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

Setareh Sanati 1, Bibi Marjan Razavi 2, Hossein Hosseinzadeh 3,1

1 Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
2 Targeted Drug Delivery Research Center, Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
3 Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

**Abstract**

Objectives: 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, anti-diabetic 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 advantage especially in humans.

**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), *Cinnamomum* (9), *Thymoquinone* (10), *Rutin* (11), *Crocus sativus* (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 capsaicin 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 anticaner 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, gastrointestinal reflux disease and gastric ulcer (17) due to the several mechanisms such as reducing the food transition time through the gastromintestinal tract and anti-Helicobacter 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,
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, herpetic 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, antithrombotic (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 Clostridium botulinum neurotoxin A and improving cognitive function are also attributed to capsaicin beneficial properties (15).

Topically applied capsaicin is used in migraine, 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, atherosclerosis, hypertension, hyperglycaemia, obesity, antiobesity, 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
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/m²) 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

---

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

| Study design                        | Constituents              | Results                                                                 | Ref  |
|-------------------------------------|---------------------------|-------------------------------------------------------------------------|------|
| In vitro, diabetic rats             | dietary capsaicin         | ↑ insulin sensitivity during hyperglycemic states                        | (40) |
| In vitro, diabetic mice             | dietary capsaicin         | stimulating GLP1 secretion                                               | (40) |
| In vitro, db/db mice                | chronic dietary capsaicin | ↓ insulin sensitivity during hyperglycemic states                        | (40) |
| In vitro, 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 palleted 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                                               | (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                         | (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
Capsicum annuum and metabolic syndrome

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 Ca²⁺ 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-anesthetized 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 GRP 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 release of hypotensive peptides such as substance P and CGRP (51, 52) | (50) |
| In vivo, ganglion-blocked guinea pigs | red pepper                | hypotensive and bradycardiac effect          | (53) |
| In vivo, urethane-anesthetized rats | microinjection of capsaicin into the NTS | inhibited the elevation of arterial blood pressure | (55) |
| In vivo, prenatally malnourished rats | capsaicin (Single dose of 50 mg/kg) on second day of postnatal life | ↓ systolic blood pressure at 4th month | (57) |
| In vivo, hypertensive rats        | capsaicin (15 mg/kg) for 7 months | improvement of endothelium-dependent relaxation in long-term increased plasma CGRP level in short-term Inhibit ACE activity | (40) |
| In vitro                         | red pepper                | ↓ systolic and diastolic blood pressure      | (40) |
| Human, hypertensive patients with alopecia | coadministration of isoflavone and capsaicin | | |

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 vasconstriction 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/kd) (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 furostan saponins in pepper seeds, named as capsicosome G, has been reported to exhibit anti-adipogenic effect. This effect of capsicosome 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                                                   | (74) |
| In vivo, obese rats           | chitosan-capciscin 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                                                                          | (77) |
| In vitro, 3T3-L1 cells        | capsaicin (2 mg/kg)                                                          | 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                      | capsaicin                                                                    | inhibit the differentiation of adipocytes                                             | (71) |
| Human, healthy Japanese females| hot pepper seed extract (50-100-200 µg/ml)                              | ↓ lipid accumulation in the adipocyte                                                | (49) |
| Human, healthy Caucasian males| capsaicin (used as appetizer)                                                | ↓ protein and fat intakes at lunch time                                               | (74) |
| Human, Japanese female        | capsaicin (added to high-fat meals)                                         | ↓ carbohydrate and energy intakes at lunch time                                        | (74) |
| Human, healthy men and women  | combination of capsaicin and green tea for 6 weeks                         | ↓ energy intake in positive energy balance                                           | (67) |
| Human, a single blind, randomized, crossover study | lunch consist of capsaicin                                                  | ↑ BAT thermogenesis                                                                   | (61) |
| Human, clinical trial         | capsaicinoids (6 mg/day) for 12 weeks                                       | ↓ plasma GLP1                                                                         | (83) |
|                              |                                                                             | ↓ plasma ghrelin                                                                       |      |
|                              |                                                                             | ↓ 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 ± 1.01 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/m² ) 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/m², 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/m² 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 antiobesity 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
could play beneficial effects in weight management via increased 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 hpyotensive 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.

