

The Role of Capsaicin in Metabolism of Glucose, Lipids and in Hypertension

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Abstract: The metabolism of glucose and lipid is the foremost supply of energy for the human body and performs a key position in lifestyles activities. However, disorders of glucose and lipid metabolism will produce a sequence of diseases such as hyperlipidemia, diabetes, obesity, arteriosclerotic cardiovascular and cerebrovascular diseases, and long-term abnormal levels of sugar, lipid, and blood pressure will injury to the organs of the whole body and cause their functions to gradually decline. At the same time, it causes damage to blood vessels, which is one of the important factors of disability and death of patients. Chili pepper is a common ingredient in the diets of various communities and civilizations across the world. Capsaicin is a key component in chili peppers. It is responsible for the fiery flavor as well as a number of health advantages. Due to advances in research during the past decade, capsaicin can regulate glucose and lipid homeostasis, improve cardiovascular function, and inhibit obesity. In addition, studies have shown that ingesting an appropriate amount of capsaicin has a good effect on the treatment and prevention of diabetes, hyperlipidemia, and hypertension. The purpose of this paper was to spotlight the role of capsaicin in the metabolism of glucose, lipids, and high blood pressure these three parts.

1. Introduction

Metabolic syndrome, which includes high blood glucose, obesity, dyslipidemia and hypertension, is a significant risk factor which causes cardiovascular disease. According to the research, it shows that capsaicin is efficient in the therapy of the metabolic syndrome. Capsaicin can affect a few indicators of the human body.

Capsaicin($C_{18}H_{27}NO_3$) is the main element of chili pepper. This substance is irritating to mammals including humans and can produce a burning sensation in the oral cavity. Capsaicin can be extracted from peppers, ginger, Chinese chives and other foods.

This essay focuses on the basic physicochemical properties of capsaicin and its usage on the treatment of a few diseases. The advantages of capsaicin in regulating glucose and lipid metabolism were summarized, and its adverse effects were also explained. In addition, common metabolic problems such as diabetes, hyperlipidemia, hypertension and obesity are introduced.

2. The introduction of capsaicin

Chili pepper has featured prominently in the diets of communities and cultures around the world since 7000 BC, and have a long history of flavoring, coloring, preserving food and have been used as a drug [1]. Nowadays, chili pepper is still an essential ingredient in daily life that they are widely used in various recipes as a kind of additive. Chili pepper does various functions in different ways, such as additive, insect repellent and even medicine. As a kind of food additive, chili pepper is always considered as a sort of food seasoning that are widely used in various cuisines. In traditional medicine, it also an important treatment of coughs, toothaches, sore throats, parasitic infections, rheumatism,

wound healing [2]. As its strong spicy flavor, it can stimulate the oral mucosa and taste nerves in rodents.

One of the major elements of chili pepper is capsaicin, which makes people feel spicy and hot thus stimulates the taste buds effectively. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) has a molecular formula of $C_{18}H_{27}NO_3$ and a molecular weight of 305.418 g/mol. As shown in figure 1, the chili paper consists of capsaicin, dihydrocapsaicin and nordihydrocapsaicin. The density, melting point and boiling point are 1.12g/cm³, 62-65 °C and 469.7 °C respectively. This organic substance is insoluble in water and soluble in some organic solution including ethyl acetate, methanol, and ethanol.

According to the statistics, it has been reported that the consumption of capsaicin in some countries, such as 2500 mg/person/day in India, 5000 mg/person/day in Thailand and 20,000 mg/person/day in Saudi Arabi [3]. Capsaicin reduces fatigue and release specific active substances through binding to sensitive receptors in the human body. Furthermore, capsaicin can protect the stomach. Because of the strong irritating properties of capsaicin, people always think that taking capsaicin may hurt the stomach. Through some researches, small doses of capsaicin wouldn't cause damage to the stomach, in turn, it would repair the damage of gastric mucosa. Children can also be protected against gastrointestinal disorders by capsaicin, including indigestion, loss of appetite and gastroesophageal reflux disease [2].

