TANG HUMANITAS MEDICINE

Review

Role of *Curcuma longa*, a traditional ayurvedic medicinal plant, in diabetes

Sudha Ponnusamy[1], Smita Zinjarde[1], Shobha Bhargava[2], Ameeta RaviKumar[1,*]

[1]*Insitute of Bioinformatics and Biotechnology (IBB), University of Pune, Ganeshkhind, Pune -411007 India;* [2]*Molecular Embryology Laboratory, Department of Zoology, University of Pune 411007, India*

ABSTRACT

Curcuma longa belongs to the family *Zingiberaceae* and can be found in the tropical and subtropical regions of the world. It is widely used in Asiatic countries, especially India and South East Asia where it is cultivated commercially as a condiment. Its rhizomes exhibit anti-inflammatory, anti-human immunodeficiency virus, anti-bacterial, antioxidant effects, nematocidal activities, antiproliferative and antiangiogenic activities and are of pharmaceutical importance. Another relevant medicinal property exhibited by it is antidiabetic property which is reviewed here. Studies on the efficacy of crude *C.longa* extracts against type 2 diabetes in murine models reveal that it demonstrates a hypoglycemic effect by lowering the blood glucose levels under *in vivo* conditions. Clinical studies have revealed the safety of curucmin (major principle component exhibiting pharmaceutical properties from *C.longa*) on humans but with very low bioavailability. In view of its effective hypoglycemic effect and its low bioavailability, further studies are needed for the characterization of the bioactive principles and formulating the development of *C.longa* extracts as a novel anti-diabetic therapeutic agent.

Keywords *Curcuma longa*, diabetes mellitus, curcuminoids, curcuminoid derivatives, glycosidases

INTRODUCTION

Plants have been an exemplary source of medicine since ancient times in India, with Ayurveda and other literature mentioning the use of plants in the treatment of various human ailments. India has about 45,000 plant species and among them, several thousands have been shown to possess medicinal properties (Grover et al., 2002). The high cost and side effects of the current pharmaceutical medications have led to an increasing search for alternative and complementary medicines to treat numerous diseases. Medicinal plant extracts from locally available herbs are cheaper with lesser side effects than conventional medicines and thus offer an attractive alternative. In view of this trend, there is a need for studies confirming the effects of these medicinal plants and their phytotherapeutic products (Verma and Singh, 2008).

One such medicinal plant *Curcuma longa* L. (Zingiberaceae) is a perennial herb growing up to 1 m high with a short stem and oblong, ovate, and pyriform rhizomes. It is distributed throughout the tropical and subtropical regions of the world, mainly in India and China. Its rhizomes are the source of a culinary spice, turmeric, which is used as a flavoring and dietary pigment apart from its demands as a dye in the textile and pharmaceutical industries (Araújo and Leon, 2001). Indian traditional medicine uses it for biliary disorders, anorexia, cough, wounds, hepatic disorders, rheumatism, and sinusitis (Ammon et al., 1992). In some parts of India, the powder is taken orally for the treatment of sore throats and is extensively used for the treatment of sprains and swellings caused by injury (Ammon and Whal, 1991). Apart from the folk medicinal value of *C.longa* rhizomes, several data in literature indicates show it to possess a variety of pharmacological activities exhibiting anti-inflammatory, anti-HIV, antimicrobial, antiproliferative, antidiabetic, antiangiogenic, nematocidal, hepatoprotective and antioxidant effects (Akram et al., 2010; Ammon and Whal, 1991; Anto et al., 1995; Anto et al., 1998; Kuttan et al., 1985; Maheshwari et al., 2006; Ramsewak et al., 2000; Roth et al., 1998; Selvam et al., 1995; Shishodia et al., 2005). Studies on *C.longa* extracts for its antioxidant, antiproliferative antimicrobial and hepatoprotective effects are abundant. However, reports on its antidiabetic properties are scarce and therefore this review explores the effect of *C. longa* extracts on diabetes mellitus which is a carbohydrate metabolism disorder afflicting more than 100 million people worldwide and by 2030 around 366 million people are predicted to be affected (WHO, 2006; Cheng and Fantus, 2005; Luna et al., 2001). Due to its potent bioactivity and bioavailability issues, *C. longa* extracts deserve to be researched more extensively in clinical trials for use in the prevention and treatment of diabetes (Anand et al., 2007).

