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**Anti-obesity effect of traditional Chinese medicine and natural products**

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**Abstract:** As obesity has become a worldwide health problem over the past three decades, more emphasis are placed on the prevention and treatment of obesity. Research in the nutrition field has recently aroused considerable interest based on the potential of traditional Chinese medicine and natural products to counteract obesity. This review focuses on the anti-obesity action using traditional Chinese medicine and natural products. Some present potent anti-obesity effects because of their ability to reduce blood lipid or blood glucose while others could be used for the treatment of obesity as lipase inhibitor, lipid metabolism regulators, appetite suppressants or fatty acid synthase inhibitor. Further study should be conducted in the mechanisms and active ingredients of traditional Chinese medicine and natural products.

**Key words:** obesity; traditional Chinese medicine; natural products.

### Introduction

The widespread prevalence of obesity has become a worldwide health problem over the past three decades. It is evident that the number of obese or overweight people is increasing not only in high-income countries, but also in middle- and low-income countries. Besides, this public health issue is also prevalent in teenagers, which causes great concern to parents. Patients with excess body fat are at increased risk of chronic diseases, including cardiovascular disease, type 2 diabetes, hypertension, osteoarthritis, depression, and thus lower the quality of life (1).

Global anti-obesity strategies focusing on lifestyle interventions and surgery, however, some evidence indicates that behavioural therapy, particularly diet therapy, for obesity is not effective in maintaining weight loss. On the one hand, weight losses are often small, and long-term success is very disappointing during dietary therapy

(2), on the other hand, biological mechanisms contribute substantially to relapse from weight loss during dietary therapy. These include a compensatory decrease in energy expenditure during dieting and compensatory adaptations that would be expected to increase appetite (3).

Besides, drugs therapy also dominate the treatment of obesity whereas pharmacologic treatment to combat obesity are still challenging for two main reasons: cost and side-effects (3). In order to treat obesity significantly, Cha-put *et al.* argued that the future "best" pharmacological agent in obesity management has to encounter mainly the three following aspects: 1) having the capacity to spontaneously change the body weight set-point without any specific dietary restriction, 2) being as specific as possible on the regulation of energy balance, and 3) being well-tolerated with the minimum of side effects (2).

Thereby, the exploration of new biochemical pathways is essential for the treatment of obesity in the near fu-

ture. Research in the nutrition field has recently aroused considerable interest based on the potential of traditional Chinese medicine and natural products to counteract obesity (4). For centuries people across the countries have been using traditional Chinese medicine and natural products for the weight control. Compared with many chemically synthesized drugs, the use of traditional Chinese medicine and natural products are cost-effective, and have fewer toxic side effects (5). Although traditional Chinese medicine has long clinical practice in the treatment of obesity, the effective anti-obesity ingredients are not fully defined and their action mechanisms have not been completely understood (6). In this review, we summarize the current knowledge of anti-obesity actions using both traditional Chinese medicine and natural products.

### Lipase inhibition

One of the most important strategies in the treatment of obesity includes development of inhibitors of nutrient digestion and absorption, in an attempt to reduce fat absorption and energy intake through gastrointestinal mechanisms (7). Lipase and pancreatic lipase are two key enzymes in dietary triacylglycerol absorption, which convert triglyceride substrates to monoacylglycerols and fatty acids. The anti-obesity mechanisms of drug include decomposing unnecessary fat tissue and inhibiting the absorption of fat from food. Lipstatin, first isolated from the *Streptomyces toxytricini*, is a remarkable inhibitor of pancreatic lipase (8). The popular anti-obesity drug orlistat (trade names Xenical and alli), is a saturated derivative of lipstatin and was clinically approved for obesity treatment. However, inhibition of fat digestion by orlistat may exacerbate postprandial glycemia, as a result of more rapid gastric emptying and a diminished incretin response

(9). In this case, the potent lipase inhibitory effect of tra-

ditional Chinese medicine and natural products makes it very likely to become a new approach for type 2 diabetes (10).

