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A review of the effects of *Capsicum annuum* L. and its constituent, capsaicin, in metabolic syndrome

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ABSTRACT

Objective(s): Metabolic syndrome, a coexisting of high blood glucose, obesity, dyslipidemia and hypertension, is an important risk factor for cardiovascular disease occurrence and mortality. Recently, there is a rising demand for herbal drugs which have less adverse effects and have shown more beneficial effects in comparison with synthetic options. Red pepper, with the scientific name of *Capsicum annuum*, belongs to the Solanaceae family. The lipid-lowering, antihypertensive, antidiabetic and anti-obesity effects of *C. annuum* have been demonstrated in several studies.

Materials and Methods: In this review, we summarized different animal and human studies on the effect of red pepper and capsaicin on different components of metabolic syndrome which are risk factors for cardiovascular diseases (CVDs).

Results: According to these studies, red pepper as well as capsaicin has ability to control of metabolic syndrome and its related disorders such as obesity, disrupted lipid profile, diabetes and its complications.

Conclusion: Red pepper has beneficial effects on metabolic syndrome and can decrease the risk of mortality due to cardiovascular diseases, but still more research projects need to be done and confirm its advantageous especially in humans.

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Introduction

Metabolic syndrome, a coexisting of high blood glucose, obesity, dyslipidemia and hypertension, is an important risk factor for cardiovascular disease occurrence and mortality (1, 2).

According to the international diabetes federation (IDF), the presence of central obesity (waist circumference ≥ 94 cm for men and ≥ 80 cm for women) and any two of the following: triglyceride ≥ 150 mg/dl , HDL cholesterol < 40 mg/dl (men), and <50 mg/dl (women) , systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg, and fasting plasma glucose ≥ 100 in a person, considered as metabolic syndrome (1).

Recently, there is a rising demand for herbal drugs because they have shown beneficial effects in the treatment of variety of disorders such as metabolic syndrome. Some of these plants and their active constituents include *Vitis vinifera*, (3) *Nigella sativa*, (4) *Allium sativum* (5), *Rosmarinus officinalis* (6), *Persea americana* (7), *Berberis vulgaris* (8), cinnamon (9), thymoquinone,(4) rutin (10), *Crocus sativus* (11), *Garcinia mangostana* (12) and *Camellia sinensis* (13).

Red pepper, with the scientific name of *Capsicum annuum*, belongs to the Solanaceae family (14). Red pepper includes different plants with common names including chili pepper, tabasco pepper, african chilies, cayenne pepper, paprika (15) and also christmas pepper (14).

Red pepper originated in the South America where they used in favor of medicinal and culinary purpose (15).

In addition to the use of capsicum fruits as a food additive, in traditional medicine, it has been used for the treatment of cough, toothache, sore throat, parasitic infections, rheumatism, wound healing (15) and also utilized as an antiseptic, counterirritant, appetite stimulator (16), antioxidant and immunomodulator (17) (Figure 1). Other effects such as antibacterial and anticancer are also related to chilies (16). Red pepper as a drug is given in atonic dyspepsia and flatulence (16) due to increasing the motility in the gastric antrum, duodenum, proximal jejunum and colon (17). It can also increase parietal, pepsin, and bile acid secretions (14). Chilies are known to protect against gastrointestinal ailments (18) including dyspepsia (17), loss of appetite, gastroesophageal reflux disease and gastric ulcer (17) due to the several mechanisms such as reducing the food transition time through the gastrointestinal tract and anti-Helico pylori effects (18). Moreover, the leaves of its plant have antioxidant activity (19).

Hot red peppers consist of spicy compounds called capsaicinoids which include capsaicin, dihydrocapsaicin, nordihydrocapsaicin and other compounds (20) (Figure 2).

The medicinal effects of chilies are related to different constituents such as capsaicin, fixed oil, thiamine,

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Figure 1. Schematic description of traditional effects of *Capsicumannuum*

protein and ascorbic acid (16).

Capsaicin, water-insoluble derivative of homovanillic acid (21) and the main active ingredient in capsicum fruits, is responsible for hot sensation to the tongue (14) and is utilized for the treatment of inflammatory disorders such as psoriasis and rheumatoid arthritis (15), diabetic neuropathy, postherpetic neuralgia, cluster headache, postmastectomy syndrome, reflex sympathetic dystrophy (16), dermatitis or eczema itching (14), postoperative nausea and vomiting, bladder hyperactivity (22), gallstone (23), anorexia, haemorrhoids, liver congestion, foodborne gastrointestinal pathogens including *Listeria monocytogenes*, *Salmonella typhimurium* and *Bacillus cereus* (17), tonsillitis and rhinitis and fibromyalgia (15). It is also used as pesticides (24) analgesic, antiobesity, antihypertensive (15, 22), antiarrhythmic, antiischemic (22, 25), and gastroprotective agent (16). It can stimulate saliva and digestive enzymes of the pancreas, small intestine (17), and also stimulate hair growth in alopecia areata. Anticoagulant activity, prevention of aspiration pneumonia (21), protecting neuromuscular junctions from C*lostridium botulinum* neurotoxin A and improving cognitive function are also attributed to capsaicin beneficial properties (15).