Chemistry of *C. longa*

Curcuminoids which account for about 3% (w/v) of the *C. longa* rhizomes are primarily responsible for the bioactivity reported (Çıkrıkçı et al., 2008). Of the naturally occurring curcuminoids, curcumin accounts for (70 - 76%) and its chemical structure, was determined by (Roughley and Whiting, 1973). Curcumin possesses three protons that are ionizable in water: the enolic proton with a pKa of ~ 8.5 and two phenolic protons with pKa of 10 - 10.5 (in a mixed alcoholic/water solvent). It melts at 176 - 177℃ and forms red-brown salts with alkali. Curcumin is soluble in ethanol, alkalis, ketone, acetic acid and chloroform; it is also insoluble in water. In the molecule of curcumin, the main chain is aliphatic, unsaturated and the aryl group can be substituted (Araújo and Leon, 2001). The two other curcuminoids that occur together with curcumin are formed by the progressive removal of one, and two, of the methoxy groups from curcumin to form demethoxycurcumin

[*]Correspondence: Ameeta RaviKumar
E-mail: ameeta@unipune.ac.in
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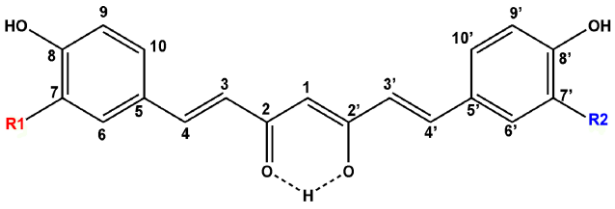

Compound	R1	R2
Curcumin	O Me	O Me
Demethoxycurcumin	H	O Me
Bisdemethoxycurcumin	H	H

Fig. 1. Structure of naturally occurring curcuminoids. Substitution of R1 and R2 with the groups mentioned results into curcumin, demethoxycurcumin and bisdemethoxycurcumin.

and *bis* demethoxycurcumin, respectively and account for around 17% and 3% of yields (Sandur et al., 2007) (Fig. 1).

C. longa in diabetes

Diet has been recognized as a corner stone in the management of diabetes mellitus. Spices are the common dietary adjuncts that contribute to the taste and flavour of foods. Besides, spices are also known to exert several beneficial physiological effects including their antidiabetic influence. Of the known dietary spices, *C. longa* has a wide range of effects on human health with studies on the crude extract and their active principle for the treatment of diabetes being carried either *in vivo* or *in vitro* (Srinivasan, 2005).

In an *in vivo* study on alloaxon-induced diabetic rats, the administration of turmeric or curcumin to diabetic rats reduced the blood sugar, hemoglobin and glycosylated hemoglobin levels significantly. Reduced oxidative stress and thiobarbituric acid reactive substances levels were also reported. A decreased influx of glucose into the polyol pathway leading to an increased NADPH/NADP ratio and an elevated activity of the potent antioxdiant enzyme glutathione peroxidase along with lower sorbitol dehydrogenase activity, catalyzing the conversion of sorbitol to fructose were reported. This could be the possible mechanism by which turmeric and curcumin would be exerting their hypoglycemic activities (Arun and Nalini, 2002).

