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The Beneficial Effects of Curcumin on Cardiovascular Diseases and Their Risk Factors

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ABSTRACT

Curcumin (diferuloylmethane) is a yellow, active substance of an herbal origin, which is mainly derived from turmeric of the ginger family. Extensive research has been focused on the therapeutic effects of this substance on diabetes, cancer, and cardiovascular diseases, and the hepatoprotective properties have attracted the attention of researchers. In addition, curcumin significantly improves oxidative stress, mitochondrial dysfunction, and inflammation. It could also modulate various cell signals in cytokines, chemokines, growth factors, and enzymes. Curcumin attenuates the blood glucose by increasing insulin levels. According to findings, consuming one gram of curcumin per day for one month could decrease total cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-density lipoprotein cholesterol. Moreover, it contributes to the control of some of the main parameters associated with the metabolic syndrome, which is an important risk factor for cardiovascular diseases. Hepatic cholesterol metabolism is also regulated by curcumin, which has a similar function to lovastatin in the long run. Curcumin has been reported to prevent the enlargement of solid tumours. Several have confirmed the therapeutic role of curcumin in the management of the metabolic syndromes and cardiovascular diseases. The present study aimed to review the therapeutic effects of curcumin.

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Introduction

Despite recent advancement in developing novel therapeutic approaches such as smart drugs and mono-targeted therapy for cancers and metabolic and cardiovascular diseases, the applications of these methods remain limited due to the high costs, complications, and difficult accessibility (1,2). In contrast, traditional and herbal medicines have widespread applications, while they are cost-effective and associated with few side-effect (3).

Curcumin (diferuloylmethane) is a natural polyphenol of an herbal origin, which is mostly extracted from turmeric of the ginger family (3). It is a popular spice in South Asian and Middle Eastern

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cuisines (5-7). The powder mainly contains fats, proteins, minerals, carbohydrates, and curcuminoids (4) (Table 1).

Table 1. Components in Parts of Curcuma longa.

Used Parts	Components	Shape	Reference
Leaves	Ar-turmerone *α*-turmerone *β*-turmerone		(3)
Roots	Ar-turmerone *β*-turmerone *α*-turmerone		(20)
Powder	Curcumine methoxycurcumin bisdemethoxycurcumin		(31 ,30)

The chemical formula of curcumin is C21H20O6, with the chemical name 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione (4). Curcumin has long been used in the traditional medicine as a therapeutic agent for various diseases, especially since 1748 (8,9). The first report regarding the therapeutic and antibacterial effects of curcumin was published in 1949 (8,9).

According to the literature, curcumin has potent anti-inflammatory, hepatoprotective, hypouricaemic, anti-pruritic, analgesic, anti-dyspeptic, anti-anxiety, antidepressant, and anti-arthritic characteristics. Moreover, it exerts beneficial effects on diabetes, Alzheimer's disease, cancer, arthritis, cardiovascular diseases, and wound healing (10-15). Some studies have demonstrated the effectiveness of curcumin in the management of acute inflammatory and chronic neuropathic pain (10,16,17).

In a study in this regard, Lao et al. (2006) reported that the curcumin doses of 500-12,000 milligrams could be tolerated by healthy volunteers (1). Although the toxic dose of curcumin in humans remains unclear, the concentrations of 8-12 g/d could be used with no side-effect (5,18). Due to the low bioavailability of curcumin in the plasma and tissues, it is widely used in combination with liposomal, nanoparticles, and phospholipid complexes and is reformulated with various oils (1). In addition, clinical trials have indicated the 2000% increase in the bioavailability of curcumin when used with piperine (1,10), which is the pungency of black pepper (Piper nigrum) and long pepper (Piper longum) (5,19). It has also been reported that the combination of curry, coriander, turmeric, cumin, fenugreek, and chilli peppers could increase the rate of vasodilatation response, while causing no changes in hemodynamic parameters (1).

The present study aimed to assess the potential therapeutic effects of curcumin on diabetes, cardiovascular diseases, liver dysfunction, and cancer.

Literature Review

IThis review was conducted via searching in databases such as PubMed, Elsevier, and Google Scholar using keywords such as curcumin, turmeric, and Curcuma longa to retrieve the articles published during 2008-2017, with the aim of collecting data on curcumin and its therapeutic effects on cardiovascular diseases, diabetes, liver disease, and cancer.