Topically applied capsaicin is used in migrane, trigeminal neuralgia, herpes zoster (17), chronic musculoskeletal pain (26) and skin disorders (15).

Different studies indicated that red pepper and its active constituent, capsaicin, have therapeutic potential in different components of metabolic syndrome.

In this review, we summarized different animal and human studies on the effect of red pepper and capsaicin on hypertension, high blood glucose, obesity and dyslipidemia which are risk factors for cardiovascular diseases (CVDs). The results showed still more research projects need to be done to confirm its advantageous especially in humans.

Methodology

In this research various databases such as PubMed, Science Direct, Scopus and Google Scholar have been involved. All the articles have been chosen in this review were collected from 1981 to 2016. The search keywords contained metabolic syndrome, hyperlipidemia,

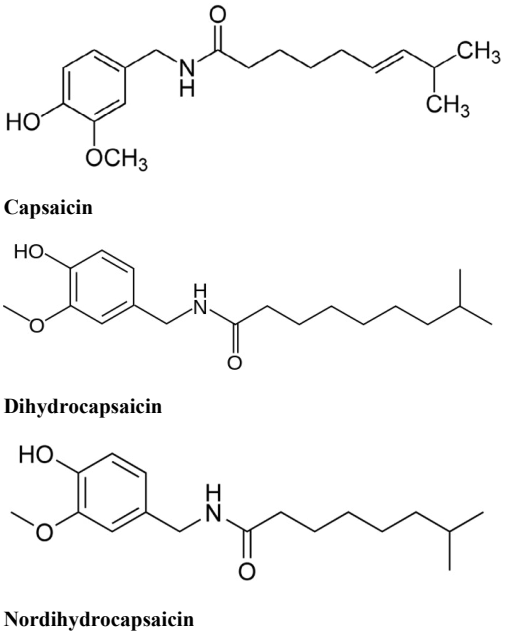

Figure 2. Chemical structures of capsaicinoids

atherosclerosis, hypertension, hyperglycaemia, obesity, antidiabetic, antihyperlipidemic, hypoglycemic, pepper, chilli, capsaicin and "*Capsicum annuum*".

Effect on lipid profile

Dyslipidemia is found as the main risk factor for cardiovascular disease (CVD), which is one of the main causes of mortality in the world (27).

Numerous studies demonstrated that red pepper and its constituent, capsaicin, could decrease total cholesterol, triglyceride, low-density lipoproteins (LDL) and increase high-density lipoproteins (HDL) level. The hypolipidemic effect of red pepper may be related to several factors including activation of peroxisome proliferators-activated receptor α (PPARα) (27), reduction of intestinal absorption of cholesterol and elevation of cholesterol and bile acid excretion in the feces (28).

Animal studies

Study on high-fat diet rats for 8 weeks showed that capsaicin decreased significantly triglyceride level (29). This lowering effect of capsaicin in serum, liver, and adipose triglyceride increased when it used together with dietary soluble fibers (30). Another study on male Wistar rats indicated that administration of 200 mg/kg the aqueous extract of red pepper improved weight gain after 4 weeks, lowered serum total cholesterol, triglyceride (TG), LDL-C and atherogenic index and elevated serum HDL-C (31).

In rabbits, administration of diet-including 1% red pepper powder supplement for 12 months could reduce cholesteryl ester transfer protein (CETP) activity, which is involved in the pathophysiology of atherosclerosis, also reduced total cholesterol, triglyceride, LDL-C, very low density lipoprotein-TG (VLDL-TG) levels, atherogenic index and significantly increased fecal TG excretion (32).

In another study on rabbits for 35 days, the intubation with 8 mg capsaicin/rabbit did not have any beneficial

Table 1. Summary of the effects of *Capsicum annuum* and capsaicin on lipid profile

Study design	Constituents	Results	Ref
In vivo, rats (high fat diet)	capsaicin (0.015%) for 8 weeks	↓TG	(29)
In vivo, male Wistar rats	red pepper (200 mg/kg aqueous extract) for 4 weeks	↑HDL-C ↓TG,TC, LDL-C, atherogenic index	(31)
In vivo, rabbits	diet including 1% red pepper powder supplement for 12 months	↓CETP,TC,TG,LDL-C,VLDL-TG, atherogenic index ↑fecal TG excretion	(32)
In vivo, rabbits (0.5% cholesterol diet)	8 mg capsaicin/rabbit (intubation) for 35 days	↓plasma cholesterol, TG ↓total cholesterol/HDL cholesterol	(28)
In vivo, rats (normal and hypercholesterolemic diet)	0.05% capsaicin for 8 weeks	↓liver TG in normal and hypercholesterolemic rats ↓hepatic cholesterol in normal rats ↓hepatic and blood peroxides in hypercholesterolemic rats	(33)
In vivo, male Wistar diabetic rats	pepper-mixed pelleted food at a ratio of 1/15 for 4 weeks	↓ TG	(42)
In vivo, birds (0.2% cholesterol diet)	capsaicin and dihydrocapsaicin orally (4mg per birds) for 6 weeks	↓ VLDL-C ↑HDL-C	(28)
In vitro, NIH-3T3 cells	six different extracts of chili pepper, dry powder (100mg)	↑HDL ↓TG	(27)
Human	FRPP pills for 12 weeks	↓TC and LDL or no changes cholesterol modulation	(34)
Human, hyperlipidemic subjects	kochujang pill (34.5 g/d) for 12 weeks	↓TC, LDL-C	(35)