Although moderate consumption of capsaicin has benefits on human health, long-term and excessive consumption of capsaicin might cause negative effects on human body. Being exposed to high or repeated doses of capsaicin results in desensitization of TRPV1, resulting in analgesic effects [4]. Getting too much capsaicin can increase blood pressure and sweating, and may even damage the nervous system and peptic ulcers.

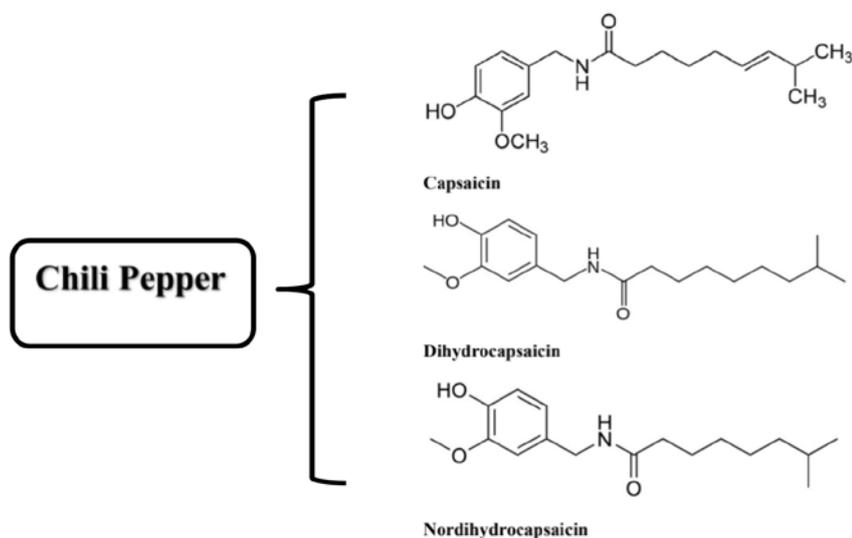


Figure 1. The chemical structure of capsaicin

3. Effect of capsaicin on diabetes

Diabetes mellitus is more commonly referred to as "diabetes". It is a metabolic syndrome that can cause abnormal high sugar levels in the blood. And the existence of diabetes mellitus raises the risk of a variety of consequences, including cardiovascular disease, peripheral vascular disease, stroke, nerve damage, kidney failure, foot damage, retinopathy, and blindness, among others [5]. The trend of morbidity and mortality of diabetes is increasing and related to global health problems.

Diabetes is due to one of two mechanisms: The first is insufficient pancreatic insulin synthesis, which is made by the pancreas and reduces blood glucose, it is also called type 1 diabetes. The second is the cells' inadequate sensitivity to the action of insulin, also called type 2 diabetes [6].

Discovered by research on metabolic syndrome, the researchers find capsaicin works by activating the Vanilloid type-1 Transient Receptor Potential Channel (TRPV1) [7]. And TRPV1 is recognized to be the molecular integrator of inflammatory mediators; As a result, TRPV1 antagonists have been

created for the treatment of chronic inflammatory diseases. [8]. In both animals and humans, capsaicin, an exogenous agonist of TRPV1 receptors, has been found to decrease food intake and increase energy expenditure [9]. TRPV1 receptors also have a crucial role in the control of glucose homeostasis, as evidenced by improvements in research over the last decade, thus TRPV1 receptors may have a significant role in the treatment and progression of diabetes, including type 1 diabetes (T1D) and type 2 diabetes mellitus (T2DM) [9, 10].

Type 1 diabetes is an autoimmune disease. It is caused by the loss of the pancreas' insulin-producing beta cells. T cells are involved in the illness, which is caused by a breakdown in immunological tolerance to self-antigens [11]. About this disease, the researcher through examined the immunomodulatory characteristics of capsaicin when given orally to two T1D mice models. It shows CP suppresses antigen-specific T lymphocytes in pancreatic lymph nodes (PLNs) when taken orally. And, when taken orally, CP causes minor changes in immunological parameters in the PLN, resulting in the suppression of a continuing immune response and the prevention of autoimmune diabetes [11].

