REVIEW ARTICLE

Curcumin: A boon as antidiabetic

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Abstract

Diabetes is a chronic illness that develops either when the pancreas does not create enough insulin or when the body is unable to utilize the insulin that is produced. Diabetes is the most spreaded disease in India, in which type II diabetes mellitus is most common type (90–95%). Natural products have gained a lot of attention as a means of managing the global epidemic that is diabetes and its complications. One of the most significant medicinal herbs is turmeric (*Curcuma longa*), which belongs to the *Zingiberaceae* family. Since ancient times, ayurveda and traditional Chinese medicine have used the spice turmeric, which is made from the root of the plant *C. longa*, to cure diabetes. Turmeric contains the polyphenol curcumin, and curcuminoids have been shown to have anti-inflammatory, anti-oxidant, hepatoprotective, nephroprotective, immunomodulatory, and anti-diabetic activities.

Key words: Alloxan, curcumin, diabetes, human studies, insulin resistance, *in vivo* animal studies, streptozotocin

INTRODUCTION

Diabetes, often known as diabetes mellitus (DM), is a collection of metabolic disorders characterized by persistently elevated blood sugar levels (hyperglycemia).[1,2] In general, there are two forms of DM: (i) Type I diabetes, also known as insulin dependent diabetes, is characterized by autoimmune destruction of beta-cells and complete lack of insulin; (ii) type II diabetes or non-insulin dependent DM (90–95% of all diabetes cases), which is distinguished by a progressive loss of β-cell insulin secretion and insulin resistance; hence, the body cannot properly use the insulin it produces; (iii) gestational DM, a disorder that is diagnosed in the second or third trimester of approximately 7% of all pregnancies; and (iv) specific types of diabetes from other causes, such as monogenic diabetes syndromes, diseases of exocrine pancreas (e.g., cystic fibrosis-related diabetes), and drug or chemical induced diabetes (e.g., nicotinic acid and glucocorticoids use), which represent <5% of patient with diabetes.[3,4] DM is a multifactorial and incurable metabolic illness that affects insulin's effectiveness or how well it is used, which can improve the metabolism of carbohydrates, proteins, and lipids and prevent long-lasting hyperglycemia.[3-5]

Natural remedies have gained a lot of attention for the treatment of diabetes and its complications, which are now a worldwide epidemic.[6-9] Since ancient times, Ayurveda and traditional Chinese medicine have used turmeric, a spice derived from the root of the *Curcuma longa* plant, as a diabetic treatment.[10] The hypoglycemic, nephroprotective, and cardioprotective effects of curcumin are sufficient. The metabolic profile of diabetes can be improved by curcumin in suitable manner.[6-10]

The scientific community has acknowledged the benefits of turmeric (*C. longa*), a common spice used in food preparation. This plant is well-known and frequently grown in South East Asia. It can be distinguished by its orange tuberous rhizomes.[11] Since ancient times, it has been employed in this region as a natural therapeutic treatment for a variety of diseased conditions. This plant has extraordinary quality that is the presence of curcumin, which exhibits anti-inflammatory and antioxidant qualities.[12] Apart from this, curcumin has important role as anti-bacterial, anti-diabetic, anti-viral, and anti-cancer activities [Figure 1].[13-15]

Diabetes in India

India, the second most affected country in the world after China, has an estimated 77 million people (one in 11 Indians) who have been officially diagnosed with diabetes. In addition, 700,000

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Received: 13-01-2023
Revised: 19-03-2023
Accepted: 30-03-2023

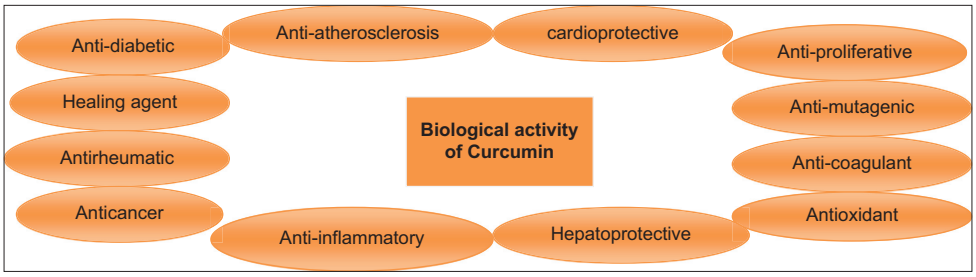

Figure 1: Biological activities of curcumin

Indians lost their life in 2020 from diabetes-related complications such hyperglycemia, kidney disease, or other conditions. India accounts for 1 in 6 (17%) of all cases of diabetes worldwide (As of October 2018, India's population accounted for around 17.5% of the world's population.). The international diabetes federation (IDF) predicts that by 2045, there will be 134 million people worldwide affected with diabetes.[1]