TG: triglyceride; HDL-C: high density lipoprotein-cholesterol; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; CETP: cholesteryl ester transfer protein; VLDL: very low density lipoprotein; FRPP: fermented red pepper paste

effect on plasma cholesterol, TG and HDL-cholesterol in normal diet which was in contrast with the effects on animal fed 0.5% cholesterol. These differences were due to affect intestinal absorption of cholesterol by capsaicin (28).

Dietary capsaicin (0.015%) was found to have a lowering effect on liver TG in both normal and hypercholesterolemic rats. Moreover, this compound reduced hepatic cholesterol in normal rats and liver and blood lipid peroxides in hypercholesterolemic rats after 8 weeks (33).

Further study of the animals such as birds which fed 0.2% cholesterol diet, indicated the daily administration of both capsaicin and more effective, dihydrocapsaicin, at a dose of 4 mg per birds for 6 weeks led to the reduction of VLDL-cholesterol and increase in HDL-cholesterol (28).

In vitro studies

The results of study on six different plant extract samples of chili pepper in NTH-3T3 cells showed that chili pepper could transactivate PPARα transcription factor moderately which helped to increasing HDL and reducing TG levels, so improved lipid profile (27).

Both *in vitro* and *in vivo* studies suggested that oxidation of LDL-cholesterol by free radicals is a key step in atherogenesis, so, we can conclude the protective effect of red pepper against atherosclerosis could be via its antioxidant and hypolipidemic effects. Still, more investigation is needed to understand these mechanisms of action (28).

Clinical studies

In a clinical trial which was conducted on 28 females with the age of 19 to 60 years for 12 weeks indicated treatment with fermented red pepper paste (FRPP) caused greater cholesterol-modulating effect than placebo group (34).

A randomized, double-blind, placebo-controlled clinical trial study on hyperlipidemic subjects for 12 weeks suggested that in addition to red pepper, *Aspergillus oryzae*-fermented kochujang (pill 34.5 g/d), a traditional fermented red pepper paste, has also lowered significantly total cholesterol and LDL-C cholesterol levels (35). Further studies should be conducted on human to prove its efficacy.

In summary, we can conclude that red pepper has a modulating effects on HDL, LDL and mainly on total cholesterol and TG level, so, it might be concluded the effect of red pepper on lipid profile is the same as the fibrates (Table 1).

Effect on hyperglycemia

Diabetes, which is correlated with some problems, including hypertension, atherosclerosis and microcirculatory disorders, increases morbidity and mortality (36, 37).

Type 2 diabetic patients are insulin resistance and most of them have metabolic syndrome (38).

C. annuum has been shown to have an antidiabetic effect via several mechanisms including inhibition of α-amylase and α-glucosidase activity (enzymes which can hydrolyze polysaccharides into glucose) (37, 38), antioxidant activity, insulin mimetic or secretagogues, weight regulation and hypolipidemic effects of this plant (39), activation of transient receptor potential vanilloid subtype 1 (TRPV1), which leads to the improvement of insulin resistance, suppress inflammation, glucose homeostasis regulation, increasing insulin sensitivity in peripheral tissues, stimulation of glucagon-like peptide-1 (GLP1) secretion, improvement in glucose tolerance, protection β cells from apoptosis, and reduction of fasting glucose/insulin level as well as expression of adipocytokine genes (40) (Figure 3).

Animal studies

An animal study showed that during hyperglycemic states, dietary capsaicin increased insulin sensitivity in

diabetic rats (40). Another study indicated that capsaicin showed antidiabetic effect by stimulating GLP1 secretion in diabetic mice (40). Study on chronic dietary capsaicin fed db/db mice also showed antidiabetic property of this agent could be due to the reduced blood glucose levels and ameliorated glucose homeostasis (40). Four weeks study on alloxan induced diabetic rats, which fed with high fat diet after treatment with 0.015% capsaicin showed that the serum levels of glucose, cholesterol and TG have been reversed (41).

To evaluate the hypoglycemic and hypolipidemic effects of red pepper in insulin-dependent diabetes mellitus, 36 male Wistar rats were randomly divided into four groups including control, pepper-treated control, diabetic group and pepper-treated diabetic group. The results showed there was no significant dissimilarity in serum glucose level between control and pepper-treated control group. Significant reduction in serum TG level in pepper-treated diabetic group after 4 weeks and significant reduction in serum glucose level in this group after 2 weeks compared to diabetic group indicated short term treatment with red pepper reduced serum glucose level, however in long term, it could only reduce TG levels in diabetic rats (42).