**Acknowledgment**

The authors are thankful to Vice Chancellor of Research, Mashhad University of Medical Sciences, Mashhad, Iran, for their support.

**References**

1. Marjani A. A Review on metabolic syndrome. J Endocrinol Metab 2012; 2:166-170.
2. Jungbauer A, Medjakovic S. Anti-inflammatory properties of culinary herbs and spices that ameliorate the effects of metabolic syndrome. Maturitas 2012; 71:227-239.
3. Akaberi M, Hosseinzadeh H. Grapes (Vitis vinifera) as a Potential Candidate for the Therapy of the Metabolic Syndrome. Phtother Res 2016; 30:540-556.
4. Razavi B, Hosseinzadeh H. A review of the effects of *Nigella sativa* L. and its constituent, thymoquinone, in metabolic syndrome. J Endocrinol Invest 2014; 37:1031–1040.
5. Hosseini A, Hosseinzadeh H. A review on the effects of *Allium sativum* (Garlic) in metabolic syndrome. J Endocrinol Invest 2015; 38:1147-1157.
6. Vahdati Hassani F, Shirani K, Hosseinzadeh H. Rosemary (*Rosmarinus officinalis*) as a potential therapeutic plant in metabolic syndrome: a review. Naunyn-Schmiedeberg’s Arch Pharmacal 2016; 389:931-949.
7. Tabeshpour J, Razavi BM, Hosseinzadeh H. Effects of avocado (*Persea americana*) on metabolic syndrome: a comprehensive systematic review. Phytother Res 2017; 31:819-837.
8. Tabeshpour J, Imenshahidi M, Hosseinzadeh H. A review of the effects of *Berberis vulgaris* and its major component, berberine, in metabolic syndrome. Iran J Basic Med Sci 2017; 20:557-568.
9. Mollaeezadeh H, Hosseinzadeh H. Cinnamon effects on metabolic syndrome: a review based on its mechanisms. Iran J Basic Med Sci 2016; 19:1258-1270.
10. Hosseinzadeh H, Nassiri-Asl M. Review of the protective effects of rutin on the metabolic function as an important dietary flavonoid. J Endocrinol Invest 2014; 37:783–788.
11. Razavi B, Hosseinzadeh H. Saffron: a promising natural medicine in the treatment of metabolic syndrome. J Sci Food Agric 2016; 97: 1679–1685.
12. Toussian Shandiz H, Razavi BM, Hosseinzadeh H. Review of *Garcinia mangostana* and its xanthones in metabolic syndrome and related complications. Phytother Res 2017; 31:1173-1182.
13. Razavi BM, Lookian F, Hosseinizadeh H. Protective effects of green tea on olanzapine-induced-metabolic syndrome in rats. Biomed Pharmacother 2017; 92: 726-731.

14. Barceloux DG. Pepper and capsaicin (Capsicum and Piper species). Dis Mon 2009; 55:380-390.

15. Singletary K. Red pepper: overview of potential health benefits. Nut Today 2011; 46:33-47.

16. Pawar SS, Bharude NV, Sonone SS, Deshmukh RS, Raut AK, Umarkar AR. Chilies as food, spice and medicine: a perspective. Int J Pharm Biol Sci 2011; 1: 311-318.

17. Maji AK, Banerji P. Phytochemistry and gastrointestinal benefits of the medicinal spice, Capsicum annum L (Chillii): a review. J Complement Integr Med 2016; 13:97-122.

18. Low Dog T. A reason to season: the therapeutic benefits of spices and culinary herbs. Explore (NY) 2006; 2:446-449.

19. Kim W-R, Kim EO, Kang K, Oidovsambuu S, Jung SH, Kim BS, et al. Antioxidant activity of phenolics in leaves of three red pepper (Capsicum annum) cultivars. J Agric Food Chem 2014; 62:850-859.

20. Ludy M-J, Moore GE, Mattes RD. The effects of capsaicin and capsaicinoids on satiety, energy expenditure and fat content in high-fat fed rats. J Nutr Biochem 2006; 17:471-478.

