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Effect of *Curcuma longa* L. and curcumin on diabetes and it's complications: A review

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ABSTRACT

Background: Diabetes mellitus, remains a metabolic disorder which is alarmingly rising in the world. It is characterized by hyperglycemia, and associates relative or absolute insulin deficiency or resistance. Disruption of the metabolism may cause lot of micro and macro vascular complications mostly affecting vital organs like kidneys, heart, eyes, and nerves. **Objective:** To discuss the potential of *C. longa* and its constituent curcumin in treatment of diabetes mellitus and its complications. **Method:** An electronic search was performed using Science Direct, Scopus, Springer link, PubMed, Google scholar and collected articles in English up to 2020 August 15 relating to *C. longa* and curcumin in treatment of diabetes mellitus and its complications. **Results:** *C. longa* root or rhizome is an indigenous herb used as a spice in Asian cuisine for thousand years and known to have various therapeutic, medicinal applications for various diseases including diabetes. Curcumin is the major polyphenolic constituent of, *C. longa*. Human and animal researches conducted using *C. longa* and curcumin have proven that, the usage of C. *longa* is beneficial for the treatment of diabetes mellitus including diabetic complications. Curcumin has been reported to prevent the development of diabetes by exerting its cellular effects via various molecular mechanisms. Therapeutic potential of curcumin has been reported against various diabetic complications such as nephropathy, retinopathy, cardiac myopathy, etc. in numerous preclinical and clinical studies. **Conclusion:** These findings might enable to design and practice novel treatment strategies for diabetes mellitus and its complications, and promote inclusion of *C. longa* in clinical practice for the treatment of diabetes mellitus and diabetes related diseases. Furthermore, *C. longa* clinically proven ailment for many diseases including diabetes could be consumed as a safe ingredient of healthy diet. More attention should be extended towards conducting further research on this valuable molecule to utilize it as a therapeutic agent for the treatment of diabetes mellitus and other human diseases.

Keywords: *Curcuma longa* Linn, Diabetes, Turmeric, Curcumin, Diabetes mellitus.

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INTRODUCTION

Since the beginning of human civilization plants have played a role which is pivotal in all aspects of human life. The development of healthcare systems in both ancient and modern cultures could have not been possible without the usage of herbs and herbal derivatives [1-5]. Hence, the role of natural products should not be underestimated because most of people in developing countries depend on natural products to meet their healthcare requirements [6]. Herbal treatments are becoming increasingly popular as there is a belief that they have no or least side effects. There is need to explore herbal medicines in the context of modern science and validate accordingly.

Among the several health problems, diabetes and its complications pose a major threat to future public health resources throughout the world [7]. According to the literature, the prevalence of type 2 diabetes mellitus (DM) is growing in epidemic proportions and accelerating in the developing world [8]. According to the International Diabetes Federation (IDF), the total number of diabetic subjects will be approx. 40.9 million in India and this is further set to rise to 69.9 million by the year 2025 [9]. It is found that diabetes is the ninth major cause of death according to the Global Burden of Disease Study conducted in 2013 [10]. It has turned out to be the biggest - silent killer today in the world. Among the several health problems diabetes and its complications pose a major threat to future public health resources throughout the world [7] and constitute enormous social and economic consequences [11].

Therefore, there is a need to search for effective and safe drugs for this dreadful ailment. According to WHO usage of herbal preparations is increasingly used by patients with chronic diseases including diabetes [12]. Scientific investigations have proven the antidiabetic activity of many medicinal plants

[13-18] including *Curcuma longa* L. [19-23]. Many studies have revealed that curcumin, a yellow-colored polyphenol found in *C. longa*, is well equipped with its bio activities to combat with disease and complications of diabetes. Present review article focuses on the therapeutic impact of *C. longa* and its major ingredient, curcumin on diabetes and its complications.

MATERIALS AND METHODS

The online literature search was carried out using the search terms "Turmeric" AND "Curcuma longa" AND "Diabetes" AND "Curcumin". Time of publication was customized from 1st January 1978 and up to the 15th August 2020. Search was carried out using PUBMED, SCIENCEDIRECT, SCOPUS, SPRINGERLINK and GOOGLE SCHOLER. From the total number of 195 journal articles, 15 and 20 were excluded due to duplication and irrelevancy (as judged by the content of the full article) respectively.