In China and Korea, *Platycodi Radix*, the roots of *Platycodon grandiflorum*, has been traditionally used as food for preventing obesity. Xu *et al.* suggested that the total saponins as well as single compound from *Platycodi Radix*, such as platycodin A, C, D, and deapioplatycodin D, strongly inhibited pancreatic lipase activity. The anti-obesity effect of *Platycodi Radix* might be due to the inhibition of pancreatic lipase by its saponins (11). Kwo-net *et al.* found that *Dioscorea nipponica* Makino appeared to have potent inhibitory activity against porcine pancreatic lipase with an IC<sub>50</sub> value of 5–10 µg/ml and was effective for preventing weight gains of both the body and adipose tissue in rodents induced by a high-fat diet. The active components present in the herb generated dioscin that belongs to the saponin family. Both dioscin and its aglycone, diosgenin, showed inhibitory potential against fat absorption (12). Moreno *et al.* indicated that the grape seed extract with rich bioactive phytochemicals, showed strong inhibitory activity against the fat-metabolizing enzymes pancreatic lipase and lipoprotein lipase. Besides, the observed reduction in intracellular lipolytic activity of cultured 3T3-L1 adipocytes may reduce the levels of circulating free fatty acids that have been linked to insulin resistance in obese patients (13,14). In addition, it has been suggested that twelve flavonoids isolated from *Glycyrrhiza glabra* roots inhibited pancreatic lipase activity in a dose-dependent manner, which therefore reduced the intestinal absorption of dietary fats and regulated lipid metabolism (15).

As a beverage for treating obesity for many years, various polyphenols (e.g., L-epicatechin, epicatechin galate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)) isolated from different types of tea (e.g., green, oolong, and black tea), showed strong inhibitory activity against pancreatic lipase. These natural ingredients could effectively reduce fat absorption and suppress weight gain.

### Reducing blood lipids

Blood lipids are lipids in the blood, either free or bound to other molecules. The concentration of blood lipids reflect the fat content in the body and the regulation of lipid mobilization. Lowering blood lipids in the body can promote the metabolism of lipids and thus facilitate weight loss. Saponins, anthraquinones, flavonoids, alkaloids, polysaccharides, unsaturated fatty acids, proteins and polyphenols, are reported to be the active ingredients from traditional Chinese medicine having blood lipid regulating effects (16). Total alkaloid of lotus leaves have significant effect on the control of body weight. The blood lipids, the Lee's indexes, the body fat percentages, the blood lipid content of the obese rats decreased significantly. The inhibitory effects of 1mg/ml lotus leaf extracts, nuciferine, N-nornuciferine and O-nornuciferin on lipase activity were 11.25%, 25.77%, 21.37% and 24.63% respectively (17). *Pructus Forsythiae*, a common Chinese traditional medicine, is recommended as healthy tea because of its extraordinary effect on anti-obesity. Previous research showed that Phillyrin, which is the bioactive ingredient in *Pructus Forsythiae*, could lower the fat index

( $P < 0.05$  or  $P < 0.01$ ) and Lee's index ( $P < 0.05$ ), reduce the level of serum triglyceride and cholesterol (18). In addition, extract from *Medicago sativa* L. has a function of weight loss in obese rats without side effects. This extract was worth of in-depth development since it exhibited a significant effect on reducing body weight, fat tissue around testicle and kidney, body fat percentage and Lee's index. Additionally, *Medicago sativa* L. showed a significant decrease of total cholesterol level and inhibitory effect on the growth of fat cells around the genitals in obese rats (19,20). Other bioactive compounds from traditional Chinese medicine exhibiting a similar effect on lowering blood lipids include extracts from Hawthorn, berberine, Ginsenoside Rh2, eucommia leaf extracts, tea polyphenols, Semen Coicis and lycium barbarum polysaccharide (21).

### Lipid metabolism regulators (increased lipolysis)

Lipolysis is the procedure that the hydrolysis of fats into fatty acids and glycerol, which is another pathway to reduce weight.