Type 2 diabetes, is distinguished by insulin resistance leads to insulin sensitivity, insulin production decreased, leading to beta-cell dysfunction in the pancreas. As a result, glucose transport into the liver, muscle cells, and fat cells is reduced, as well as an increase in the breakdown of fat [12]. Type 2 diabetes affects up to 95% of diabetics which mainly affects persons in their forties and fifties.

One present research found that capsaicin has a number of pharmacological effects which can reduce the plasma glucose level [13]. One crossover trial had 12 healthy volunteers who completed the OGTT while given either a placebo or 5 grams of capsicum. The HPLC technique was used to quantify insulin secretion and capsaicin levels in plasma. At 30 and 45 minutes, plasma glucose levels in volunteers who took capsicum were considerably lower than those in the placebo group, according to the findings of the OGTT. Overall discovered that 5 grams of capsicum included capsaicin levels linked to lower blood glucose levels and maintaining insulin levels. And they have clinical implications for type 2 diabetes treatment [13].

In a study of obese diabetic mice (ob mice), the researchers fed ob mice a normal, low, or high capsaicin diet for several weeks. As shown in Table 1, it was shown that both low and high dosages of dietary capsaicin effectively reduced the rise in fasting blood glucose and insulin levels [14]. In the same way, dietary capsaicin stimulation of glucagon-like peptide-1 (GLP1) secretion, improved glucose and insulin tolerance significantly. Furthermore, the potential effects of dietary capsaicin on glucose homeostasis are likely linked to genus-level changes in particular bacteria. By boosting short-chain fatty acids, modulating gastrointestinal hormones, and suppressing pro-inflammatory cytokines, dietary capsaicin-induced changes in bacteria lead to better glucose homeostasis [14].

GDM (gestational diabetes mellitus) is characterized as carbohydrate intolerance that begins or is first noticed during pregnancy [15]. Globally, GDM is estimated to affect 16 percent to 18 percent of pregnancies [16]. The synthesis of insulin-blocking chemicals by the placenta causes this type of diabetes [17].

One research invites some pregnant women with GDM were randomly allocated to the capsaicin group or the placebo group for a few weeks. The conclusion drawn from the experimental results is that supplementing with capsaicin-rich chili reduced the prevalence of large-for-gestational-age infants and improved postprandial hyperglycemia and insulin levels in the blood that are excessive as well as fasting lipid metabolic abnormalities in women with GDM [15].

Table 1. Summary of the effects of Capsicum in type 2 diabetes

Research design	Substances	Result	Reference
Diabetic mice	Dietary capsaicin	Reduced the rise in fasting blood glucose	[13]
Diabetic mice	Dietary capsaicin	Improved glucose and insulin tolerance	[13]
Diabetic mice	Dietary capsaicin	Glucagon-like peptide-1 secretion stimulation	[13]
Diabetic mice	Dietary capsaicin	Improve glucose homeostasis	[13]
Human	Capsaicin 5g	Decreased plasma glucose levels and the preservation of insulin levels	[14]

4. Effect of capsaicin on hyperlipidemia

Hyperlipidemia is a condition in which blood lipid levels are abnormally high, which can lead to diseases such as atherosclerosis, coronary artery disease, pancreatitis, and other major health problems.

Primary hyperlipidemia and secondary hyperlipidemia are two types of hyperlipidemias. Congenital and genetic factors are linked to primary hyperlipidemia. Single or several gene deficiencies induce problems in receptors, enzymes, or apolipoproteins involved in lipoprotein transport and metabolism. It's either because of external stimuli or because of unknown mechanisms. Metabolic illnesses, such as diabetes, hypertension, obesity, liver and kidney disease, and so on, are the most common causes of secondary hyperlipidemia. Age, gender, season, alcohol intake, smoking, food, physical activity, mental stress, emotional activity, and so on all play a large role.