Diabetes mellitus

DM is the name given to a group of disorders characterized by chronic hyperglycemia, polyuria, polydipsia, polyphagia, emaciation, and weakness due to disturbance in carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion and/or insulin action [24]. The word diabetes is originated from the French word named "jiyabatis" which means punctured pitcher or a pitcher with a leak, so that the water sprinkles out of it. The word diabetes is derived from the "diobos" a fountain meaning similar to that of the fountain. In Greek language the "diabetes", means "to run through a siphon" and the term "mellitus" means honey [25]. Defects in insulin secretion, insulin action, or both occur mainly due to the pancreatic β-cell dysfunction and cause hypoglycemic condition [26-27]. The chronic hyperglycemia of DM is associated with long-term damage, dysfunction, and failure of various organs [28]. Long term elevation in blood glucose levels is the reason for these associated macro- and micro-vascular complications including heart diseases, stroke, blindness and kidney diseases [29]. Kangralkar, *et al* (2010), mentioned that except for hyperglycemia, several other factors including hyperlipidemia and oxidative stress play great role in pathogenesis of DM causing a high risk of complications [30].

Curcuma longa Linn and curcumin

Curcuma longa Linn (Turmeric) is a spice that has been used throughout the history in South Asian and Middle Eastern cuisine. For thousand years, this orange-yellow pigments or polyphenols extracted from genus Curcuma plants mainly from *C. longa* has been used in Asian countries as a food spice [31]. Turmeric is used for culinary, medical, religious and cosmetic purposes in South Asian countries including Sri Lanka since a time immemorial. Turmeric give a distinctive yellow color and a flavor to curries [32] and it is used in the diary and other food industries as a coloring agent [33-34]. Ancient Hindus used turmeric to treat sprains and swellings [35].

The prominent curcuminoid found is curcumin [31] and identified as a "functional food" as it provides preventive, protective and/or curative function against one or more diseases, in addition to its adequate nutritional benefits [36]. Curcuminoids (diferuloylmethane) such as curcumin or derivatives of curcumin like desmethoxycurcumin and bisdemethoxycurcumin are considered as bioactive compounds present in *C. longa* [37]. Curcuminoids comprised of mainly curcumin which gives a glamourous yellow colour [38-41]. The other curcuminoids are demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), cyclocurcumin and ar-turmerone [42–44]. Curcumin undergoes glucuronidation and excretion curcumin is poorly absorbed in the circulation [45-46]. To increase the bioavailability of curcumin biofunctionalized nanoparticles and lipid-based delivery system are used in experiments [46].

Due to its well-established and documented therapeutic potential to lower blood sugar, antimicrobial and wound healing activities, Turmeric has been used to treat in traditional medicine since ages [42, 47-49] including China and Southeast Asia [50]. The extensive use of this multi therapeutic plant is well documented in Ayurveda Medical system. Various ailments including asthma, cough, bronchial diseases, allergy, skin diseases, anorexia, diabetic wounds, sinusitis, rheumatism, diabetic wounds, urinary tract infection liver disorder etc. has been treated by this aromatic plant [35, 33]. According to Aggarwal and co-workers (2004) turmeric was used in Chinese medicine as well for the treatment of different diseases including abdominal pain [50]. Curcumin, the active ingredient of turmeric has been as a folk remedy, to treat eye infections, wounds dressing, bites, burns and skin disorders [45]. As it had been used over thousands of years, for therapeutic purposes in many parts of the world the nomenclature used to call turmeric is very broad [51]. The therapeutic activities, for which turmeric used in ancient era, have been confirmed today by the scientific community with evidence-based research. Curcumin a natural flavonoid, possesses a variety of pharmacological qualities including anti-inflammatory, antioxidant, anti-angiogenic anticarcinogenic, and apoptogenic, antimicrobial and neuroprotective activities [52-54]. The most fascinating fact of this herb is that it has a good safety record. Neither any animal study or human study proves any toxicity associated with *C. longa* or its chemical compounds, and it does not demonstrate toxicity even at higher doses [55-57]. A dose escalation study using, healthy volunteers, undertaken to detect the maximum tolerated dose and safety of a single dose of standardized curcumin powder found that administration of doses from 500 to 12,000 mg of curcumin was found to be profoundly well tolerated [57]. However, Pari *et al* (2008) have mentioned that high doses of curcumin have shown to have adverse effects including nausea, diarrhea, increased liver function tests, and increased risk of bleeding [58].