The hypoglycemic effect of *C.longa* rhizomes on genetically diabetic KK-A^y mice which carry both the heterozygous lethal yellow obese (Ay) and diabetic genes was studied. The genetically diabetic KK-A^y shows severe obesity, the principal cause of diabetes, to be insulin resistance which may be due to defects in both the insulin receptor and post receptor signalling systems, including glucose uptake, pentose pathways, and impaired insulin sensitive phosphodiesterase in fat cells (Srinivasan and Ramarao, 2007). *C.longa* rhizomes ethanol extract significantly suppressed an increase in blood glucose levels in type 2 diabetic KK-A^y mice. In an *in vitro* evaluation, the extract stimulated human adipocyte differentiation in a dose-dependent manner and showed human peroxisome proliferator-activated receptor (PPAR)-γ ligand-binding activity. The main constituents of the extract were identified as curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone, which also had a PPAR-γ ligand-binding activity. These results indicate that turmeric is a promising ingredient of functional food for the prevention and/or amelioration of type 2 diabetes and that curcumin, demethoxycurcumin, bisdemethoxycurcumin, along with ar-turmerone mainly contribute to the effects via PPAR-γ activation (Kuroda et al., 2005; Nishiyama et al., 2005).

Effect of *C.longa* on oxidative stress

On studying the effect of curcumin on the inhibition of cellular reactive oxygen species (ROS) generation, it was reported that, curcumin abolished both phorbol-12 myristate-13 acetate and thapsigargin-induced ROS generation in cells in control and diabetic subjects. The pattern of these ROS inhibitory effects as a function of dose-dependency suggested that curcumin mechanistically interfered with protein kinase C (PKC) and calcium regulation. Simultaneous measurements of ROS and Ca^{2+} influx suggested that a rise in cytosolic Ca^{2+} may be a trigger for increased ROS generation, Thus, the antioxidant and antiangiogenic actions of curcumin, as a mechanism of the inhibition of Ca^{2+} entry and PKC activity, should be further exploited to develop suitable and novel drugs for the treatment of diabetic retinopathy and other diabetic complications (Balasubramanyam et al., 2003).

Jain et al. (2009) studied the effects on curcumin on levels of interleukine (IL)-6, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)-α, hyperglycemia, and oxidative stress by using a U937 monocytes cell-culture model and the streptozotocin (SZT) Sprague–Dawley rats diabetic rat model. Results show that the effects of high glucose on lipid peroxidation, IL-6, IL-8, MCP-1, and TNF-α secretion were inhibited by curcumin in cultured monocytes. In the rat model, diabetes caused a significant increase in blood levels of IL-6, MCP-1, TNF-α, glucose, hemoglobin-alpha-1, and oxidative stress, which was significantly decreased in curcumin-supplemented rats. Thus, curcumin can decrease markers of vascular inflammation and oxidative stress levels in both a cell-culture model and in the blood of diabetic rats. This suggests that curcumin supplementation can reduce glycemia and the risk of vascular inflammation in diabetes.

C.longa in diabetic nephropathy

Chronic hyperglycaemia in diabetes leads to the overproduction of free radicals which contribute to the development of diabetic nephropathy. On studying the effect of curcumin on diabetic nephropathy in SZT-induced diabetic wistar rats, the renal damage was assessed by the amount of proteins excreted in the urine and the extent of leaching of renal tubular enzymes: N-acetyl-glucosamine, lactate dehydrogenase (LDH), aspartate aminotransferase, alanine transaminase, alkaline and acid phosphatases. The integrity of the kidneys was assessed by measuring the activities of several key enzymes of the renal tissue: glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, and LDH (carbohydrate metabolism), aldose reductase and sorbitol dehydrogenase (polyol pathway), transaminases, ATPases and membrane PUFA/SFA ratio (membrane integrity). Data on enzymuria, albuminuria, activity of kidney ATPases and fatty acid composition of renal membranes in the diabetic condition suggested that dietary curcumin brought about significant beneficial modulation of the progression of renal lesions in diabetes. These findings were also confirmed by histological examination of kidney sections. It is inferred that this beneficial ameliorating influence of dietary curcumin on diabetic nephropathy is possibly mediated through its ability to lower blood cholesterol levels (Suresh and Srinivasan, 1998). Sharma et al. also reported the nephroprotective and antioxidant actions of curcumin (Sharma et al., 2006). The renal function was assessed by creatinine, blood urea nitrogen, creatinine and urea clearance and urine albumin excretion. Oxidative stress was measured by renal malonaldehyde, reduced glutathione and the anti-oxidant enzymes superoxide dismutase and catalase. Diabetic rats also exhibited renal dysfunction, as evidenced by reduced creatinine