Effects of Curcumin on Cell Signalling Pathways, Hormones, and Enzymes

Curcumin has been reported to mimic cortisone-like effects on acute inflammation, while it is half effective in the treatment of chronic inflammation. This feature has been ascribed to the inhibitory effects of curcumin on both prostaglandins of the arachidonic acid, as well as the function of neutrophils during inflammatory phases (20). Moreover, curcumin could improve oxidative stress, mitochondrial dysfunction, and inflammation (3,19,21). Curcumin has been reported to modulate various cell signalling pathways, including the cytokines, chemokines, growth factors, and enzymes (3). By ubiquitin-proteasome-calpain-mediated proteolysis, curcumin could down-regulate the protein expression of scavenger receptors (22), which is a cell surface protein involved in cholesterol homeostasis and plays a key role in controlling cholesterol, oxidized low-density lipoprotein uptake, and accumulation in macrophage foam cells. The mentioned process is the mechanism of atherosclerosis progression (22,23).

Curcumin could also regulate hormones, growth factors and both their receptors, and nuclear and transcription factors (22). It also induces the synthesis of lipoprotein lipase, peroxisome proliferator-activated receptor alpha, peroxisome proliferator-activated receptor gamma, and cholesteryl ester transfer protein, leading to the catabolism of triglyceride-rich lipoproteins (5,7).

Systemic inflammation leads to the release of inflammatory cytokines, which remain in the plasma. In the first line of the immune system, monocytes attach to the endothelium layer of the vessels (10,24). G-protein-coupled receptors cause the immune cells to increase the chemotaxis chemokines for monocyte conduction, including the monocyte chemoattractant/chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-1b (10,25).

Recent studies regarding the inflammatory cytokines in humans, curcumin has inhibitory effects on basic protein molecules, mitogen-activated protein kinase, and nuclear factor-κB, affecting gene expression and pro-inflammatory cytokines, such as interleukin-1 beta (IL-1B), tumor necrosis factor (TNFa), and MCP-1. These effects are mediated by the monocytes, astrocytes, and alveolar macrophages that are stimulated by lipopolysaccharides (10,26,27).

Curcumin could suppress interleukins one, two, six, eight, and 12 and reduce high-sensitivity C-reactive protein (hs-CRP) levels as a practical inflammatory biomarker with increased activity during cardiovascular events (10). Additionally, apolipoprotein A1 and paraoxonase have been reported to increase as a result of curcumin consumption (10,28). In obese individuals, curcumin could diminish the levels of VEGF, IL-1B, and IL-4 (Figure 1), while in ischemic patients, it may have protective effects against ischemia-reperfusion injury (10,29).

Clinical Trials	Growth Factors
Curcumin could decrease the risk of myocardial infarction, low-density lipoprotein, total cholesterol, triglyceride, HbA1c, body mass index, and risk of non-alcoholic fatty liver disease.	Curcumin could decrease FGF HGF EGF VEGF

Effects of Curcumin on Diabetes

There are approximately 382 million diabetes patients across the world, and this number is predicted to reach 592 million by 2035 (30,31). Diabetes mellitus is characterized by the high levels of plasma glucose (3). The three known types of diabetes include diabetes type I, diabetes type II, and gestational diabetes. The main symptoms of diabetes are polyuria, polydipsia, and polyphagia (3). Diabetes type I and II are respectively resulted from pancreas failure to produce insulin and developing insulin resistance. In gestational diabetes, pregnant women with no diabetic background present with the elevated levels of blood glucose mostly in the third trimester, requiring screening in weeks 24-28 of pregnancy (3).

Oxidative stress is considered to be the most important risk factors for diabetes pathogenesis (3,32). In 1972, Torres et al. discovered the hypoglycaemic effects of curcumin (3,33). Moreover, curcumin could affect gluconeogenesis, glycolysis, and lipid metabolism (3,34). It also increases the level of plasma insulin and lipoprotein lipase (LPL) activity. Combination of curcumin with vitamin C and yogurt could reduce the levels of blood glucose, hemoglobin (Hb), and HbA1C, thereby preventing weight loss (3,35). Additionally, curcumin consumption has been associated with small pancreatic islets and decreased lymphocyte penetration rate (3,36).

Curcumin attenuates the blood glucose by increasing the insulin level and LPL activity (37). Increased bioavailability of curcumin within 30 minutes to one hour has been reported after the co-administration of piperine (20 mg), which results in the inhibition of glucuronidation in the liver and bowels (8,38).