21. Pappou AD, Yosipovitch G. Topical capsaicin. The fire of a ‘hot’ medicine is reignited. Expert Opin Pharmacother 2010; 11:1359-1371.

22. Hayman M, Kam PC. Capsaicin: a review of its pharmacology and clinical applications. Curr Anaesth Crit Care 2008; 19:338-343.

23. Srinivasan K. Spices as influencers of body metabolism: an overview of three decades of research. Food Res Int 2005; 38:77-86.

24. Wesolowska A, Jadczak D, Grzeszczuk M. Chemical composition of the pepper fruit extracts of hot cultivars Capsicum annum L. Acta Sci Pol Hortorum Cultus 2011; 10:171-184.

25. D’Alonzo AJ, Grover GJ, Darbenzio RB, Hess TA, Sloph PG, Dewonczyk S, et al. In vitro effects of capsaicin: antiarrhythmic and antiischemic activity. Eur J Pharmacol 1995; 272:269-278.

26. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004; 328:991.

27. Mueller M, Beck V, Jungbauer A. PPARalpha activation by chronic pain. BMJ 2004; 328:991.

28. Negulesco J A, Noel S A, Newman, H A I. Effect of pure capsaicinoids (capsaicin and dihydrocapsaicin) on plasma lipids and lipoprotein concentrations of turkey pouls. Atherosclerosis 1987; 64:85-90.

29. Kempalak RK, Srinivasan K. Beneficial influence of dietary curcumin, capsaicin and garlic on erythrocyte integrity in spontaneously hypertensive rats: effects on nociception and cardiovascular regulation. Eur J Pharmacol 1981; 72:209-217.

30. Pande S, Srinivasan K. Potentiation of hypolipidemic and weight-reducing influence of dietary tender cluster bean (Cyamopsis tetragonoloba) when combined with capsaicin in high-fat fed rats. J Agric Food Chem 2012; 60:8155-8162.

31. Otunola G, Oloyede O, Oladiji A, Afolayan A. Hypolipidemic effect of aqueous extracts of selected spices and their mixture on diet-induced hypercholesterolemia in Wistar rats. Can J Pure Appl Sci 2012; 6:2063-2071.

32. Kwon MJ, Song YS, Choi MS, Song YO. Red pepper attenuates cholesteryl ester transfer protein activity and atherosclerosis in cholesterol-fed rabbits. Clin Chim Acta 2003; 332:37-44.

33. Manjunatha H, Srinivasan K. Hypolipidemic and antioxidant effects of dietary curcumin and capsaicin in induced hypercholesterolemic rats. Lipids 2007; 42:1133-1142.

34. Kim Y, Park YJ, Yang S-O, Kim S-H, Hyun S-H, Cho S, et al. Hypoxanthine levels in human urine as a screening indicator for the plasma total cholesterol and low-density lipoprotein modulation activities of fermented red pepper paste. Nut Res 2010; 30:455-461.

35. Lim J-H, Jung E-S, Choi E-K, Jeong D-Y, Jo S-W, Jin J-H, et al. Supplementation with Aspergillus oryzae-fermented kochujang lowers serum cholesterol in subjects with hyperlipidemia. Clin Nut 2015; 34:383-387.

36. Lievebr FR, Okparume DE, Erhiriie EO, O. EL. The roles of capsaicin in diabetes mellitus. Wilulod 2013; 6:22-27.

37. Watcharachaisoponsiri T, Sornchan P, Charoenkiatkul S, SutThisansee U. The a-glucosidase and a-amylase inhibitory activity from different chili pepper extracts. Int Food Res J 2016; 23:1439-1445.

38. Tundis R, Loizzo MR, Menichini F, Bonesi M, Conforti F, Statti G, et al. Comparative study on the chemical composition, antioxidant properties and hypoglycaemic activities of two Capsicum annum L. cultivars (Acanicumum small and Cerasiferum). Foods Hum Nutr 2011; 66:261-269.

39. Earnest EO, Lawrence E, Lievebr FR. The roles of capsaicin in diabetes mellitus. Wilulod 2013; 6:22-27.

40. Sun F, Xiong S, Zhu Z. Dietary Capsaicin Protects Cardiometabolic Organs from Dysfunction. Nutrients 2016; 8.

41. Magied MMA, Salama NAR, Ali MR. Hypoglycemic and hypolipidemic effects of Intragastric Administration of Dried Red Chili Pepper (Capsicum Annum) in Alloxan-Induced Diabetic Male Albino Rats Fed with High-Fat-Diet. J Food Nut Res 2014; 2:850-856.