Effect of curcumin on diabetes mellitus

Most valuable therapeutic effect of curcumin is hypoglycemic action. The major pathogenesis of DM is insulin resistance where there is little or no biological effect of tissues or cells for insulin [59]. Guo [60], declared that this condition would cause more complicated consequences like cardiovascular disease, hyperlipidemia and hyperuricemia. Numerous in vivo and vitro studies indicated that curcumin plays a role of "star molecule" in the prevention and treatment of insulin resistance and DM [48, 50]. Many clinical and animal experiments (alloxan-induced rat models, streptozotocin (STZ)-induced rats models and in STZ nicotinamide–induced rats models) have shown that effectiveness of curcumin against DM. [61]. Oral administration of various dosages of curcumin were able to prevent loss of body weight, reduce levels of glucose, hemoglobin, glycosylated hemoglobin in the blood [62] and

improve the insulin sensitivity [61] El-Moselhy *et al*., [63] mention that in rat models of high-fat diet induced insulin resistance and DM, oral administration of curcumin showed an antihyperglycemic effect and improved insulin sensitivity. They suggested that the results were the attributes of anti-inflammatory properties of *C. longa*, which were evident to attenuate Tumor Necrosis Factor alpha (TNF-α) levels.

Antidiabetic effects of curcumin is well established using human subjects in recent years [19, 65, 22, 23]. According to Thota]*et al*. [19], curcumin significantly decreased the post prandial glycemia. In brief, there was a reduction in the body weight, BMI, blood glucose levels [22, 23, 64, 65]. Moreover, curcumin significantly reduced glycated hemoglobin (HbA_1C), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) levels, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in subjects within 8 weeks [22]. Ponnusamy and co-workers [66] identified the active principle (s) from *C. longa* rhizome which is responsible for pancreatic α-amylase inhibitory activity. In addition, various mechanisms have been suggested on antidiabetic activity of curcumins. Some of the examples include (a) capability of exhibit potent human pancreatic α-amylase (HPA) inhibitory activity [22], (b) activates pancreatic sites to lower blood sugar levels [22] and (c) exert a direct stimulatory effect on pancreatic β-cell function [67].

With an intervention of 9-months in a prediabetic population administering 1500 mg/day of curcumin, the number of individuals who developed DM was lowered significantly [31]. On the other hand, curcuminoids have been effectively used on patients with established type 2 DM [68] Further curcumin promotes its hypoglycemic and insulin sensitizing effects by mechanisms like lowering plasmatic glycaemia and inflammation-induced hyperglycemia, reducing hepatic glucose production stimulating glucose uptake by the up-regulation of glucose transporter type 4 (GLUT4), glucose transporter type 2 (GLUT2) and genes glucose transporter type 3(GLUT3) expressions and the activation of Adenosine Monophosphate-activated Protein kinase (AMP kinase), stimulating insulin secretion from pancreatic tissues, improving the functionality of pancreatic cells and reducing insulin resistance, and promoting the actions of ligands in pancreas [69, 70] Lia and co-workers [71] found that curcumin and its metabolites enhanced insulin sensitivity in high glucose - induced insulin-resistant HepG2 cells (HepG2- A human liver tumor cell line). They suggested that insulin sensitivity is improved by enhancing of the phosphatidylinositol 3-kinase (PI3K), Akt/Protein kinase B (AKT /PKB) and glycogen synthase kinase 3 beta (GSK3B) pathway and suppression and activation of extracellular signal-regulated kinases (ERK) c-Jun N-terminal kinase (JNK). Moreover, curcumin induced nuclear factor erythroid 2-related factor 2 (Nrf2) mediators which attenuates insulin resistance by reducing reactive oxygen species (ROS)-mediated insulin resistance in hepatocytes [72]. Wang and co-workers [73] suggested that curcumin prevents hepatic insulin resistance in diabetic mice, by suppressing the endoplasmic reticular Stress (ER stress) and inhibits lipolysis via suppression of Endoplasmic Reticular stress (ER stress) in adipose tissue. Another mechanism suggested is suppression of jun N-terminal kinases (JNKs) and p38 (A class of mitogen-activated protein kinases (MAPKs) pathways to attenuating insulin resistance in Hep G2 cells (A human liver tumor cell line) [74]. The beneficial effects of curcumin on DM have also been noted citing an enhancement of insulin sensitivity and lowering of blood glucose levels in multiple animal diabetic models [21, 48, 75-82].