In vitro studies

In vitro study confirmed that one of the antidiabetic mechanisms of capsaicin could be the inhibitory activity against α-amylase and α-glucosidase, according to the antioxidant activity of the plant (43).

Clinical studies

The result of randomized cross-over intervention study on 36 subjects (mean age 12-46 years and body mass index 4.6-26.3 kg/m^2) for 4 weeks suggested that the postprandial increase in plasma glucose level due to the chili meal after a chili-containing diet (CAC) needed less amount of insulin than that needed for control group with a bland meal after a bland diet (BAB). This study also demonstrated that if chili is eaten regularly has the best effect (44).

Another human study has proved that a single meal with capsaicin caused increase in postprandial plasma GLP1 concentrations, which plays main role in the management of glucose metabolism, and decreased postprandial plasma ghrelin concentrations which is a stimulator of food intake and acts as an orexigenic hormone (40).

In addition to its effect on type 2 diabetes, randomized double-blind placebo-controlled trial on 44 pregnant women with gestational diabetes mellitus (GDM) for 4 weeks, indicated 5 mg/dl capsaicin, improved fasting lipid metabolic problems. Furthermore, this agent decreased postprandial hyperglycemia and hyperinsulinemia in GDM (45).

Clinical studies also demonstrated that in healthy human subjects who received capsaicin, glucose absorption from gastrointestinal tract and glucagon release were increased (40).

In summary, it could be suggested the usage of red chili pepper in diabetes mainly because of its reduction in blood glucose level with different mechanisms of action (Table 2).

Effect on high blood pressure

One of the main risk factors for CVD is hypertension which is referred to the instability between vasodilation

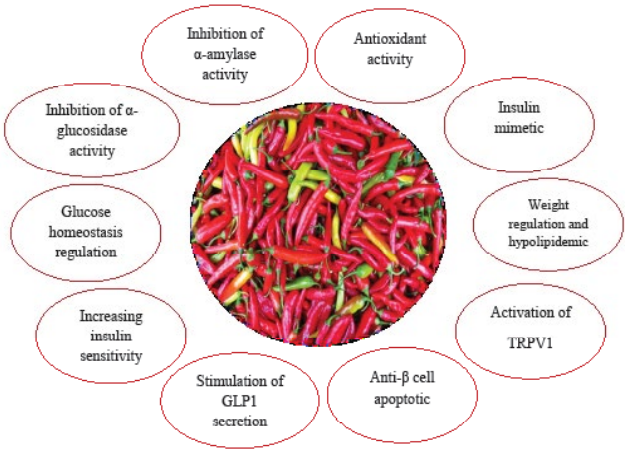

Figure 3. Schematic description showing the mechanisms of *Capsicum annuum* antidiabetic effects GLP1: glucagon-like peptide-1; TRPV1: transient receptor potential vanilloid subtype 1

Table 1. Summary of the effects of *Capsicum annuum* and capsaicin on lipid profile

Study design	Constituents	Results	Ref
In vivo, diabetic rats	dietary capsaicin	↑ insulin sensitivity during hyperglycemic states	(40)
In vivo, diabetic mice	dietary capsaicin	stimulating GLP1 secretion	(40)
In vivo, db/db mice	chronic dietary capsaicin	↓ blood glucose levels ameliorated glucose homeostasis	(40)
In vivo, alloxan induced diabetic rats (high fat diet)	capsaicin (0.015%) for 4 Weeks	↓serum levels of glucose ↓ serum levels of cholesterol ↓ serum levels of TG	(41)
In vivo, male Wistar rats	pepper-mixed pelleted food at a ratio of 1/15 for two weeks	↓ serum glucose level in pepper-treated diabetic group	(42)
Human, randomized cross-over intervention study	chili meal for 4 weeks	postprandial increase in plasma glucose level in CAC group < BAB group	(44)
Human	capsaicin (single meal)	↑ postprandial plasma GLP1 ↓ postprandial plasma ghrelin	(40)
Human, randomized double-blind placebo-controlled trial on pregnant women with GDM	capsaicin (5mg/dl) for 4 weeks	↓ postprandial hyperglycemia and hyperinsulinemia	(45)
Human, healthy subjects	capsaicin	↑ glucose absorption from gastrointestinal tract ↑ glucagon release were increased	(40)

TG: triglyceride; HDL-C: high density lipoprotein-cholesterol; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; CETP: cholesteryl ester transfer protein; VLDL: very low density lipoprotein; FRPP: fermented red pepper paste

and vasoconstriction (40).

Red pepper and its constituent, capsaicin, exerted their antihypertensive effect by several mechanisms, including releasing vasodilator neuropeptides through TRPV1 activation (46), stimulating of natriuresis and diuresis (47), an angiotensin-converting-enzyme (ACE) inhibitory activity (48, 49) and L-type Ca^{2+} channel inhibition in smooth muscle cells (40).