Gene therapy and islet transplantation are considered to be the definite treatments for diabetes (2,30). In 1972, studies investigated the alternation of fasting blood glucose from 1400 mg/l to 700 mg/l in a patient with chronic type II diabetes with the use of curcumin (1,39). According to the findings, curcumin therapy could prevent the increasing of angiotensin-converting enzyme/angiotensin II ratio in diabetic patients and improve kidney function in the patients with diabetic nephropathy.

Effects of Curcumin on Heart and Hyperlipidemia

Cardiovascular diseases are the leading cause of mortality across the world, including myocardial infarction, dyslipidemia, and acute coronary syndrome (1). Furthermore, atherosclerosis is a major cause of mortality and morbidity in developing and developed countries (22,40). Atherosclerosis is a multifactorial disease, in which genetic and environmental risk factors, ageing, and high dietary intake of lipids lead to the elevation of plasma cholesterol and triglyceride levels (18,44).

Following by the effects of renin-angiotensin system (RAS) and ANG-II on the endothelial dysfunction, inflammation, fibrinolytic imbalance, and plaque instability progression of atherosclerosis have been reported to occur (42,43). The dura-

tion of hypertriglyceridemia and hyperlipidemia has proven to be a risk factors for atherosclerosis (18,44). Clinical examinations on mice have indicated the significant preventive effects of curcumin on the recurrence of atherosclerosis in the aorta and carotid wall (42,43). In fact, the management of lipid profile by curcumin consumption could decrease the incidence rate of atherosclerosis (18). Mice maintained on high-fat diets have also shown a significant reduction in the serum cholesterol level compared to the mice receiving a normal diet (18).

High-density lipoprotein (HDL) is a small, dense particle in the plasma (5,45). Lipase and lipid transfer proteins are remodelled by the HDL (5). The plasma concentrations of HDL protect the heart and brain vessels, thereby preventing atherosclerosis and cerebrovascular disease. Several studies have investigated the benefits of increased plasma levels of HDL cholesterol (HDLc) (5,46). Serum levels of HDLc have a predictive value for the risk of cardiovascular events, and curcumin has been shown to exert lovastatin-like effects on HDLc (18).

High plasma levels of cholesterol lead to its deposition in the wall of the coronary arteries (22), and foam cells accumulate low-density lipoprotein (LDL) (22,44,47,48). The statin extracted from natural herbs and Aspergillus terreus is prescribed in the first step (18,44). Nutritionists believe that dietary management could contribute to the control of hyperlipidemia (18).

According to the literature, despite the effects of curcumin on the reduction of hypertriglyceridemia, it has no effects on hyperlipidemia. However, few studies have shown that curcumin is ineffective in the treatment of these conditions (18,49). It is notable that these studies have been conducted with short treatment durations, using either an inappropriate diet or insufficient doses of curcumin (18,50). For instance, Akram et al. (2010) claimed that low daily doses of curcumin (1.6-3.2 mg/kg of the body weight) could decrease LDLc and triglyceride, while its higher doses could only alter plasma cholesterol and triglyceride levels (20). In this regard, an in-vitro research on mice receiving an atherogenic diet for 18 weeks indicated an atherosclerotic lesion in the ascending aorta (18). On the other hand, the microscopic specimens showed no visible intimal lesions. For six weeks, the mice were simultaneously administered with curcumin and lovastatin, and the laboratory assessments showed the reduction of cholesterol. It is also notable that after 12 weeks of curcumin and lovastatin administration, the total cholesterol level in the plasma reduced. Moreover, plasma triglycerides (e.g., cholesterol) were suppressed after six weeks of treatment. The researchers also reported the preventive effects of curcumin on developing atherosclerotic lesions and suppressing the atherogenic markers due to a high-fat diet (18).

Some studies have indicated that curcumin is only effective in the mice with high-fat/cholesterol diets (18,51) through decreasing the uptake and delivery of cholesterol from the intestinal surfaces and increasing the conversion of cholesterol into bile acids in the liver (20).

Curcumin has been reported to prevent the activation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) through a transcriptional mechanism (18). HMG-CoA reductase regulates the rate of enzymes in the biosynthesis of curcumin and is able to control the human 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) regulator gene, which encodes HMG-CoA reductase in the liver (10). In addition, curcumin is considered to be a HMGR transcription inhibitor (18).

Curcumin is a lipid expression modulator, which regulates cholesterol metabolism (18). Clinical studies have demonstrated that curcumin is effective against atherosclerosis in humans and animals (5,7,18,52). The animal studies in this regard have denoted that curcumin could reduce LDLc and triglyceride, while increasing HDLc (5).