Pathogenesis of DM has an important connection with ER-stress and inflammatory cytokines secretion [83, 84]. Synthesizing of proinsulin and converting it the active form of Insulin, storage of Insulin in secretory granules is a responsibility of pancreatic β-cells in glucose homeostasis [85]. Any harmful event like lipotoxicity, glucotoxicity, oxidative stress, or inflammation take place in cellular level causing β-cells death or dysfunction may develop DM in a person [86]. During the last decade, a number of in vitro and in vivo studies have been conducted on the antidiabetic properties of curcumin, especially in type 2 DM introducing many mechanisms which could describe curcumins' antihyperglycemic activity [87, 88]. A study conducted by Ye, *et al* [89] showed that curcumins suppressed the ER stress / c Jun-N-terminal-kinase (JNK) /Insulin Receptor Substrate 1 (IRS-1) signaling and decreased palmitate-induced insulin resistance in human umbilical vein endothelial cells. In addition, curcumins maintained the ER stress protein homeostasis by inhibiting peptidase activity and inducing autophagy to degrade damaged or aggregated proteins. According to Rashid and co-worker [90], curcumins demonstrated considerable antidiabetic activity due to its significant antioxidant and anti-inflammatory properties. These authors showed that curcumin suppressed nuclear factor kappa-light-chain enhancer of activated B cells (nuclear NF-kb) as well as reducing caspase-12 levels and cleaving caspase-3 in response to ER stress. In addition, curcumin restored STZ-induced reduced level of the nuclear factor erythroid 2–related factor 2 (nuclear Nrf-2) and heme oxygenase-1, (HO-1) [90]. Further, curcumin has been reported to block the stimulatory effect of insulin in 3T3-L1("3-day transfer, inoculum 3×10^5 cells"-a cell line derived from (mouse) 3T3 cells and used in biological research on adipose tissue) adipocytes [91] and shown to have an immediate, irreversible inhibitory effect in primary rat adipocytes suggesting a more direct interaction of curcumin with the glucose transporter [92]. This inhibition likely represents an interaction of curcumin with the major transporter in cells, GLUT4, however, little is known about the potential interaction of curcumin with the more widely expressed glucose transporter isoform, GLUT1. Curcumin has hypoglycemic effect via directly binding of GLUT proteins in intestinal epithelial cells which further responsible for the reduction of absorption of dietary glucose [93]. Curcumin had exhibited significant reduction (by 37%) in the glucose levels of STZ-diabetic rats. It also significantly decreased levels of inflammatory cytokines, and prevented 8-oxo-2'-deoxyguanosine (8-oxodG) in pancreatic tissues of STZ-diabetic rats [94].

Effects of curcumin on diabetic wound healing

Like other forms of macrovascular diseases, peripheral vascular disease (PVD) is more common in DM. The distribution of vascular disease in lower limb is thought to be different in DM with more frequent involvement of vessels below the knee (distal disease). PVD is frequently asymptomatic in people with DM and may present with ischemic foot ulceration or gangrene. Distal disease may allow a reasonable blood supply to be maintained to the large muscles involved in walking while critically impairing supply to the skin of feet. PVD and poor wound healing cause minor breaks in the skin allowing them to enlarge and to become infected. Poor glycemic control, neuropathy, repetitive traumas, peripheral arterial disease are all

responsible for foot ulceration [95] and in DM foot ulcer is a harmful complication. Approximately 22% of diabetic individuals are reported to be affected by the chronic wounds and 15% are affected by leg ulceration during their lifetime [96]. Curcumin contains anti-microbial activity which is beneficial for wound healing [97] Due to its richness in anti-inflammatory action curcumin is capable to increase the wound closure rate in STZ-induced diabetic mice model by reduced inflammatory induction and antioxidant activity. Nuclear factor erythroid 2-related factor 2 (Nrf2), a redox sensitive transcription factor, is the key regulator of intracellular redox homeostasis which induces the expression of cytoprotective genes and increases the production of antioxidants that scavenge free radicals. Nrf_2 combat with oxidative stress and enhance the process of wound healing in several pathophysiological conditions, including DM and its complications such as diabetic foot ulcer, and chronic kidney disease, and diabetic nephropathy [98] Curcumin is such a Nrf_2 activator which activates the factors which are cytoprotective [99]. Curcumin and *C. longa* increased wound closure rate by reduced inflammatory induction and antioxidant activity Streptozotocin-induced diabetic mice model. Curcumin extracts improves wound healing by increasing granulation tissue, fibroblasts proliferation and collagen deposition in STZ-induced diabetic rats [100]. Another study revealed that healing was accelerated in STZ- induced diabetic rats as curcumin enhanced the healing process by neo vasculogenesis, and increased expressions of vascular endothelial growth factor (VEGF), TGF- β, hypoxia-inducible growth factor-1α(HIF-1α), stromal cell-derived growth factor-1α(SDF-1), and heme oxygenase-1 (HO-1)which is essential for wound healing [101]. Elburki *et al* [102] has recently determined that curcumin caused a significant reduction in pathologically excessive levels of inducible MMPs, local and systemic inflammation and prevented from hyperglycemia- and bacteria-induced connective tissue which is unfavorable for wound healing. Curcuminoids has shown to possess significant anti-inflammatory, antioxidant, anti-carcinogenic, anti-coagulant, anti-infective and anti-diabetic effects [65, 77, 103].