42. Raghani M, Baluchnejadmogarad T, Sohrabi Z, Sadeghi M. Anti-hyperglycemic and hypolipidemic effect of oral administration of Capsicum frutescens in male STZ-diabetic rats. J Med Plants 2004; 2:47-52.

43. Chen L, Kang Y-H. In Vitro Inhibitory Potential Against Key Enzymes Relevant for Hyperglycemia and Hypertension of Red Pepper (Capsicum annum L.) Inducing Péricarp, Placenta, and Stalk. J Food Biochem 2014; 38:300-306.

44. Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. Effects of chili consumption on postprandial glucose, insulin, and energy metabolism. Am J Clin Nutr 2006; 84:63-69.

45. Yuan LJ, Qin Y, Wang L, Zeng Y, Chang H, Wang J, et al. Capsaicin-containing chili improved postprandial hyperglycemia, hyperinsulinemia, and fasting lipid disorders in women with gestational diabetes mellitus and lowered the incidence of large-for-gestational-age newborns. Clin Nutr 2016; 35:388-393.

46. Deng PY, Li YJ. Calcitonin gene-related peptide and hypertension. Peptides 2005; 26:1676-1685.

47. Zhang MJ, Yin YW, Li BH, Liu Y, Liao SQ, Gao CY, et al. The role of TRPV1 in improving VSMC function and attenuating hypertension. Prog Biophys Mol Biol 2015; 117:212-216.

48. Adelegha SA, Oboh G. Phytochemistry and mode of action of some tropical spices in the management of type-2 diabetes and hypertension. African J Pharm Pharmacol 2013; 7:332-46.

49. Yuan G, Choi Y, Lee S-M, Kim Y, Jeong H-S, Lee J. Antiobesity activity of methanol extract from hot pepper (Capsicum annum L.) seeds in 3T3-L1 adipocyte. Food Sci Biotechnol 2010; 19:1123-1127.

50. Virus RM, Knueper MM, McManus DQ, Brody MJ, Gebhardt GE. Capsaicin treatment in adult Wistar-Kyoto and spontaneously hypertensive rats: effects on nociceptive behavior and cardiovascular regulation. Eur J Pharmacol 1981; 72:209-217.

51. Rioux F, Lemieux M, Roy G. Capsaicin-sensitive primary afferents are involved in the hypotensive effect of neurotenin in ganglion-blocked guinea pigs. Peptides 1989; 10:1033-40.