Raspberry ketone, a bioactive compound with a similar structure of capsaicin, was previously reported to exhibit capsaicin-like anti-obesity effects. The effect of raspberry ketone on preventing obesity and fatty liver appears to stem from the action in altering the lipid metabolism, or more specifically, in increasing norepinephrine-induced lipolysis in white adipocytes. Raspberry ketone not only prevented the high-fat-diet-induced elevations in body weight, the weights of the liver and visceral adipose tissues (epididymal, retroperitoneal, and mesenteric), but also decreased these weights and hepatic triacylglycerol content after they had been increased by a high-fat diet. Moreover, Raspberry ketone significantly increased norepinephrine-induced lipolysis associated with the translocation of hormone-sensitive lipase from the cytosol to lipid droplets in rat epididymal fat cells (22). It's noticeable that the diet products based on raspberry ketone is becoming more and more prevalent in Japan. In European and American countries, the famous diet food is hydroxycitric acid (HCA), a present alimentary acid in some varieties of tropical fruits. It has been reported to have beneficial weight and fat mass loss effects. The primary mechanism of HCA seems to be a competitive inhibitor of the ATP-citrate enzyme lyase. ATP-citrate enzyme lyase catalyzes the conversion of citrate and CoA to oxalacetate and Acetyl Coenzyme A (acetyl-CoA), primary construction of fat acid blocks and the synthesis of the cholesterol (23,24). Evodiamine, a widely distributed Chinese herb, is the main active alkali of *Tetradium rutilicarpum* and plays an important role in the regulation of body fat deposition. The main mechanism is to raise energy consumption by reducing body temperature and promoting fat decomposition (25,26). Carnitine, known as ergogenic aid, have effects on differentiation of 3T3-L1 Cells and also improves lipid metabolism and insulin-like growth factors (IGFs) and IGF binding proteins in rat (27).

In China, raw Garlic Extract is always considered as nutraceutical ingredient for the prevention of obesity. Moreover, recent research presents the anti-obesity effects via regulating lipid metabolism in an animal model. It indicated that supplementation with methanolic extract of black garlic decreased the final body weight, the relative masses of the liver and fat tissues, serum triacylglyceride

levels, and hepatic oxidative stress. Among lipogenesis-related genes, supplementation with extract of black garlic upregulated AMP-activated protein kinase (AMPK), Forkhead box protein O1 (FOXO1); regarding adipokine regulation, supplementation with extract of black garlic increased the adiponectin expression level to normal level; regarding lipolysis, supplementation with extract of black garlic normalized LPL and perilipin expression levels and also increased Sirtuin 1 (Sirt1), Adipose triacylglyceride lipase (ATGL), Hormone sensitive lipase (HSL) expression levels; meanwhile, regarding fatty acid oxidation/transport and glucose transport, extract of black garlic upregulated Acyl-CoA oxidase (ACO) and Carnitine palmitoyltransferase 1 (CPT-1) but downregulated Cluster of differentiation 36 (CD36) and Glucose transporter type 4 (GLUT4) (28).

### **Appetite suppressants**

Appetite suppressants may enable better targets for drugs treating obesity through energy intake reduction by influencing the level of serotonin, histamine, dopamine and triggering a feeling of satiety or fullness. An example of a natural appetite suppressant is *Camellia sinensis* found in Green tea catechins. Green tea catechins belongs to polyphenolic compounds, present in the unfermented dried leaves of the plant, is traditionally reported to have anti-obesity effects. The mechanism of green tea catechins is that it influences sympathetic nervous system activity, increasing energy expenditure and promoting the oxidation of fat. Other potential mechanisms include modifications in appetite, up-regulation of enzymes involved in hepatic fat oxidation, and decreased nutrient absorption (29). *Garcinia cambogia*, another appetite suppressant. Jain *et al.* suggested that dose-dependent reduction in food intake (12–26%) was observed when *Garcinia cambogia* was taken with a dose between 100 and 150 mg/kg body weight ( $p < 0.05$ ). Appetite suppression persisted for 6 h and food intake was restored within 24 h after termination of the treatment (30,31). Hydroxycitric acid, which is rich in the dried fruit rind of *Garcinia cambogia*, has been shown to be active in suppressing appetite and body fat accumulation in experimental animals (32). Besides, *Robinia pseudoacacia* were found to exert a marked and significant effect on the suppression of food consumption, especially to have a long-lasting inhibition of gastric emptying (33). *Citrus aurantium*, mainly planted in tropical and subtropical countries, is used for herbal medicine to suppress appetite and control body weight. Liu *et al.* identified and isolated nine new pregnane glycosides along with six known compounds from the roots of *Cynanchum auriculatum*. The most abundantly known pregnane glycoside, wilfosioid K1N (10) with similar structures to that of P57 isolated from *Hoodia gordonii* showed significant appetite suppressing effect, and further led to loss of body weight in rats (34,35). *Hovenia acerba* vinegar is an anti-obesity product in the market, which is known for its function to lower serum total cholesterol, plasma triglyceride levels and atherogenic index. Moreover, it's reported that n-butanol extract of *hovenia acerba* might have an appetite-suppressing effect on rats (36).