Effect on curcumin on diabetic nephropathy

Diabetic nephropathy can be developed in both Type 1 and 2 DM patients. According to Babu and Srinivasan (1998), revealed the capability of reducing albuminuria and ameliorated renal structured lesions in STZ-induced diabetic rats by curcumin [104].

Effect of curcumin on diabetic neuropathy

There are strong evidences from animal studies regarding the positive effects of curcumin in diabetic, diabetic retinopathy and insulin sensitivity [105, 106]. All the evidences are in support of the idea that curcumin in adjuvant therapy of type 2 DM might be helpful through its antiangiogenic and anti-toxic activities. It is reported that curcumin has multiple potential health benefits in metabolic syndrome, pain and kidney damage due to its anti-inflammatory and anti-oxidative effects [22, 107, 108, 109, 110, 111]. In a study conducted by Jiménez-Osorio *et al* [112] among the diabetic protomeric chronic kidney patients it was observed that supplementation with curcumin enhanced the expression of phosphatidylinositol-3 kinases in a progressive manner. In addition, Turmeric improved activation of the insulin receptor and its downstream pathways [20, 112, 113]. Administration of curcumin at the doses of 100 and 200 mg/kg, b.w./day for 8 weeks in diabetic rats improved the renal function, inhibition of free radicals, oxidative stress, apoptosis and caveolin-1 (cav-1) phosphorylation in the kidneys. In addition, *In vitro* experiments also proved the inhibition of free radicals by curcumin using the cultured mouse podocytes [114]. Experiments have proven that curcumin not only prevented alleviation of superoxide synthesis downregulated Wnt/β-catenin signaling [115]. Curcumin increased the concentration of high-density lipoprotein (HDL), antioxidant enzymes and decreased the lipid profile in male Wistar diabetic rats. Curcumin has been shown to provide protection to kidneys and also prevented cellular vacuolation, morphological irregularity and damage in size β-cells [116]. In vivo experiments showed that capability of curcumin to excrete less albumin, urea, creatinine, and inorganic phosphorus. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatine, and inorganic phosphorus in diabetic animals [117].

Diabetes cause nerve damage which known as diabetic neuropathy. It includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system [118]. Diabetes related neuropathy may manifest as polyneuropathy, mononeuropathy and/or autonomic neuropathy [119]. Distal symmetrical polyneuropathy is commonest form of neuropathy and is manifested as distal sensory loss. Hyperesthesia, paraesthesis and pain also occur. Paraesthesis is characteristically perceived as a sensation of numbness, tingling, sharpness or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals. Pain typically involves lower extremities, usually presents at rest and worsens at night. Physical examination reveals sensory loss of ankle reflexes and abnormal position sense. As diabetic neuropathy progresses, pain subsides and eventually disappears, and a sense of deficit in the lower extremities persists [120]. Symptoms and signs of autonomic neuropathy may typically involve cardiovascular, gastrointestinal, genitourinary, sudomotor and metabolic systems. When cardiovascular system is affected it causes a resting tachycardia and orthostatic hypotension. Gastroparesis and bladder emptying abnormalities are likely related to autonomic neuropathy. Nocturnal diarrhoea, alternating with constipation, is a common feature of DM related gastrointestinal autonomic neuropathy [121]. Neuropathic pain is one of the most common complications of DM [122]. Neuropathic pain may be defined as a symptom resulting from neural injury to peripheral or central components of the pain transmission system. Diabetic peripheral neuropathic pain involves the deep muscular aches, lancinating pains and a persistent burning or tingling sensation, usually in the legs and feet. Patients with diabetic peripheral neuropathic pain may also experience allodynia and hyperalgesia [123]. Pain associated with diabetic neuropathy exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life [123]. The distal symmetric sensory or sensorimotor polyneuropathy (DSP) represents the most relevant clinical manifestation affecting approximately 30% of the hospital-based population and 25% of community-based samples of diabetic patients [124]. The most important aetiological factors that have been associated with DSP are poor glycemic control, DM duration and height, with possible roles for hypertension, age, smoking, hypoinsulinaemia, and dyslipidemia. End-stage renal disease due to type 2 diabetic nephropathy is a very common condition that is associated with high worldwide levels of mortality and morbidity. Both proteinuria and Transforming growth factor beta (TGF-β) may contribute to the development of end-stage renal disease in patients with diabetic