52. Wimalawansa SJ. The effects of neonatal capsaicin on behavioral and cardiovascular regulation. Eur J Pharmacol 1981; 72:209-217.
53. Lubovic L, de Jong W, de Wied D. Cardiovascular effects of substance P and capsaicin microinjected into the nucleus tractus solitarii of the rat. Brain Res 1987; 422:312-318.
54. Massi M, Polidori C, Perfumi M, Ciccodippo R, De Caro G, Bacciarelli C, et al. Effect of capsaicin neonatal treatment on the salt intake of the adult rat. Pharmacol Biochem Behav 1991; 40:163-168.
55. Perez H, Ruiz S, Soto-Moyano R. Prenatal malnutrition-induced hypertension in young rats is prevented by neonatal capsaicin treatment. Neurosci Lett 2002; 328:253-256.
56. Potenza MA, De Salvatore G, Montagnani M, Serio M, Mitolo-Chieppa D. Vasodilatation induced by capsaicin in rat mesenteric vessels is probably independent of nitric oxide synthesis. Pharmacol Res 1994; 30:253-261.
57. Yang D, Luo Z, Ma S, Wang WT, Ma L, Zhong J, et al. Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. Cell Metab 2010; 12:130-141.
58. Sessa WC. A new way to lower blood pressure: pass the chili peppers please! Cell Metab 2010; 12:109-110.
59. Wang Q, Ma S, Li D, Zhang Y, Tang B, Qiu C, et al. Dietary capsaicin ameliorates pressure overload-induced cardiac hypertrophy and fibrosis through the transient receptor potential vanilloid type 1. Am J Hypertens 2014; 27:1521-1529.
60. Kwon Y-I, Apostolidis E, Shetty K. Evaluation of pepper (Capsicum annum) for management of diabetes and hypertension. J Food Biochem 2007; 31:370-385.
61. Fatane S, Marte F, La Rosa FC, La Rocca R, Capsaicin and arterial hypertensive crisis. Int J Cardiol 2010; 144:e26-27.
62. Fatane S, Marte F, Di Bella G, Cerrito M, Coglitore S. Capsaicin, arterial hypertensive crisis and acute myocardial infarction associated with high levels of thyroid stimulating hormone. Int J Cardiol 2009; 134:130-132.
63. Dutta A, Deshpande SB. Mechanisms underlying the hypertensive response induced by capsaicin. Int J Cardiol 2010; 145:358-359.
64. Baek J, Lee J, Kim K, Kim T, Kim D, Kim C, et al. Inhibitory effects of Capsicum annuum L. water extracts on lipoprotein lipase activity in 3T3-L1 cells. Nutr Res Pract 2013; 7:96-102.
65. Gamboa-Gomez CI, Rocha-Guzman NE, Gallegos-Infante JA, Moreno-Jimenez MR, Vazquez-Cabral BD, Gonzalez-Laredo RF. Plants with potential use on obesity and its complications. Excli J 2015; 14:809-831.
66. Woo H-M, Kang J-H, Kawada T, Yoo H, Sung M-K, Yu R, et al. Active spice-derived components can inhibit inflammatory responses of adipose tissue in obesity by suppressing inflammatory actions of macrophages and release of monocyte chemoattractant protein-1 from adipocytes. Life Sci 2007; 80:926-931.
67. Reina HC, Smeets A, Martinussen T, Moller P, Westerterp-Plantenga M. Effects of capsaicin, green tea and CH-19 sweet pepper on appetite and energy intake in humans. J Funct Foods 2016; 20:148-158.
68. Zhang H, Matsuda H, Nakamura S, Yoshikawa M. Effects of amide constituents from pepper on adipogenesis in 3T3-L1 cells. Bioorg Med Chem Lett 2008; 18:3272-3277.
69. Marrelli M, Menichini F, Contofr F. Hypolipidemic and Antioxidant Properties of Hot Pepper Flower (Capsicum annum L). Plant Foods Hum Nutr 2016; 71:301-306.
70. Do MS, Hong SE, Ha JH, Choi SM, Ahn IS, Yoon JY, et al. Increased lipolytic activity by high-pungency red pepper extract (var. chungyang) in rat adipocytes in vitro. J Food Sci Nutr 2004; 9:34-38.
71. Hwang J-T, Park I-J, Shin J-J, Lee YK, Lee SK, Baik HW, et al. Genisten, EGCG, and capsaicin in hibit adipocyte differentiation process via activating AMP-activated protein kinase. Biochem Biophys Res Commun 2010; 338:694-699.
72. Kang J-H, Kim C-S, Han I-S, Kawada T, Yu R. Capsaicin, a spicy component of hot peppers, modulates adipokine gene expression and protein release from obese-mouse adipose tissues and isolated adipocytes, and suppresses the inflammatory responses of adipose tissue macrophages. Peps Lett 2007; 581:4389-4396.