Nowadays, the treatment of hyperlipidemia is mainly through controlling ideal weight, doing some exercise, controlling daily diet, and drug therapy. Because of unhealthy lifestyles, especially the intake of high-fat, high-calorie diets, the number of obese people worldwide has risen sharply. And there are certain risks associated with drug treatment. The scientists hope to build on studies of the effect of dietary capsaicin on blood lipids. The prevalence of hyperlipidemia is decreased by adding a certain amount of dietary capsaicin to the daily diet.

One study showed that capsaicin was effective in reducing serum cholesterol levels in hyperlipidemic animals, with little effect on triglyceride levels. And it shows that capsaicinoids can significantly reduce LDL levels but have little effect on HDL levels [18]. However, another study showed that after long-term regular intake of capsaicin to experimental animals, it can not only effectively reduce the serum total cholesterol content of the experimental animals but also significantly reduce the serum triglyceride level. It also shows that capsaicin can observably lower LDL levels since massively increasing HDL levels. However, since the experimental animals used in the two experiments are different, the reason for the difference may be related to the species of animals used [19]. These studies have shown that long-term and low-dose intake of capsaicin can significantly reduce serum cholesterol levels. The main reason is that the serum of experimental animals has significantly lower LDL-C levels and significantly higher HDL-C levels. In addition, capsaicin dramatically lowered MDA levels while increasing SOD activity.

Capsaicin's protective mechanisms against lipid metabolic problems by eating beef fat, oxidative stress, and dysbacteriosis in mice were investigated in another study. According to the findings, capsaicin reduced blood TC, TG, and LDL-C levels while increasing serum HDL-C levels in mice with feeding the beef fat. Capsaicin's cholesterol-lowering effect may be since stimulates cholesterol conversion to bile acids by increasing fecal excretion and upregulating cholesterol 7-hydroxylase expression. SREBP, which regulates fat creation by activating genes involved in fatty acid and triglyceride synthesis, can be affected by cholesterol and its metabolites. Capsaicin decreased the rise of SREBP-1c, ChREBP, and ACC in mouse liver caused by beef fat, while AMPK activation also

suppressed SREBP-1c and ACC expression. Synthetic fatty acids are transported, differentiated, sustained, and oxidized in the human body. The transport of free fatty acids to the mitochondrial matrix is regulated by CPT-1. ADRP increases intracellular lipid levels and is linked to the number of lipids found in cells and tissues. Capsaicin consumption resulted in a large decrease in ADRP levels and a considerable increase in CPT-1 levels in the mouse liver. Capsaicin, which impacts fat synthesis, transport, and differentiation, is connected to lipid homeostasis in mice when they are fed high beef fat, according to these findings [20]. The relation was shown in Figure 2. These studies can suggest that long-term and low-dose intake of capsaicin may have a good effect in preventing diseases such as hyperlipidemia.

