage, and Brussels sprouts. In one of the investigations, the inhibitory impact of the isothiocyanate sulforaphane on adipogenesis in 3T3-L1 cells was examined. According to a study, SFN prevents adipocyte differentiation by suppressing the expression of the adipogenic factors peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα) and therefore decreases lipid accumulation hence obesity reduction lowers the risk for type 2 diabetes, hypertension, and coronary heart disease (Choi, 2012). Similarly, another study's findings indicate that SFN might inhibit adipogenesis by downregulation of PPARγ and C/EBPα and repress lipogenesis through activation of the AMPK pathway, hence causing anti-obesity effect (Kyeong, 2014).

In diet-induced obese male rats, teasaponin, an extract from tea, has been demonstrated to reduce central leptin resistance and inflammation. It was shown that teasaponin decreased both inflammatory signalling and proinflammatory cytokines in the mediobasal hypothalamus. Furthermore, teasaponin treatment improved the hypothalamic expression of the anorexigenic peptide proopiomelanocortin, restored leptin-induced phosphorylated Signal Transducer and Activator of Transcription-3 (p-STAT3) signalling in the arcuate nucleus, and improved the anorexigenic effects of central leptin administration. These results suggest that teasaponin may find new application as an anti-inflammatory and anti-obesity drug (Yu, 2013).

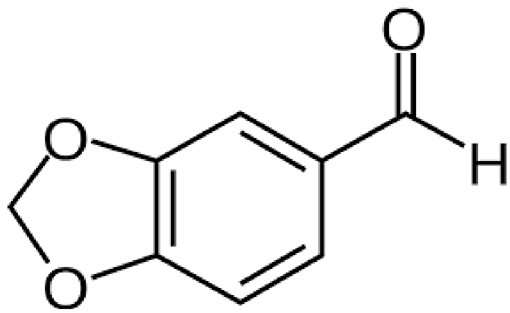
By improving leptin-mediated signals in the hypothalamus, up-regulating AMPK activation, and suppressing the expression of PPARγ in the liver, KBH-1, a herbal mixture consisting of

Table 1: Summary of the phytoconstituents with mechanism and therapeutic indication.

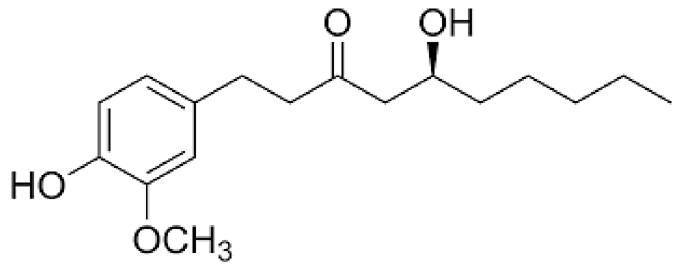
Sl. No.	Phytoconstituents	Molecular mechanism	Therapeutic indication	Model/Assay used	References
1	Curcumin	Attenuating lipogenic gene expression in the liver and the inflammatory response in the adipose tissue.	Insulin Resistance, Obesity.	Low fat diet, or HFD fed C57BL/6J mice	Shao, 2012
2	Limonene	Affects autonomic nerves, enhances lipolysis through a histaminergic response.	Appetite, body Weigh.	Urethane-anesthetized rat	Shen, 2005
3	Cinnamaldehyde	Adipose tissue up-regulation of genes related to fatty acid oxidation.	Anti-hyperglycemic and anti-obesity effects.	MGN3-1 cell line, a ghrelin secreting cell model,	Camacho, 2015
4	Crocin	Dysregulates mRNA expression of tumour necrosis factor (TNF)-alpha, adiponectin and leptin.	Oxidative stress-induced apoptosis and inhibits platelet aggregation.	Overweight women	Thushara, 2013
5	Berberine	Lipid metabolism, inflammatory response and changes in intestinal microenvironment.	Obesity	Intestinal flora of obese Kunming mice	Huang, 2019
6	Sulforaphane	Inhibiting adipogenesis through down-regulation of PPARγ and C/EBPα and by suppressing lipogenesis through activation of the AMPK pathway.	Obesity	High-fat diet induced obesity in C57BL/6N mice.	Choi, 2012
7	Teasaponin	Enhanced the anorexigenic effect of central leptin administration, restored leptin phosphorylated signal transducer and activator of transcription-3 (p-STAT3) signaling in the arcuate nucleus, and increased hypothalamic expression of the anorexigenic peptide proopiomelanocortin.	Antiobesity and antiinflammatory agent	Diet-induced obese male mice.	Yu, 2013
8	Piperonal	Activated adiponectin/AMPK axis may inhibit p70S6 kinase signaling and the ER stress response.	Hepatic steatosis and insulin resistance.	High fat diet fed mice.	Li, 2013
9	6-gingerol	Stimulating both plasma adiponectin and muscular adiponectin receptor signaling.	Ectopic Lipid Accumulation, Mitochondrial Dysfunction and Insulin Resistance in Skeletal Muscle.	Naturally ageing rats.	Anaysa, 2020
10	Ajoene	Suppressed accumulation of lipids in 3T3-L1 adipocytes during the differentiation phase.	Decreased cell viability and increased apoptosis.	Mouse embryo fibroblast cell line, 3T3-L1.	Ambati, 2009
11	Capsaicin	Increased expression of adiponectin and other adipokines including Peroxisome Proliferator-Activated Receptor (PPAR) α, PPARγ, visfatin, and adipsin.	Reduce visceral obesity and inflammation and increase insulin sensitivity.	Male C57BL/6 mice fed a 60% HFD	Lejeune 2003, Lee 2013
12	Resveratrol	Decreased adipocyte size, increased sirtuin 1 expression, decreased NF-κB activation and improved insulin sensitivity in visceral but not subcutaneous WAT from HFS-fed animals.	Beneficial metabolic and inflammatory adaptations in visceral white adipose tissue.	High-Fat, high-Sugar (HFS) diet in White Adipose Tissue (WAT) from rhesus monkeys.	Jimenez-Gomez, 2013