Animal studies

An animal study on capsaicin have revealed pretreatment with 5 mg/ml capsaicin led to the reduction in mean systemic arterial blood pressure in both hypertensive (SHR) and normotensive rats (WKY). However, the sensitivity to angiotensin-2 and norepinephrine pressor effect was decreased by capsaicin treatment in WKY rats (50).

Another study on ganglion-blocked guinea pigs suggested that hypotensive and tachycardic effects of the red pepper were due to the stimulation of capsaicin-sensitive neurons, which caused the release of hypotensive peptides such as substance P (SP) and calcitonin gene related peptide (CGRP) (51, 52).

In urethane-anaesthetized rats, the microinjection of both capsaicin and substance P into the nucleus tractus solitarii (NTS) showed a relation between these agents and changes in blood pressure and also in heart rate. It means both capsaicin and substance P have hypotensive and bradycardiac properties which the effects of capsaicin were more prominent (53).

In another study the effect of capsaicin-neonatal treatment on the salt intake of the adult rats has been investigated. In this study rats were treated with 50 mg/kg capsaicin on days 1-2 of their life. The results showed that in the adult rats, neonatal-capsaicin pretreatment did not change salt appetite or salt preference in reaction to mineralocorticoid or renin, also capsaicin treatment reduced sodium excretion caused by furosemide-treatment by decreasing salt intake (54).

Single dose of 50 mg/kg capsaicin in prenatally malnourished rats on second day of postnatal life inhibited the elevation of arterial blood pressure in malnourished rats, due to its preventive effect against elevation of corticosterone level in plasma. However, capsaicin did not change arterial blood pressure significantly in normal animals (55).

Another study have indicated that, capsaicin, depending on the species and part of the blood vessel used, found to exhibit either dilation or contraction in peripheral blood vessels. Cerebral arteries, rabbit ear artery and cat cerebral blood vessels are models of this hypothesis, that capsaicin had a biphasic effect on them (56).

Study on adult spontaneously hypertensive rats (SHR) for 7 months, indicated that systolic blood pressure was started to fall in capsaicin-treated rats (15 mg/kg) at 4th month (57).

Recent studies focused on TRPV1 that its activation by capsaicin led to the release of nitric oxide (NO) from endothelial cells (40), which was contributed to improved vascular and impaired endothelial function (58). The activation of this receptor also released CGRP from capsaicin-sensitive nerves. Long-term capsaicin treatment decreased blood pressure by improvement of endothelium-dependent relaxation in genetically hypertensive rats, however the acute administration lowered blood pressure by increased plasma CGRP level (40).

The results of a study on TRPV1 knockout (KO) and their wild-type (WT) mice suggested in response to pressure overload, TRPV1 activation by feeding with chow plus 0.01% capsaicin for 10 weeks exhibited cardiac protective effects in WT mice (59). Thus, TRPV1 may be a good target for hypertension and hypertension-related CVD medication (47).

In vitro studies

In vitro studies showed that red pepper had angiotensin converting enzyme inhibitory activity besides its α-glucosidase and α-amylase inhibitory effects, so, it can be used for prevention of hyperglycemia-induced hypertension, however, clinical studies are necessary to confirm its efficacy (43, 60).

Clinical studies

Study on hypertensive patients with alopecia revealed coadministration of isoflavone and capsaicin, led to increased insulin-like growth factor 1 serum

Table 3. Summary of the effects of *Capsicum annuum* and capsaicin on high blood pressure

Study design	Constituents	Results	Ref
In vivo, hypertensive and normotensive rats	capsaicin (5 mg/ml)	↓ mean systemic arterial blood pressure in hypertensive and normotensive rats ↓ sensitivity to angiotensin-2 and norepinephrine in normotensive rats	(50)
In vivo, ganglion-blocked guinea pigs	red pepper	release of hypotensive peptides such as substance P and CGRP	(51, 52)
In vivo, urethane-anaesthetized rats	microinjection of capsaicin into the NTS	hypotensive and bradycardiac effect	(53)
In vivo, prenatally malnourished rats	capsaicin (Single dose of 50 mg/kg) on second day of postnatal life	inhibited the elevation of arterial blood pressure	(55)
In vivo, hypertensive rats	capsaicin (15 mg/kg) for 7 months	↓ systolic blood pressure at 4th month	(57)
In vivo, genetically hypertensive rats	capsaicin (Long-term and short-term treatment)	improvement of endothelium-dependent relaxation in long-term increased plasma CGRP level in short-term	(40)
In vitro	red pepper	Inhibit ACE activity	(43, 60)
Human, hypertensive patients with alopecia	coadministration of isoflavone and capsaicin	↓ systolic and diastolic blood pressure	(40)

CGRP: calcitonin gene related peptide; NTS: nucleus tractus solitarii; ACE: angiotensin converting enzyme

levels which caused significant reduction in systolic and diastolic blood pressure (40).