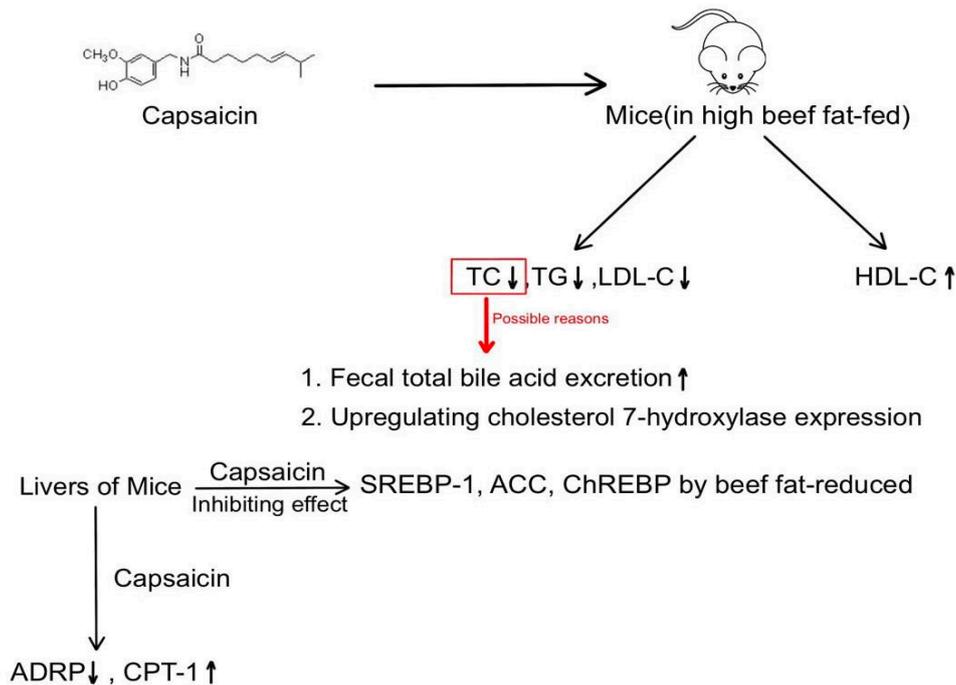


Figure 2. Capsaicin's effect on mice given a high-fat beef diet

5. Effect of capsaicin on obesity

5.1 Effect of capsaicin on obesity

The feature of obesity is a chronic inflammatory state. Excess-free fatty acids released by adipose tissue during obesity can lead to decreased insulin sensitivity in muscle, adipose tissue, and liver, so obesity may even be the cause of diabetes. Capsaicin is an effective ingredient in anti-inflammation. Some studies have shown that capsaicin does have an inhibitory effect on obesity.

The experiment which uses adipose tissues from obese mice shows that capsaicin can significantly enhance adiponectin mRNA expression and released protein in the mesenteric adipose tissues [21]. It can also affect the release of adipokine proteins from adipocytes isolated from obese mice. Studies on the production of pro-inflammatory mediators such as nitric oxide, TNF- α and MCP-1 by ELISA shows that capsaicin has an inhibitory effect on the activation of macrophages stimulated by mesenteric adipose tissue conditioned medium. Capsaicin can also ameliorate the obesity-induced inflammatory phenotypes by modulating adipokine release and inhibiting macrophage infiltration into adipose tissue. Through these, it shows that capsaicin may be a useful ingredient for people to reduce the inflammation caused by obesity and the obesity-related changes [21].

There is also a study about the effect of capsaicin on the changes in the blood glucose of obese KK-Ay mice. Through this experiment, it indicates that the fatty acid composition of total liver lipids was not significantly different. However, the intake of capsaicin inhibits the increase of blood sugar level.

Because of the activation of the sensory nervous system, increased energy consumption after ingestion of capsaicin is associated with their anti-obesity effects. A research group in Japan has demonstrated that ingesting 10 mg/kg of capsaicin can significantly increase energy consumption and inhibit body fat accumulation [22].

5.2 Clinical study on the effect of capsaicin on weight-loss

Through some clinical experiments, they show that the consumption of foods containing capsaicin was associated with lower obesity rates. Capsaicin can cause lipid oxidation, increase oxygen consumption and body temperature during maintaining weight, thus will lead to improving the consumption of energy. Enhancing lipid oxidation and energy expenditure may be in favor of controlling weight.

Capsaicin can also affect appetite. The mechanism of the weight-loss effects of capsaicin is to adjust appetite and satiety. Through this, the macronutrients intake can be controlled.

Capsaicin is a very effective ingredient for weight control [1]. As obesity becomes more and more prevalent, capsaicin may can be a means of treatment to treat obesity. Therefore, a further understanding of the effects and mechanisms of dietary capsaicin intake and metabolic health may provide significant implications for the early prevention and treatment of obesity.

It can be seen from the above that capsaicin brings many benefits to people's health, and almost no adverse effects caused by capsaicin have been found in various studies. Therefore, capsaicin is very suitable for people's daily diet or the preparation of medicines.

6. Effect of capsaicin on hypertension

Hypertension is an increase in arterial systolic and/or diastolic blood pressure. Hypertension is a systemic condition marked by functional or biological abnormalities in organs such as the heart, brain, and nephridium, among others.