Structure 6: Sulforaphane.



Structure 7: Piperonal.



Structure 8: 6-gingerol.

Saururus chinensis, Curcuma longa, and *Polygala tenuifolia*, including onji-saponin B and curcumin, improved the hepatic steatosis and leptin resistance of the hypothalamus in an HFD-induced obesity rat model. Thus, KBH-1 extract can be utilised as a preventative step to address obesity-related problems or as a functional dietary supplement (Lee, 2016).

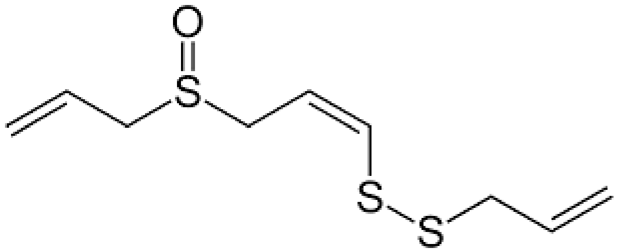
Vanilla and camphor wood contain fragrant aldehyde piperonal. In mice fed a high-fat diet, piperonal supplementation decreased the levels of hepatic lipids, liver dysfunction, and plasma levels of insulin and glucose. The 3T3-L1 adipocytes' mRNA expression and adiponectin secretion were both significantly enhanced by piperonal. In response to dietary piperonal, mice given the HFD exhibited significantly increased levels of circulating adiponectin and hepatic AMP-activated Protein Kinase (AMPK); these events were connected to the livers' activation of glucose transporter-2 translocation and suppression of sterol regulatory element binding protein-1c. In the livers of mice given an HFD, piperonal also markedly decreased the expression of Endoplasmic Reticulum (ER) stress indicators. In mice, piperonal may activate the adiponectin/AMPK pathway. Activated adiponectin/AMPK axis may suppress p70S6 kinase signalling and the ER stress response, with protective effects on insulin resistance and hepatic steatosis (Li, 2013).

Research was conducted to assess the green tea extract high in polyphenols stimulates thermogenesis in mice through adiponectin signalling. According to a study, obesogenic diets increase the level of adiponectin, and adipokine is responsible for green tea extract's ability to activate thermogenesis in mice that have been given obesity-inducing diets (Anaysa, 2020).

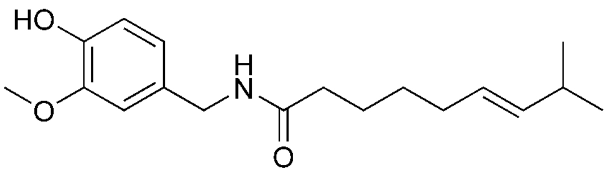
In a study, 6-gingerol is examined for its dual effects on rat models of natural ageing, including its stimulation of adiponectin signalling in the blood and the muscles. Findings suggested that in the skeletal muscle of ageing rats, 6-gingerol may reduce insulin resistance, improve ectopic lipid buildup, and mitochondrial dysfunction. These benefits are dependent, at least in part, on the combined activation of the AMPK/PGC-1α signalling pathway by muscle AdipoR1 and plasma levels of adiponectin, both of which are increased (Liu, 2018).