### **Fatty acid synthetase inhibitor**

Recently, animal fatty acid synthase (FAS), which participate in energy metabolism, is reported as a therapeutic target for the control of appetite and body weight. Considerable research has been focused on identifying novel inhibitors of the enzyme.

Large quantities of traditional Chinese medicine are considered as natural and synthetic FAS inhibitors. Jiang *et al.* assessed the inhibitory activities on FAS of spices extracts in Chinese menu and found that 20 among 22 spices extracts (90.9 %) exhibited inhibitory activities on FAS, with IC<sub>50</sub> values ranging from 1.72 to 810.7 µg/ml. Among them, the FAS inhibitory effects of seven spices—cassia bark, *Cinnamomum cassia*, lilac, *Syzygium aromaticum*, star anise, *Illicium verum*, *Fructus Tsaoko*, *Amomum tsaoko* Crevost, katsumadai seed, *Alpinia katsumadai* Hayata, sweet fruit, *Myristica fragrans* Houtt., nutmeg, *Myristica fragrans* Houtt.—were very strong, with the IC<sub>50</sub> values ranging from 1.72 to 9.40 µg/ml, indicating that these spices showed much stronger inhibition than classical well-known FAS inhibitors such as cerulenin (IC<sub>50</sub>=20 µg/ml) and EGCG (IC<sub>50</sub>=24 µg/ml) (37).

C75, a member of  $\alpha$ -methylene- $\gamma$ -butyrolactones, was first discovered as a fatty acid synthase inhibitor and anti-tumor agent. C75 blocked the normal fasting-induced rise in blood free fatty acids and ketones due either to decreased adipose tissue lipolysis and hepatic ketogenesis or increased fatty acid and ketone utilization by peripheral tissues, notably skeletal muscle (38). Tea polyphenols is another a fatty acid synthase inhibitor. Tian *et al.* discovered that tea polyphenols inhibit FAS in both reversible and irreversible manners. Epigallocatechin gallate (EGCG) and epicatechin gallate (ECG) inhibit FAS with IC<sub>50</sub> values of 52 µM and 42 µM mainly by reacting on the beta-ketoacyl reductase (KR) domain of FAS. The inhibitory ability of catechin gallate (CG) is 15 and 12 folds higher than that of EGCG and ECG (39,40). Nowadays, great progress has been made in the study of fatty acid synthase inhibitor from traditional Chinese medicine. *Tuber fleecflower stem extract* (TFS) could potentially inhibit fatty acid synthase (FAS). It was shown that TFS inhibit FAS non-competitively against substrate acetyl-CoA and malonyl-CoA. Ketoacyl reductase in FAS was one of the reacted sites that TFS attacked on. In addition, TFS significantly reduced food intake, body weight and FAS activities in livers of diet-induced obesity SD rats and mice via oral administration (41,42). Other bioactive traditional Chinese medicine are *Alpinia officinarum* Hance, *Lico-rice*, *Polygonum multiflorum*, *Parasitic loranthus*, *Ginkgo leaf*, *Chrysanthemum*, *Cerasus humilis*, and *Folium cortex eucommiae*.

### **Reducing blood sugar and insulin resistance**

In recent years, the prevalence of type 2 diabetes has skyrocketed to such an extent that an increasing number of people paid more attention to this chronic disease. Insulin resistance is strongly associated with obesity and type 2 (non-insulin-dependent) diabetes, which is a state in which insulin produces a less-than-expected biological effect for both glucose disposal in skeletal muscle and suppression of endogenous glucose production primarily in the liver. Reducing resistance to insulin is an important

therapeutic target in obesity and type 2 diabetes.