and urea clearance and proteinuria, along with a marked increase in oxidative stress, as determined by lipid peroxidation and the activities of key anti-oxidant enzymes. Chronic treatment with curcumin significantly attenuated both renal dysfunction and oxidative stress in diabetic rats. In an another study for evaluating the effect of diabetic nephropathy in SZT-induced male Sprague-Dawley rats, the up regulation of vasoactive factors (endothelial nitric oxide synthase and enothelin-1), transforming growth factor-β1 and extracellular matrix proteins (fibronectin and extradomain-B–containing fibronectin) in the kidneys were reported. These changes were associated with increased oxidative stress, mesangial expansion, and p300 and nuclear factor-κB activity that were prevented with curcumin treatment. Thus, the beneficial effects of curcumin were mediated through the inhibition of p300 and nuclear factor-κB (Chiu et al., 2009).

Effect of *C.longa* on glycosidases

Lekshmi et al. reported tumerin a proteinaceous water-soluble peptide inhibitor (Lekshmi et al., 2011), turmerin, isolated from turmeric rhizomes inhibitory potential against α-glucosidase and α-amylase along with its antioxidant property. Turmerin inhibited α-amylase and α-glucosidase activities with IC_{50} values of 31 and 192 µg/mL, respectively. Turmerin showed good diphenyl-1-picrylhydrazyl and superoxide IC_{50} values of 29 and 48 µg/mL, respectively and a moderate 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid IC_{50} value of 83 µg/mL, radical scavenging and Fe(II) chelation IC_{50} values of 101 µg/mL. The inhibitory potential showed by turmerin against enzymes linked to type 2 diabetes, as well as its moderate antioxidant capacity, could rationalize the traditional usage of turmeric rhizome preparations against diabetes. In another study by (Lekshmi et al., 2012), on evaluating the antidiabetic capacity of *C.longa* volatile oils in terms of its inhibitory effects on glucosidases, Ar-Turmerone, the major volatile component in the rhizome showed potent α-glucosidase (IC_{50} = 0.28 µg) and α-amylase (IC_{50}= 24.5 µg) inhibition. Moreover, drying rhizomes was found to enhance the α-glucosidase (IC_{50} = 1.32 - 0.38 µg/ml) and α-amylase (IC_{50} = 64.7 - 34.3 38 µg/ml) inhibitory capacities of volatile oils.

Sudha et al. have reported that the isoporpanol extract of *C. longa* rhizomes exhibited a potent human pancreatic α-amylase inhibition with an IC_{50} value of 0.16 µg/ml, suggesting it to have a potent lead inhibitor molecule (Sudha et al., 2010). Bioactivity guided isolation of the rhizome isopropanol extract led to the identification by HPLC and NMR of bisdemethoxycurcumin as a lead small molecule inhibitor of porcine and human pancreatic α-amylase with an IC_{50} value of 0.026 and 0.025 mM, respectively (Sudha et al., 2012). Kinetic analysis revealed that by using starch as the substrate; human pancreatic α-amylase exhibited an uncompetitive mode of inhibition with an apparent *Ki ′* of 3.0 µM. The study gains importance as bisdemethoxycurcumin could be a good drug candidate in the development of newer inhibitors of HPA and of functional foods for controlling starch digestion in order to reduce post-prandial hyperglycemia.

In another study, a lectin from *C.longa* L. purified by aqueous extraction, 80% ammonium sulfate precipitation and ConA Sepharose affinity chromatography exhibited a high α-glucosidase inhibitory activity with an IC_{50} of 8 mg/mL (Petnual et al., 2010).