nephropathy. Khajehdehi *et al* [125] investigated the effects of turmeric on serum and urinary transforming growth factor beta (TGF-β), interleukin 8 (IL-8), and tumor necrosis factor alpha (TNF-α), as well as proteinuria, in patients with overt type 2 diabetic nephropathy. Randomly assigned trial group were given 500 mg of turmeric, three times a day for 2 months. Serum concentrations of TGF-β, IL-8, urinary protein excretion were significantly decreased after turmeric supplementation in comparison. No adverse effects related to turmeric supplementation were observed during the trial. The authors of this study concluded that short-term turmeric supplementation can attenuate proteinuria, TGF-β, and IL-8 in patients with overt type 2 diabetic nephropathy and can be administered as a safe adjuvant therapy for these patients.

It is well known that curcumin decreases the inflammatory responses through inhibition of cyclooxygenase 2, lipoxygenase 5 and nitric oxide synthase [126]. In addition, the antinociceptive effects of curcumin have been demonstrated in different pain models such as orofacial and inflammatory pain [127-128]. Recently, it was also shown that curcumin exerts anti-hyperalgesic effects in a mouse model of neuropathic pain [129]. It was shown that chronic hyperglycemia is responsible for the increase of oxidative stress by combining free radical genesis and inefficient antioxidant protection systems and this oxidative stress is involved in the development of diabetic peripheral neuropathy in STZ-induced diabetic rats [130]. Curcumin as the major component of turmeric has considerable effects on nervous system such as, neuroprotective effect in different models of neurogenerative disease, antidepressant and antinociceptive. Review of literature suggests several putative mechanisms for neuronal effects of curcumin. Several studies have shown that curcumin can improve the metabolic status in different diabetic conditions. Curcumin can reverse insulin receptor and malate dehydrogenase down regulation, protein kinase B (Akt) up regulation and the over activity of β2-adrenoceptor in the skeletal muscle of streptozotocin induced diabetic rats [131]. The prior researches also demonstrated that curcumin increased the release of monoamines in the brain of mice or rats [132, 129], suggesting curcumin may activate the descending monoamine system to contribute to its analgesic actions.

Effect of curcumin on diabetic myopathy

Many studies reveal that curcumin possess the anti-inflammatory action [34, 133, 134] and thrombo suppressive activity [133, 135, 136] which provides diabetic patients a protection against myocardial infarction. Atherosclerosis is an inflammation-associated cardiovascular condition. Inflammation is often found in type 2 DM patients and this may be the cause for DM associated atherosclerosis [137]. Recent findings indicated that the anti-inflammatory activity in curcumin would be beneficial for DM as the association between cardiovascular conditions and DM is very common. There is a concept that plasma fibrinogen may be a risk factor for atherogenesis and coronary heart diseases [138, 139]. Ramirez-Bosca *et al* [140], confirmed that by administering 20 mg of hydroalcoholic extract of *C. longa* for 15 days, subjects who had abnormally high values of plasma fibrinogen, decreased the fibrinogen levels significantly. They suggested that Turmeric would be a safe drug which could be utilized to lower fibrinogen selectively.

Curcumin extract has shown positive effects on several metabolic syndromes, in animal models [79, 141, 142, 143, 144] and in humans [145]. In addition, curcumin can inhibit inflammation [146] oxidative stress and aortic fatty streak development in rabbits [147]. Due to its high antioxidant activity and lack of toxicity, the researchers suggested that *C. longa* might be a useful complement to standard hypo-lipidemic drugs in the prevention and treatment of atherosclerosis [148].