Some studies have denoted stable levels of LDLc and apoB after curcumin administration. However, elevated levels of the HDLc/total cholesterol ratio have also been reported (5,28). An animal study in this regard demonstrated that curcumin administration for 18 weeks declined total cholesterol, LDLc, apoB, and triglyceride in the plasma (5,18). In addition, curcumin has proven more effective than lovastatin in some cases (5,18). The reported effectiveness of curcumin in the treatment of the symptoms in rats with common carotid occlusion has confirmed its therapeutic and protective effects against cerebrovascular diseases (5,53).

Evidently, systemic inflammation is associated with a wide range of diseases, such as cardiovascular diseases (10, 54). According to a study by Esmaily et al. (2015), using one gram of curcumin per day for one month could decrease total cholesterol, LDLc, triglycerides, and HDLc in obese individuals (10,55). In another study, curcuminoid was reported to decrease infarction following coronary artery bypass grafting (CABG) (1). In these patients, the level of N-terminal pro-B-type and CRP declined after open heart surgery (1). Furthermore, the expression of vascular endothelial growth factor A and angiopoietin-1 was adjusted in curcumin therapy, positively influencing the treatment of the rats with ischemic induction (1). Variable therapeutic doses of curcumin have been

recommended for the treatment of diabetic patients with cardiac ischemia (1).

Anti-inflammatory Effects of Curcumin on the Cardiovascular System

Endothelial function plays a pivotal role in the immunity of humans against various diseases (56). Cardiac ischemia impairs the endothelial cells (56,57). After myocardial infarction, inflammatory mediators play a key role in determining the area of the myocardial infarct (56-58). After cardiac ischemia, reactive oxygen species (ROS) are immediately released, especially in the presence of reperfusion (56,59). Additionally, cardiomyocytes express the adhesion molecules, mitogen-activated protein, and redox-sensitive transcription factors that are activated by inflammatory molecules (56).

The inflammatory cascade and ROS regulate Ca2+ in the sarcoplasmic reticulum and contraction (56). In the human study, curcumin therapy reduces ROS, MCP, and interleukin-8 (56,60). Phosphate and oxalate are able to decrease the distribution of Ca2+ (56,59), and the controlled distribution of Ca2+ improves cardiac contractions (56,58,61). Recent studies regarding myeloperoxidase have shown the reduced rate of neutrophils in the myocardium ischemic area (56,60).

Curcumin could prevents the increase in TNF-α and matrix metalloproteinases, thereby resulting in ventricular function and stroke volume improvement by suppressing collagen remodelling (56). The nitric oxide (NO) pathway is a substantial factor involved in oxidative stress-induced cardiomyopathy (62). The NO free radical is generated by three isozymes, among which endothelial NOS and neuronal NOS are known for their key role in cardiovascular events (62,63). Clinical research has indicated that curcumin is able to attenuate the oxidative effects of NOS (62) and prevent the progression of cardiomyopathy, particularly in diabetes (62).

According to the literature, curcumin acts as a preventive agent against DNA damage (62,63). There are some factors with considerable predictive values for the assessment of cardiac risk factors, such as serum CRP, which has a strong correlation with cerebrovascular diseases (64). In this regard, a clinical research investigated the effects of curcumin (1,200 mg-2 g) on the reduction of hs-CRP serum level, and the tolerated dose of curcumin was reported to be 12 grams (64).

Hepatoprotective Effects of Curcumin

Steatohepatitis, cirrhosis, and liver cancer due to non-alcoholic fatty liver disease (NAFLD) are highly prevalent in developed countries (42). Although details are scarce regarding the pathways of NAFLD formation and progression, it is quite clear that inflammation, fatty acid syntheses, and oxidative stress are significantly involved in this condition (42). In addition, NAFLD pathogenesis could be due to the production of pro-inflammatory mediators, such as angiotensin (ANG) and pro-oxidant cytokines (42,65). It has been suggested that the elevated expression of ANG-II in animal models could be effective in the formation of NAFLD. In diet-induced, obese mice, curcumin has shown beneficial effects on NAFLD. NAFLD and cardiovascular diseases, which are considered more fatal than liver dysfunction complications, are directly correlated (42,65). NAFLD increases the diameter of medial the layer of the carotid artery due to flow alternation. The AGT-II gene is a common factor in atherosclerotic plaque and NAFLD pathogenesis (42). RAS blockers represent a therapeutic approach to the management of NAFLD and atherosclerosis (66).