Among these studies, two studies have reported two cases of arterial hypertensive crises caused by taking large amount of chili peppers (61, 62). That was due to the increase vasoconstriction by catecholamines and angiotensin, increase cardiac activity or decrease vasodilation (63).

Many studies regarding the antihypertensive effect of the red pepper have been conducted on animals especially mice and rats, thus, to prove this effect on human, we need more clinical investigations (Table 3).

Effect on obesity

Abnormal metabolism of energy had led to storage of excess energy in fat cells. This is considered as obesity, another component of the metabolic syndrome, which is the most widespread disease (64, 65).

Several studies reported that red chili pepper exhibited anti-obesity effect by different mechanisms including thermogenesis, satiety, fat oxidation (66), elevation of energy expenditure (20), reduction of energy intake (67), prevention of adipogenesis (68), restriction the activity of lipoprotein lipase (64) and pancreatic lipase (69), stimulation of lipolysis in adipose tissue (70), inhibition of the differentiation of adipocytes (71) and modulating adipokine release from adipose tissues (72) (Figure 4). For examples, in animal studies, capsaicin exhibited antiobesity effects via inhibition of the generation white fat cells and restricted the activity of lipoprotein lipase (64).

Animal studies

Feeding rodents with a diet containing 0.014% capsaicin resulted in a significant reduction in visceral fat weight without any changes in calorie intake. This hypothesis is based on blood flow of the adipose tissue and intestine (73).

Adipokines, which play major roles in the management of food intake, insulin sensitivity, energy metabolism and the vascular micro-environment, secreted from adipose tissues and involved in the obesity-induced inflammation and also obesity-related complications. Based on documents capsaicin can be used to suppress obesity-induced inflammation by modulating of adipokine release from adipose tissues in obese mice (72).

Other study showed that addition of capsaicin to the high fat diet (HFD) reduced the weight of perineal adipose tissue in rats. However, the addition of capsaicin to a high carbohydrate diet (HCD) reduced the weight of the epididymal adipose tissue. These results showed that ingestion of food containing capsaicin could reduce adiposity (74).

Because of the pungency, the uses of red pepper have been reduced. Moreover, chitosan, a nano-peptide with weight control activity, can increase the intestinal absorption of capsaicin. So, preparation of chitosan-capsaicin microsphere (CCMs) has less pungency. Study on CCMs effects on obese rats for 5 weeks showed that CCMs may be used as an antiobesity drug in future because of its better ability to control body weight specially at high doses (3382 mg/kg/d) which its ability to control body weight was more than orlistat (75 mg/kg/d) (75).

Besides the antiobesity effect of dietary capsaicin, cerebral injection and topical application have also reduced body weight increase (76). For examples, animal studies have reported that the results of topical application of 0.075% capsaicin in mice fed HFD for 8 weeks and mice fed HFD for 7 weeks together with capsaicin and continuing to fed HFD for another 7 weeks, were the same. It means that topical administration of capsaicin in pre-obese mice has the same effect as observed in the post-obese mice. The antiobesity effects of topical capsaicin include reducing of weight gain and visceral fat without reducing food intake, decrease inflammation and increase insulin sensitivity. Reducing lipid accumulation in mesenteric adipose tissue was due to the moderately decrease in the expression of tumor necrosis factor α (TNF- α) and IL-6 and also up regulation of adipokines particularly adiponectin and leptin (77).

In vitro studies

In an experiment which was performed on stimulated 3T3-L1 cells, capsaicin (2 mg/kg) could prevent adipogenesis and upregulated adiponectin expression (68). Adiponectin is adipokine which is secreted from adipose tissues or adipocytes, caused improving insulin sensitivity and attenuated the progress of atherosclerosis (72).

Furthermore, the other study indicated that *C. annuum* extract had an inhibitory effect on pancreatic lipase, which is responsible for TG hydrolyzes (69).

The findings of another study showed that the methanolic extract of *C. annuum* (50-100-200 µg/ml) showed anti adipogenesis and down-regulating effect on the expression of adipogenic transcription factors (65). In a study on 3T3-L1 cells, the activity of glycerol 3 phosphate dehydrogenase (G3PD) has been decreased significantly by this methanolic extract (64), however, aqueous extract of *C. annuum* inhibited the activity of lipoprotein lipase in 3T3-L1 cells (65).

The results of another study on 3T3-L1 cells suggested, capsaicin could activate 5' AMP-activated protein kinase (AMPK), which acts as a possible target molecule of antiobesity by inhibition of the differentiation of adipocytes (71).

Another *in vitro* study, exhibited hot pepper seed extract at a concentration of 50-100-200 µg/ml significantly inhibited adipocyte differentiation by decreased adipocyte's colour intensity, so, lipid accumulation in the adipocyte has been decreased (49).

A derivative of furostanol saponins in pepper seeds, named as capsicoside G, has been reported to exhibit anti-adipogenic effect. This effect of capsicoside G may be due to the inhibition of the accumulation of lipid droplets and differentiation in 3T3-L1 adipocytes and inhibition of the expression of the major adipogenic transcription factors and the genes of their target through differentiation preadipocytes to adipocytes by the activation of the AMPK (78).