Research was done to examine the relationship between berberine's ability to restore GLP-1 secretion and the protection of colon enterocytes against mitochondrial overheating in diet-induced obese mice. According to a study, mice with the DIO mutation have reduced GLP-1 expression in the colon enterocytes under conditions of mitochondrial stress. An increase in abundance of ATP, increase in complex I activity, and a decrease in the activities of complexes II and IV were detected together with cristae loss, membrane rupture, and mitochondrial enlargement. These modifications were linked to dysbiosis and a decrease in SCFAs in the colon of DIO animals. Colon enterocytes of DIO mice were examined for mitochondrial stress responses in order to reduce GLP-1. In the restoration of GLP-1 expression, berberine, which may act through direct and indirect pathways, reduced the stress (Sun, 2018).

The study investigated if TRPV1 had been associated and whether changes in the gut microbiota and SCFA composition mediated the anti-obesity benefits of CAP in mice fed an HFD. The results of the study demonstrate that the anti-obesity and decreased food intake effects of CAP were observed independent of TRPV1 channel activation, and that these effects are mediated by alterations in the gut microbiota populations and SCFA levels (Wang, 2020).



Structure 9: Ajoene.

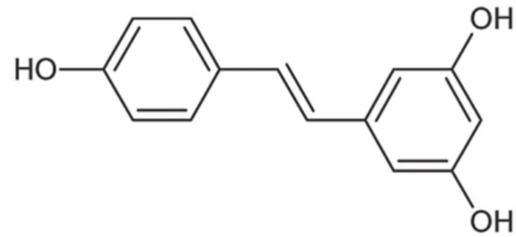


Structure 10: Capsaicin.

Garlic's ajoene has been demonstrated to affect adipocytes. According to the study's findings, ajoene exerts strong effects on 3T3-L1 adipocytes by inhibiting adipogenesis and inducing apoptosis. The amount of lipid droplets and their lipid content decreased by Oil Red O staining, which further corroborated the findings that ajoene significantly decreased lipid formation in maturing preadipocytes in a dose-dependent manner (Ambati, 2009).

Study reported that consumption of foods having capsaicin was linked with lowering obesity. It was further shown that capsaicin assists in weight maintenance by causing sustained fat oxidation during weight maintenance as compared to placebo (Lejeune, 2003). Another study found that topical administration of 0.075% capsaicin to male mice fed a high-fat diet dramatically decreased visceral fat and weight gain by influencing adipokines. Treatment reduced triglycerides, total cholesterol, and fasting glucose. According to an RT-PCR study, adiponectin and other adipokines such as visfatin, adipsin, PPARγ, and Peroxisome Proliferator-Activated Receptor (PPAR) α are more highly expressed (Lee, 2013).

Resveratrol has been shown in a study to improve adipose insulin signalling and decrease inflammation in the adipose tissue of rhesus monkeys fed a diet high in fat and sugar. Researchers discovered that long-term resveratrol administration results in positive metabolic and inflammatory changes in visceral WAT from diet-induced obese monkeys. In visceral WAT, resveratrol causes an increase in small adipocytes and SIRT1 protein levels while suppressing NF-κB activation and target gene expression (Jimenez-Gomez, 2013) (Table 1).



Structure 11: Resveratrol.

CONCLUSION

Adiponectin, a hormone produced by adipose tissue, is crucial for preventing insulin resistance, diabetes, and atherosclerosis. The hormone leptin controls appetite, weight, and reproductive health. It also has an impact on foetal development, pro-inflammatory immune responses, angiogenesis, and lipolysis. Insulin resistance, which is accompanied with hyperinsulinemia to maintain normal plasma glucose concentrations, is a state of decreased biological response to normal circulating insulin levels. Obesity and insulin resistance are interrelated and various phytochemicals with the diverse structural background have the potential to mitigate the risk of obesity and insulin resistance due to their affinity to the various receptors and synergy of combined constituents. Most of the phytochemicals have antioxidant property due to presence of chlorophyll/diverse pigments and polyphenolic compounds and these antioxidants plays crucial role in reducing the oxidative stress thereby reducing the chronic inflammation in non-communicable disease including obesity, diabetes, hypertension and cancer. This review is an attempt to explore the phytoconstituents focused mainly on antiobesity and antidiabetic agents having the role in adipocyte biology.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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