73. Leung FW. Capsaicin-sensitive intestinal mucosal afferent mechanism and body fat distribution. Life Sci 2008; 83:1-5.
74. Yoshioka M, St-Pierre S, Drapeau V, Dionne I, Doucet E, Suzuki M, et al. Effects of red pepper on appetite and energy intake. Br J Nutr 1999; 82:115-123.
75. Tan S, Gao B, Tao Y, Guo J, Su Z-Q. Antiobes effects of Capsaicin-Clinton Microsphere (CCMS) in Obese Rats Induced by High Fat Diet. J Agr Food Chem 2014; 62:1866-74.
76. Falchi M, Bertelli A, Ferrara F, Galizzo R, Galizzo S, Gharib C, et al. Intracerebroventricular capsaicin influences the body weight increasing of rats. Brain Res Bull 2007; 75:253-256.
77. Lee GR, Shin MK, Yoon DJ, Kim AR, Yu R, Park NH, et al. Topical application of capsaicin reduces visceral adipose fat by affecting adipokine levels in high-fat diet-induced obese mice. Obesity 2013; 21:115-122.
78. Sung J, Lee J. Capsicoside G, a furostanol saponin from pepper (Capsicum annuum L.) seeds, suppresses adipogenesis through activation of AMP-activated protein kinase in 3T3-L1 cells. J Funct Foods 2016; 20:148-158.
79. Whiting S, Derbyshire E, Tiwari BK. Capsainoids and capsinoids. A potential role for weight management? A systematic review of the evidence. Appetite 2012; 59:341-348.
80. Yoshioka M, Imanaga M, Ueyama H, Yamane M, Kubo Y, Boivin A, et al. Maximum tolerable dose of red pepper decreases fat intake independently of spicy sensation in the mouth. Br J Nut 2004; 91:991-995.
81. Yoshioka M, St-Pierre S, Suzuki M, Tremblay A. Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. Br J Nutr 1998; 80:503-510.
82. Westerterp-Plantenga M, Diepvens K, Joosen AM, Berube-Parent S, Tremblay A. Metabolic effects of spices, teas, and caffeine. Physiol Behav 2006; 89:229-234.
83. Nieman DC, Cialdella-Kam L, Knab AM, Shanal S. Influence of red pepper spice and turmeric on inflammation and oxidative stress biomarkers in overweight females: a metabolomics approach. Plant Foods Hum Nutr 2012; 67:415-421.
84. Ohnuki K, Niwa S, Maeda S, Inoue N, Yazawa S, Shichiki T. CH-19 sweet, a non-pungent cultivar of red pepper, increased body temperature and oxygen consumption in humans. Biosci Biotechnol Biochem 20016; 5:2033-2036.
85. Hachiya S, Kawahata F, Ohnuki K, Inoue N, Yoseda H, Yazawa S, et al. Inhibitory effects of CH-19 Sweet, a non-pungent cultivar of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. Br J Nutr 1998; 80:503-510.
86. Yoshioka M, Imanaga M, Ueyama H, Yamane M, Kubo Y, Boivin A, et al. Maximum tolerable dose of red pepper decreases fat intake independently of spicy sensation in the mouth. Br J Nut 2004; 91:991-995.
87. Hachiya S, Kawahata F, Ohnuki K, Inoue N, Yoseda H, Yazawa S, et al. Inhibitory effects of CH-19 Sweet, a non-pungent cultivar of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. Br J Nutr 1998; 80:503-510.
88. Westerterp-Plantenga M, Diepvens K, Joosen AM, Berube-Parent S, Tremblay A. Metabolic effects of spices, teas, and caffeine. Physiol Behav 2006; 89:229-234.
89. Nieman DC, Cialdella-Kam L, Knab AM, Shanal S. Influence of red pepper spice and turmeric on inflammation and oxidative stress biomarkers in overweight females: a metabolomics approach. Plant Foods Hum Nutr 2012; 67:415-421.
90. Ohnuki K, Niwa S, Maeda S, Inoue N, Yazawa S, Shichiki T. CH-19 sweet, a non-pungent cultivar of red pepper, increased body temperature and oxygen consumption in humans. Biosci Biotechnol Biochem 20016; 5:2033-2036.
91. Hachiya S, Kawahata F, Ohnuki K, Inoue N, Yoseda H, Yazawa S, et al. Inhibitory effects of CH-19 Sweet, a non-pungent cultivar of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. Br J Nutr 1998; 80:503-510.
92. Westerterp-Plantenga M, Diepvens K, Joosen AM, Berube-Parent S, Tremblay A. Metabolic effects of spices, teas, and caffeine. Physiol Behav 2006; 89:229-234.
93. Nieman DC, Cialdella-Kam L, Knab AM, Shanal S. Influence of red pepper spice and turmeric on inflammation and oxidative stress biomarkers in overweight females: a metabolomics approach. Plant Foods Hum Nutr 2012; 67:415-421.