Moreover, clinical trial revealed that curcumin lowers the atherogenic risks by reducing the insulin resistance, triglyceride, uric acid, visceral fat and total body fat in diabetic patients. Daily treatment of curcumin extract has significantly decrease the low-density lipoprotein (LDL) and Apolipoprotein B (apo B) levels and increase the high-density lipoprotein (HDL) and apolipoprotein A (apo A) in healthy subjects [140] and improve relevant metabolic profiles in type 2 diabetic population [149]. Soetikno and co-workers [150] observed that STZ-induced male Sprague–Dawley rats fed curcumin (100 mg/kg/day) for 8 weeks, demonstrated that they significantly prevented diabetes-induced translocation of Protein kinase C alpha (PKCα) and Protein kinase C Beta 2 (PK-β2) to membranous fraction and diabetes-induced increased phosphorylation of p38MAPK (A class of mitogen-activated protein kinases (MAPKs)and extracellular regulated-signal kinase (ERK)1/2 in left ventricular tissues of diabetic rats. Hence they suggested that Curcumin would be an adjuvant therapy for the prevention of diabetic cardiomyopathy.

Effect of curcumin on diabetic retinopathy

Diabetic retinopathy is a major preventable cause of visual loss in adults
and categorized into two groups: non-proliferative and proliferative. The indications of non-proliferative retinopathy are retinal vascular aneurysms, blot haemorrhages and cotton wool spots. The indication of proliferative diabetic neuropathy is appearance of neovascularization in response to retinal hypoxia. Two research groups [106, 151] showed the potential effects of treatment with curcumin in mice with diabetic retinopathy induced by the administration of STZ were observed with transmission electron microscope, PCR, and immunoblotting. The first study demonstrated that an 8-week diet enriched with 0.01% curcumin or 0.5% *C. longa* reduced vascular endothelial growth factor (VEGF) expression in treated mice when compared to controls. In the second study, a 16-week treatment with 1 g of curcumin per kg of body weight reduced retinal glutathione, superoxide dismutase, catalase, Tumor necrosis factor-α (TNF-α), and VEGF levels and mitigated diabetic typical endothelial features. Several investigators have examined curcumin's influence in diabetic retinopathy and nephropathy [152, 153] and found that curcumin demonstrated protective effects on the kidney and retina of animals with DM [154, 155].

Effect of curcumin on bone health

A study conducted by Deodhar *et al* [156] investigated that curcumin carries antiarthritic properties which stabilize protection against rheumatoid arthritis. Anti-inflammatory activity would provide this beneficial protection against arthritis [133, 134]. Dietary supplement of curcumin reduced DM-stimulated bone resorptive activity and the number of osteoclasts in an investigation using blood and femoral and tibial bone analysis under non-pathological conditions [157]. Moreover, curcumin suppressed the increased bone resorptive activity through the prevention of osteoclastogenes is associated with inhibition of the

expression of c-fos and c-jun (Proteins related to osteoclast activities) in the diabetic rats. In a study conducted by Park and co-workers [158] it was reported that curcumin inhibited osteoclast genesis by reducing receptor activator of nuclear factor kappa-B ligand (RANKL) expression, which affect the immune system and control bone regeneration and remodeling. In another investigation conducted by Cirano *et al* in 2018, revealed that bone healing was curcumin favored by curcumin, in the DM rats, optimizing the gene expression of key bone-related markers [159]. The micro-CT (micro computed tomography) assays showed that the harmful impact of DM in terms of bone volume was reversed by curcumin therapy, which also had positive effects on the percentage of bone–implant contact (BIC) in diabetic rats.

CONCLUSION

Curcumin is a polyphenol derived from the rhizome of *C. longa* or turmeric which is used as a spice over 2000 years mainly in Asian culinary. It has been traditionally used for the treatment of a wide variety of diseases including DM, wounds, gastrointestinal complications, respiratory ailment etc. Research findings demonstrated several other properties for curcumin including anti-inflammatory, antioxidant, antiviral, cytoprotective and hypoglycemic activities which is beneficial for management of DM and its complications. As the predictions quote about the accelerating numbers in the metabolic disorder of DM, we could equip mankind with this tiny golden colour molecule by performing more research on it for a safer world.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

Data is available on request from the corresponding author.

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