Essential hypertension and secondary hypertension are two types of hypertensions. Essential hypertension is a separate disease with an unknown etiology and the predominant clinical manifestation of increased blood pressure. It is responsible for more than 90% of hypertensive individuals. Symptomatic hypertension is another name for secondary hypertension. It has a definite cause, and hypertension is only one of the disease's clinical symptoms. Blood pressure might be high for a short time or for a long time.

In addition to taking medicine, there are other ways to control high blood pressure. People can also lower their risk of hypertension by watching what they eat regularly. The researchers plan to improve on prior studies on the effects of dietary capsaicin on blood pressure. The risk of hypertension is reduced by including a specific amount of dietary capsaicin in one's daily diet.

Capsaicin causes sensory nerve endings around blood arteries to emit CGRP and substance P, which might affect cardiovascular function [23]. Capsaicin has been shown to have direct effects on the vasculature of pigs and rats, relaxing the coronary, mesenteric, and so on [24]. However, activation of TRPV1 in rats and dogs has been shown to elicit vasoconstriction in the mesenteric, coronary, and skeletal muscle arteries [25-27]. Furthermore, capsaicin-induced coronary artery relaxation in humans and pigs is most likely due to a CGRP-independent mechanism [28]. Furthermore, capsaicin-induced NO release was unaffected by sensory nerve denervation in newborns, showing that nerve fibers around blood vessels are not involved in capsaicin-induced relaxation [29].

The direct activation of capsaicin on endothelial cell TRPV1 channels in this research affords experimental evidence for the advantageous effect of the capsaicin from food on lowering hypertension. TRPV1 activation improves endothelial-dimple relaxation in the mesenteric artery and decreases arterial pressure through boosting PKA and eNOS phosphorylation as well as plasma NO concentrations in ECs. As a result, stimulation of endothelium TRPV1 could be considered as a potential hypertension therapeutic method. According to the findings of this study, dietary capsaicin decreases blood pressure in SHR. The mechanistic evidence suggests that the vascular advantage is due to prolonged stimulation of endothelial TRPV1 channels, which mediate enhanced Ca²⁺ inflow

and subsequent activation of PKA and eNOS. As a result, the possibility of endothelium-dependent relaxation is explained by NO production in SHR and the mice feeding the capsaicin. The findings of this study shed insight into the physiological importance of endothelial TRPV1 channels in blood pressure management over time. For some patients with hypertension and related blood vessel damage, long-term dietary capsaicin may be a useful lifestyle option [30].

7. Adverse effect

From the conclusions of the current study, topical capsaicin has the effect to treat painful diabetic neuropathy [31]. However extreme burning, which may produce redness wherever the cream is administered, is one of the capsaicin for diabetes adverse effects. Because of the heat it produces, topical capsaicin should not be administered on an open wound or sore. At the same time, it means that when capsaicin is applied to the skin, it might irritate the eyes, nose, and throat. Capsicum should not be used on delicate skin or near the eyes.

Other research indicates that when capsaicin is taken by mouth is most likely safe and can be used for a short period of time. However, too much capsaicin is harmful to the mouth, stomach, and intestinal organs. Sweating, vomiting, and diarrhea are all possible adverse reactions. Inhaling capsaicin-containing sprays can induce coughing, runny nose, difficulty breathing, tears, nausea, nasal pain, and temporary blindness [32].

8. Conclusions

In summary, this paper argued that the judicious use of capsaicin maybe can help with metabolic syndrome and cardiovascular disease treatment. During the experiment, capsaicin can effectively reduce serum cholesterol and triglyceride, further reducing the risk of cardiovascular disease. And it can also effectively lower blood sugar, accelerate energy metabolism and reduce fat accumulation, thereby reducing the prevalence of diabetes and reducing inflammation due to obesity. However, there are still some problems regarding the practicality of capsaicin due to the limited scope of the trial, the chance, and inaccuracy of the experimental data, the small number of individuals, or the varied species of subjects. Future studies need to increase the subject population or select experimental animals with a similar system to humans. And the studies should also consider how to reduce the side effects of capsaicin without affecting the therapeutic effect of capsaicin. The tolerance of different populations to capsaicin is also one of the influencing factors to be considered.

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