Effect of *C.logna* in diabetes and hypercholesterolemia

Hypercholesterolemia is a common feature observed in diabetes leading to atheroscelerosis and coronary heart disease. In another *in vivo* study, (Suresh and Srinivsan., 1995) have reported the influence of dietary curcumin on the progression of experimentally-induced diabetes by feeding cholesterol to albino rats. Diabetic rats maintained on a curcumin diet for 8 weeks excreted less albumin, urea, creatinine, and inorganic phosphorus. Urinary excretions of the electrolytes sodium and potassium were also significantly lowered under curcumin treatment. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatinine, and inorganic phosphorus in diabetic animals. On the other hand, glucose excretion or the fasting sugar level was unaffected by dietary curcumin, and so also the body weights did not improved to any significant extent. Thus, the study reveals that curcumin feeding improves the metabolic status in diabetic conditions, with no effect on hyperglycemic status or body weight. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence and its antioxidant and free-radical-scavenging properties (Suresh and Srinivasan, 1995). In another study, the hypolipidemic actions of curcumin in rats with SZT-induced diabetes showed that dietary curcumin lowered the blood cholesterol significantly by decreasing the low density lipoprotein-very low density lipoprotein fraction along with a significant decrease in blood triglyceride and phospholipids. In a parallel study, wherein diabetic animals were maintained on a high cholesterol diet, the extents of hypercholesterolemia and phospholipidemia were higher than those maintained on the control diet. Curcumin lowered cholesterol and phospholipid levels in these animals also. Liver cholesterol and triglyceride and phospholipid contents were elevated under diabetic conditions. Dietary curcumin showed a distinct tendency to counter these changes in lipid fractions of the liver. This effect of curcumin was also seen in diabetic animals maintained on a high-cholesterol diet. Dietary curcumin significantly countered renal cholesterol and triglyceride elevations in diabetic rats. The mechanism of action has revealed a significant high activity of hepatic cholesterol-7-α-hydroxylase in curcumin-fed diabetic animals, suggesting a higher rate of cholesterol catabolism (Suresh and Srinivasan, 1997).

Derivatives and analogues of curcumin in diabetes

Natural curcumin, demethoxycurcumin and bisdemethoxycurcumin isolated from *Curcuma longa* (turmeric), and synthetic curcumin analogs ($A_{1–7}$,$B_{1–7}$,$C_{1–6}$ and $D_{1–7}$) were evaluated *in vitro* for the α-glucosidase inhibitory activity via UV and circular dichroism (CD) spectroscopy. The results indicated that bisdemethoxycurcumin showed a remarkable inhibitory effect with IC_{50} of 23.0 µM, and the synthetic compounds A_2, B_2, C_2 and D_2 showed potent inhibitory effects with IC_{50} of 2.8, 2.6, 1.6 and 8.2 µM, respectively. A kinetic study showed that the mechanism of α-glucosidase inhibition of bisdemethoxycurcumin and C_2 were non-competitive. The structure activity relationship revealed that the *ortho* dihydroxyl groups could form a tighter interaction with α-glucosidase to exert more potential inhibitory activities (Du et al., 2006).

THC, one of the major colorless metabolites of curcumin, is its partially reduced derivative. It is obtained by the partial hydrogenation of curcumin (Anand et al., 2008). It possesses antidiabetic, antiinflammatory and antioxidant activities. The oral administration of THC to diabetic rats showed a decrease in the levels of blood glucose and plasma glycoproteins. The levels of plasma insulin and tissue sialic acid were increased where as the levels of tissue hexose, hexosamine and fucose were near normal in diabetic rats treated with THC. The present study indicates that the THC possesses a significant beneficial effect on glycoprotein moiety in addition to its antidiabetic effect. This effect of THC is more prominent than curcumin