Pomelo peels could be used as a dietary therapy and the potential source of drug for insulin resistance. Ding *et al.* found that extracts of pomelo peels blocked the body weight gain, lowered fasting blood glucose, serum total cholesterol, liver lipid levels, and improved glucose tolerance and insulin resistance. It can also lowered serum insulin levels in HF diet-fed mice (43). Panax notoginseng saponins, the principal ingredients extracted from the traditional Chinese medicinal herb Panax notoginseng, exhibited a considerable anti-obesity action, significantly increase insulin sensitivity and improve glucose homeostasis in KK-Ay mice which is clinically significant for the management of diabetes. Panax notoginseng saponins significantly decreased the serum insulin levels and insulin resistance index on day 30 along with the improvement in fasting blood glucose levels and glucose tolerance, demonstrating that the hypoglycemic effect of PNS in KK-Ay mice may be due to an improvement in insulin sensitivity (44).

Alpha-glucosidase inhibitors, oral anti-diabetic drugs preventing the digestion of carbohydrates, exhibit various anti-diabetic or anti-obesity effects in addition to the suppression of postprandial hyperglycemia. Alpha-glucosidase inhibitors from various natural products, such as soy-bean isoflavone, total flavonoids from mulberry leaves, Luteolin, 1-Deoxynojirimycin from Mulberry leaves, soyasaponin, glycyrrhizin, show significant effects on reducing blood sugar levels and insulin resistance. Specifically, an *in-vitro* study was carried out by Prashanth *et al.* who studied  $\alpha$ -glucosidase inhibitory activity of ethanolic extract of *M. indica* (mangiferin) and suggested the potential applications of mangiferin in obesity and diabetes (45,46). Furthermore, mulberry leaf has a potential for the treatment of hyperglycemia and hyperlipidemia in diabetes. Oral administration of mulberry leaf at 50-200 mg/kg body weight daily for 5 weeks significantly reduced the levels of fasting blood glucose, glycosylated serum protein, serum total cholesterol, and serum triglyceride, and increased the body weight, fasting insulin, C-peptide, liver glycogen, liver glucokinase, and serum high-density lipoprotein cholesterol. Moreover, mulberry leaf promoted marked pancreatic  $\beta$ -cell regeneration and insulin secretion, and reduced liver fat accumulation in diabetic rats (47,48).

## Conclusions

Nowadays, a number of obesity-treatment drugs in the market cause dissatisfaction among the public due to its high costs and potentially hazardous side-effects. Conversely, traditional Chinese medicine and natural products are developed as alternative strategy for treating obesity, opening new gateways in therapeutics and drug discovery and development.

Some traditional Chinese medicine and natural products present potent anti-obesity effects because of their ability to reduce blood lipid or blood glucose, others could be used for the treatment of obesity as lipase inhibitor, lipid metabolism regulators, appetite suppressants or fatty acid synthase inhibitor. Moreover, there might be some other natural products possessing multi-functional anti-obesity activities.

Widely concerns on the safety of obesity-treatment

drugs lead to the attention on traditional Chinese medicine and natural products in anti-obesity field. However, traditional Chinese medicine as a complementary therapy approach to obesity leads to serious considerations.

Compared to western herbal medicines, which are often standardized extracts of single herbs used for particular conditions, the adoption of traditional Chinese medicines in industrialized countries is impeded by a lack of quality control and the absence of scientific and clinical proof of their effectiveness. It is widely acknowledged that Western and Chinese medical practices represent totally different philosophies towards human health. Western medicine has methodically looked at the relationship between structure and function and designed drugs targeted against pathogens and/or diseased cells and tissues. Chinese medicine, on the other hand, defines health in terms of balance, and medications are designed to restore that balance by interacting with a wide variety of targets. Therefore, to uncover the mystery of traditional Chinese medicines and increase its application, the therapeutic approach using traditional Chinese medicine and natural products require a rigorous approach that includes chemical standardization, biological assays, animal models, and clinical trials (49).

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