Clinical studies

Different clinical investigations showed that foods containing capsaicin increased fat oxidation and energy expenditure especially at high doses, promoted negative

Table 4. Summary of the effects of *Capsicum annuum* and capsaicin on obesity

Study design	Constituents	Results	Ref
In vivo, rodents	diet containing 0.014% capsaicin	↓ visceral fat weight	(73)
In vivo, rats	capsaicin (addition to HFD and HCD)	↓ weight of perineal adipose tissue ↓ weight of the epididymal adipose tissue	(74)
In vivo, obese rats	chitosan-capsaicin microsphere (3382 mg/kg/d) for 5 weeks	ability to control body weight > orlistat (75 mg/kg/d)	(75)
In vivo, mice (fed HFD)	0.075% capsaicin (topical application)	↓ weight gain ↓ visceral fat ↓ lipid accumulation in mesenteric adipose tissue ↑ insulin sensitivity	(77)
In vitro, 3T3-L1 cells	capsaicin (2 mg/kg)	prevent adipogenesis up-regulate adiponectin expression	(68)
In vitro, 3T3-L1 cells	methanolic extract of *C. annuum* (50-100-200 µg/ml)	↓ activity of G3PD	(64, 65)
In vitro, 3T3-L1 cells	capsaicin	inhibit the differentiation of adipocytes	(71)
In vitro	hot pepper seed extract (50-100-200 µg/ml)	↓ lipid accumulation in the adipocyte	(49)
Human, healthy Japanese females	red pepper (added to breakfast)	↓ protein and fat intakes at lunch time	(74)
Human, healthy Caucasian males	red pepper (used as appetizer)	↓ carbohydrate and energy intakes at lunch time	(74)
Human, Japanese female	red pepper (added to high-fat meals)	↑ BAT thermogenesis ↑ lipid oxidation	(81)
Human, healthy men and women	combination of capsaicin and green tea for 6 weeks	↓ energy intake in positive energy balance ↑ satiety in negative energy balance	(67)
Human, a single blind, randomized, crossover study	lunch consist of capsaicin	↑ plasma GLP1 ↓ plasma ghrelin	(83)
Human, clinical trial	capsaicinoids (6 mg/day) for 12 weeks	↓ abdominal fat	(65)

HFD: high fat diet; HCD: high carbohydrate diet; G3PD: glycerol 3 phosphate dehydrogenase; BAT: brown adipose tissue; GLP1: glucagon-like peptide-1

energy balance and restrained orexigenic sensations such as hunger and desire to eat (20) whether they received an oral or non-oral capsaicin (79). This study also showed that capsaicin increased core body and skin temperature, however, the magnitude of its thermogenic and appetitive effects is small (20).

Moreover, when red pepper was added to breakfast in 13 healthy Japanese females (age 25.8 ± 2.8 years, weight 54.2 ±6.4 kg, height 1.57 ± 0.04 m, body fat 25.3 ± 4.7%), protein and fat intakes at lunch time decreased but when it used as appetizer, carbohydrate and energy intakes at lunch time decreased in 10 healthy Caucasian males (age 32.9 ±7.8 years, weight 72.5± 10.1 kg, height 1.75±0.06m) (74).

Male and female Japanese has the same response in decreasing fat intake, this is dissimilar to Caucasians (80).

Study on the effect of dietary red pepper on energy metabolism in 13 Japanese female have shown that adding of the red pepper to high-fat meals, increased brown adipose tissue (BAT) thermogenesis (81) induced by β adrenergic stimulation (66, 82), and lipid oxidation (81). However, addition to high carbohydrate meals resulted in increasing the oiliness of the meal (81).

The findings of a study on 10 healthy men and 17 healthy women (mean age 26.9±6.3 years, mean BMI 22.2±2.7 kg/m^2) for 6 weeks (3 weeks of positive energy balance and 3 weeks of negative energy balance) showed that the ingestion of capsaicin in combination with green tea caused significant reduction of energy intake in positive energy balance, increased satiety and restrained hunger in negative energy balance more than ingestion of capsaicin alone. In this study during negative energy balance body weight was decreased by 0.44 ± 0.2 kg, thus, it may be helpful in weight loss (67).

A single blind, randomized, crossover study which was conducted on 19 healthy women and 11 healthy men (BMI 20-30 kg/m^2, age 18-60 years) suggested that an acute lunch consist of capsaicin, increased plasma GLP1 and decreased plasma ghrelin concentrations, but, it had no impact on satiety, energy expenditure and peptide YY (PYY) (83).

A randomized double-blind, placebo-controlled, cross-over study suggested that 4-week supplementation with 1g/day of red pepper spice in 62 obese females with the body mass index ≥27 kg/m^2 and the age of 40-75 years indicated that this culinary amount of red pepper, did not change inflammation in systematically inflamed obese females (84).