Curcumin has been reported to improve the hyperplasia of the biliary system, liver fatty changes, and induction of liver necrosis owing to the aflatoxin content (20) (Table 2). To date, single therapy for metabolic dysfunction remains unacceptable, while lifestyle management and control of hyperglycemia and hyperlipidemia are recommended (42,66). Although herbal medicines are used in the treatment of metabolic syndrome, their mechanism of action remains unclear (42,65).

According to reports, hepatic cholesterol metabolism is regulated by curcumin, as well as long-term treatment with lovastatin (5,18). During the treatment with curcumin in these studies, a significant reduction was observed in the body weight of the subjects (42). In a clinical trial in this regard, 0.1-0.25 gram of sodium curcumin and 0.1 gram of calcium cholate (cholic acid salt), which is known as curcunat, were administered to patients with biliary diseases, resulting in rapid gallbladder emptying. Moreover, the oral administration of curcunat for three weeks was reported to control cholecystitis (8, 67).

Evidently, the current findings have confirmed the hepatoprotective effects of curcumin against Aspergillus, aflatoxins, acetaminophen, galactosamine, and carbon tetrachloride (20). In addition, liver aminotransferases function has been reported to improve with the use of curcumin (42). In another study, 40 milligrams of curcumin were reported to stimulate gallbladder contraction (1). spice in the South Asian and Middle Eastern cuisine. Studies on various types of diseases and animals have revealed the effective doses of this compound.

Table 2. Clinical Trials on Effects of Curcumin in Cardiovascular Diseases, Dyslipidemia, Diabetes, Metabolic Syndrome, and Non-alcoholic Fatty Liver Disease

Disease	Curcumin Dose	Clinical Outcomes	Reference
MI after CABG	4 g/three days before surgery until five days after surgery	MI significantly decreased after CABG.	53
ACS	1. Low Dose (15 mg/day q8hr) 2. Moderate Dose (30 mg/day q8hr) 3. High Dose (60 mg/day q8hr)	LDL and total cholesterol decreased by low dose.	54
Dyslipidemia	2 g/day for 30 days	TG decreased, and no effects were observed on other lipid profile parameters.	55
	630 mg three times per day for 12 weeks	Serum lipid decreased, and no effects were observed on body weight and glucose homeostasis.	56
DM	50 mg twice daily for eight weeks	Prevention of endothelial dysfunction Comparable effects to atorvastatin	57
	250 mg twice per day for six months	Control of metabolic profiles and decreasing the risk of atherosclerosis	58
	2 g/day for four weeks	Effective with metformin in controlling blood glucose	59
	80 mg/day for three months	Reduction of HbA1C, serum LDLc, and BMI	60
	250 mg twice per day for nine months	Prevention of pre-diabetes progression to type II diabetes mellitus	61
MetS	1. Black Seeds (1.5 g/day) 2. Turmeric (2.4 g/day) 3. Combination of 900 mg Black Seeds and 1.5 g of Turmeric/day	Black seed and turmeric improved BMI, WC, and BF%	62
NAFLD	1000 mg/day twice per day for eight weeks	Acid uric and serum lipids decreased.	63
	1,000 mg/day twice per day for eight weeks	Liver fatty grades and transaminase level improved.	64
	70 mg/day	BMI, total cholesterol, LDL, TG, ALT, AST, and glucose decreased./beneficial for NAFLD	65

MI: myocardial infarction; CABG: coronary artery bypass graft; LDL: low-density lipoprotein; TG: triglyceride; ACS: acute coronary syndrome; HbA1C: hemoglobin A1C; BMI: body mass index; MetS: metabolic syndrome; WC: waist circumference; BF%: body fat percentage; NAFLD: non-alcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Conclusion

As a result of industrialization in many countries, the prevalence rate of metabolic syndrome and atherosclerosis has increased. Curcumin is considered to be a cost-efficient herbal medicine with few side-effects, which could modulate cell signals to control the progression and prevention of some chronic diseases, such as coronary artery disease and NAFLD.

Curcumin could manage the serum levels of insulin, suppress the atherogenic markers, and reduce the major risk factors for plaque rupture. Furthermore, hepatic cholesterol metabolism is regulated by curcumin, and long-term treatment with this agent could act similar to lovastatin.

Although most of the investigations in this regard have been conducted on animals, the benefits of curcumin are evident in experimental studies. This compound could be used as a therapeutic agent for the management of metabolic syndrome

and cardiovascular diseases.

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Conflict of Interest

The authors declare no conflict of interest.

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