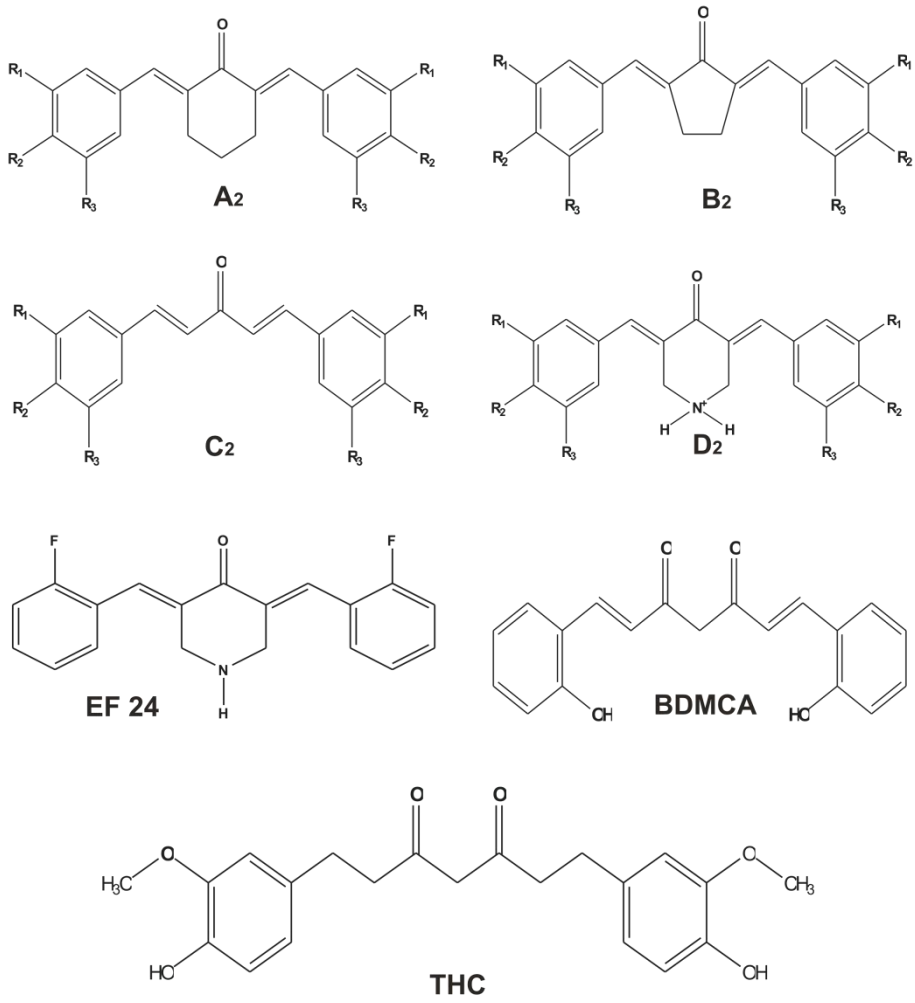

Fig. 2. Curuminoid analogues. Structures of curcuminoid analogues reported to exhibit hypoglycemic effect. A_2, B_2, C_2, D_2; R_1=R_2=OH; R_3=H; BDMCA, bis-o-hydroxycinnamoylmethane analogue; THC, Tetrahydrocurcumin.

(Pari and Murugan, 2007).

In an another study by (Srinivasan et al., 2003), antioxidant defense by Bis-o-hydroxycinnamoylmethane analogue (BDMCA) an analogue of the naturally occurring curcuminoid, bisdemethoxycurcumin in SZT-induced diabetes in male wistar rats and its possible protection of pancreatic β-cells against gradual loss under diabetic conditions was evaluated. The levels of plasma glucose and glycated hemoglobin which were elevated in diabetic rats were reduced after treatment with the drug. The antioxidant levels showed an increase in the case of treated diabetic rats. The islets were shrunken in diabetic rats in comparison to normal rats. On the other hand, treated diabetic rats showed an expansion of the shrunken islets back to normal. The experimental drug BDMCA enhanced the antioxidant defense against reactive oxygen species produced under hyperglycemic conditions and thus protected the pancreatic β -cells against loss and exhibited antidiabetic properties. A study by (Sivabalan and Anuradha, 2010) on a synthetic analog of bisdemethoxycurcumin, BDMCA resulted in higher bioavaibility and stability. Bisdemethoxycurcumin analogue and curcumin *in vitro* lower the gluconeogenesis in the hepatocytes and function as antioxidants. Both BDMCA and curcumin delay intestinal glucose absorption with BDMCA delaying it more effectively as compared to curcumin. Some of these analogues are shown in Fig. 2.