In a clinical trial, administration of capsaicinoids for 12 weeks at a dose of 6 mg/day in subjects with the age of 42 years and BMI 30.4, confirmed the effect of capsaicin on abdominal fat reduction (65).

According to the results of a study on 11 healthy volunteers, CH-19 sweet (a non-pungent cultivar of red pepper) can increase thermogenesis and energy consumption, less than that of observed in hot red pepper (85, 86).

So, it could be suggested that the differences in red pepper's colors and pungency led to different energy homeostasis (87).

According to documents, the antiobesity mechanism of capsaicin is partially similar to phentermine, an anti-obesity drug, which both increased energy expenditure and decreased food intake. Orlistat, another antiobesity drug, has pancreatic lipase inhibitory activity, which is in common with one of the antiobesity mechanism of capsaicin. Orlistat (75 mg/kg/d) has better ability in controlling of weight gain than capsaicin (30 mg/kg/d) in rats fed a high fat diet for 5 weeks. Moreover, capsaicin can increase GLP1 concentration as the same as liraglutide, which is a FDA-approved drug for obesity (88).

Taken together, red chili pepper containing capsaicin

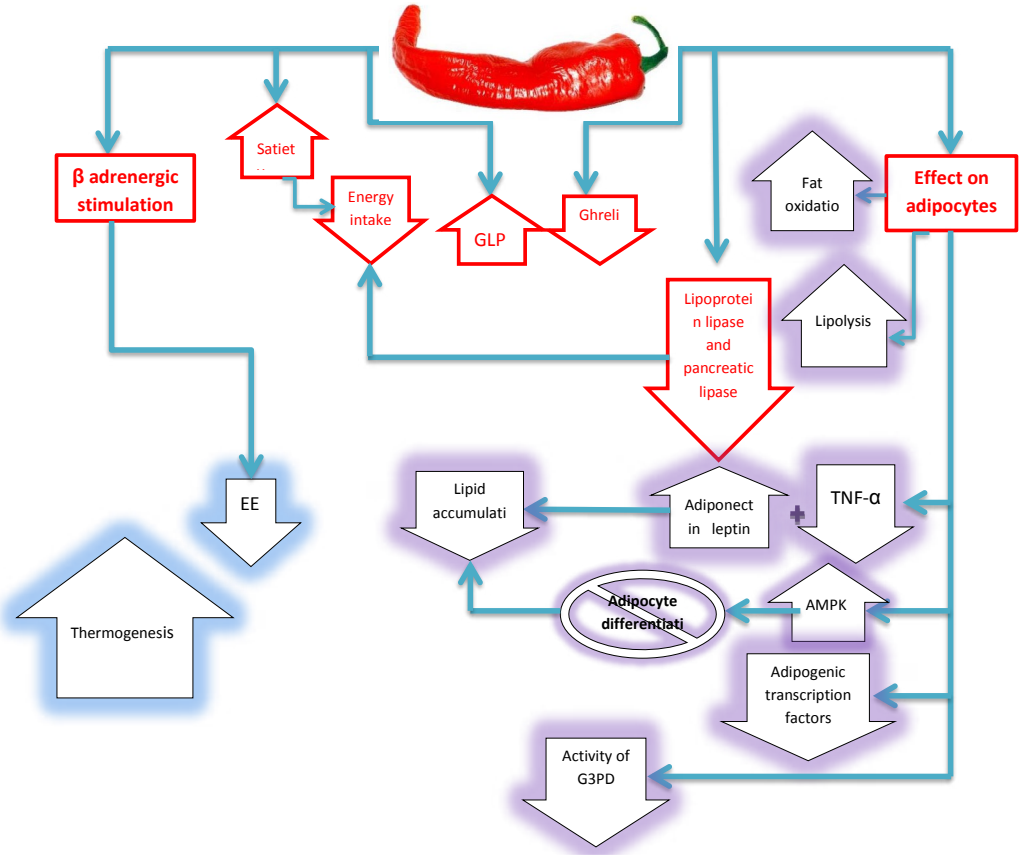

Figure 4. Schematic description showing the mechanisms of *Capsicum annuum* and capsaicin antidiabetic effects.

could play beneficial effects in weight management via increase energy expenditure, satiety, fat oxidation and thermogenesis which are the main mechanisms of antiobesity effect of capsaicin (Table 4).

Conclusion

This review article, which summarized *in vitro* and *in vivo* studies, indicated red pepper and its active constituent, capsaicin, had anti hyperlipidemic effect mostly by reduction of cholesterol intestinal absorption and elevation of cholesterol and TG excretion in feces. Moreover, red pepper possessed beneficial hypeotensive and anti-diabetic by several mechanisms (Figure 4). Red pepper also had an antiobesity effect which its efficacy was partially the same as some antiobesity drugs. So we have concluded that red pepper had beneficial effect on metabolic syndrome and could decrease the risk of mortality due to cardiovascular diseases, but we still need more clinical studies to confirm its effectiveness in human.

Conflict of Interest

The authors declare that they have no conflict of interest.

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