With these current derivatives available, they are more potent andiabetic agents as compared to their natural analogues; however, bioavailability of these analogues still remains to be assessed.

Bioavailability of curcumin

Curcumin, a polyphenolic compound possesses diverse pharmacologic effects with Phase I clinical trials showing that curcumin are safe even at high doses (12 g/day) in humans but exhibit poor bioavailability. Major reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination. To improve the bioavailability of curcumin, numerous approaches have been undertaken. These approaches involve, for example, the use of adjuvant-like piperine that interferes with glucuronidation; the use of liposomal curcumin or curcumin nanoparticles; the use of curcumin phospholipid complex; and the use of structural analogues of curcumin (e.g., EF-24). The latter have been reported to have a rapid absorption with a peak plasma half-life. An enhanced bioavailability of curcumin in the near future is likely to bring this promising natural product to the forefront of therapeutic agents for the treatment of human disease (Anand et al., 2007).

Curcumin, the most active polyphenolic constituent of turmeric curcuminoids obtained from the rhizome *Curcuma longa*, holds a high place in ayurvedic medicine and its role in conventional disease management has also been established. Its bioavailability due to insolubility in water becomes a limiting factor. Increasing its solubility followed by assessment of the effect of the oral consumption of soluble curcumin on pathological parameters on healthy human volunteers was

undertaken (Gandhi et al., 2011). Soluble curcumin was found to improve the liver functions, kidney functions and ameliorated the lipid profile, blood glucose in healthy volunteers, only in 15 days of oral consumption. Enhanced bioavailability of soluble curcumin in the near future is likely to bring this promising natural product to the forefront of therapeutic agents for the treatment of human diseases.

Clinical trials of curcuma longa in diabetes

Wickenberg et al. studied the effect of *C. longa* on postprandial plasma glucose, insulin levels and glycemic index (GI) in healthy subjects (Wickenberg et al., 2010). Fourteen healthy subjects were assessed in a crossover trial. 75 g oral glucose tolerance test (OGTT) was administered together with capsules containing a placebo or *C. longa* powder. Finger-prick capillary and venous blood samples were collected before, and 15, 30, 45, 60, 90, and 120 min after the start of the OGTT to measure the glucose and insulin levels, respectively. The ingestion of 6 g *C. longa* increased postprandial serum insulin levels, but did not seem to affect plasma glucose levels or GI, in healthy subjects. The results indicate that *C. longa* may have an effect on insulin secretion. In another clinical trial, the effects of NCB-02 (a standardized preparation of curcuminoids), atorvastatin and a placebo on endothelial function and its biomarkers in patients with type 2 diabetes mellitus were evaluated. 72 patients with type 2 diabetes were randomized to receive NCB-02 (two capsules containing curcumin 150 mg twice daily), atorvastatin 10 mg once daily or a placebo for 8 weeks. An endothelial function assessment was performed at baseline and post-treatment. NCB-02 had a favorable effect, comparable to that of atorvastatin, on endothelial dysfunction in association with reductions in inflammatory cytokines and markers of oxidative stress. Further studies are needed to evaluate the potential long-term effects of NCB-02 and its combination with other herbal antioxidants (Usharani et al., 2008).

CONCLUSION

Like other spices, *Curucma longa* is used by the pharmaceutical, food and aroma industries due to its chemical constituents and its wide therapeutic applications. It is also widely used in folk medicine and as an edible plant. Several studies have identified the bioactive compounds of its rhizome and demonstrated its beneficial physiological and metabolic properties as a hypoglycemic plant. The bioavailability and solubility of curcuminoids responsible for most of the therapeutic implications are the limiting factors in their use. Clinical trials on turmeric extracts and the bioactive components have reported to be safe for human use for varying ailments. Synthetic curuminoid analogues are developed that shows improved solubility, stability and bioavailability.

CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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