Type I diabetes is less common in India than in western nations, and 90–95% of Indians with diabetes who are diagnosed with type II. The body mass index of just around one-third of type II diabetes in India is >25.[2] According to a 2004 study, the environmental and lifestyle changes brought on by industrialization and the migration of people from rural to urban areas may be to blame for the incidence of type II diabetes among Indians. The consumption of animal foods has increased among Asian communities as a result of this lifestyle change. This shift was observed in India, where urban residents consumed 32% more energy from animal fats than rural dwellers (17% did). In addition, due to the early onset of these alterations in life, chronic long-term consequences are more common. India now has 65 million diabetics, up from 26 million in 1990. The prevalence was determined to be 11.8% among adults over the age of 50, according to the Ministry of Health and Family Welfare 2019 National Diabetes and Diabetic Retinopathy Survey report. According to the demographic and health survey, 6.5% of adults under 50 have diabetes, and 5.7% have prediabetes. Both male (12%) and female (11.7%) populations shared a similar prevalence. In urban regions, it was higher. Surveys of diabetics up to the age of 50 revealed that 16.9% of them had the sight-threatening condition diabetic retinopathy. According to the report, the prevalence of diabetic retinopathy was 18.6% in the 60–69-year-old age group, 18.3% in the 70–79-year old age group, and 18.4% in those over the age of 80. In the 50–59 age range, a lower frequency of 14.3% was noted. In states like Tamil Nadu and Kerala, which are economically and epidemiologically developed and have a large number of research institutes that undertake prevalence studies, diabetes prevalence rates are claimed to be high.[1-3]

CHEMICAL STRUCTURE OF CURCUMIN

Curcumin has a hepta-carbon linker and three major functional groups: Alpha, beta-keto-enol tautomerism, exists in enolic form in organic solvent and keto form in water.[16] Due to its hydrophobic nature, curcumin is poorly soluble in water, whereas highly soluble in organic solvent.[17]

Curcumin symmetrically consists of four chemical structures aryl side chains which are linked by linker chain with a di-keto functional group, two double bond, and active methylene group. These sites are potential site for modification for improving the efficacy of Curcumin. Modification of the structure of the curcumin enhances the pharmacological activity, physicochemical, and pharmacokinetic properties with the enhancement of its receptor-binding capacity.[18-23]

Epidemiological studies have advised that nutritious diets (fruits and vegetable) help balance obesity (body weight) and protect from cardiovascular disease, cancer, and diabetes.[24-26] However, the role of food component is difficult to be determined in disease prevention and treatment.[27-32]

ANTIDIABETIC EFFECT OF CURCUMIN: *IN VIVO* ANIMAL STUDIES

A previous review by Meng *et al*., in 2013,[33] focuses mainly on the antioxidant and anti-inflammatory properties of Curcumin and it also summarizes the effect of curcumin against different diabetic complexities, such as vasculopathy and nephropathy.

Streptozotocin (STZ)-Induced Diabetes Model

In few studies, using STZ-induced diabetes animal models, the effect of Curcumin was examined and is shown in Table 1. Type II DM *in vivo* in Wistar rats by a single intraperitoneal injection of STZ (60 mg/kg body weight) in the study by Babu and Srinivasan[33] carried out by a diet supplement of Curcumin (0.5% diet) for 8 weeks. Supplemental curcumin significantly reduced the progression and damage of kidney lesions. The levels of the urine enzymes alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and acid phosphatase were also decreased with curcumin administration. Renal glucose-6-phosphatase and lactate dehydrogenase activities were decreased, while ATPase activities were raised by curcumin

Table 1: Evidence of antidiabetic effects of curcumin: *In vivo* streptozotocin-induced diabetes animal studies

Animal	Concentration of Curcumin	Serum effect	Other effect	References
Wistar rats	80 mg/kg body weight/day; 45 days	• Decrease in glucose level • Increase in insulin level	• Decrease in lipid peroxidation Kidney: • Increase in superoxide dismutase (SOD) activity • Increase in catalase level • Increase in GPx activity Kidney and liver: • Decrease in Thiobarbituric acid reactive substance level (TBARS) • Decrease in H_2O_2 level	[35]
Albino Wistar rats	30 mg/kg body weight/day; 8 weeks	• Decrease in glucose level • Decrease in cholesterol level • Increase in Urea level • Increase in creatinine level	• Decrease in Body weight • Decrease in kidney lipid peroxidation • Increase in kidney SOD activity • Increase in creatinine activity	[36]
Albino Wistar rats	0.5% of diet; 8 weeks	• Decrease in phospholipid level • Increase in polyunsaturated fatty acid(PUFA) /saturated fatty acid (SFA)	• Decrease in renal lesion progression level • Decrease in kidney weight • Decrease in renal damage • Increase in ATPase activity	[34]
Wistar-NIN rats	0.01% Curcumin; 8 weeks	• Decrease in insulin level • Increase in SOD activity	• Decrease in TBARS level • Decrease in glutathione –S-transferase activity • Increase in pancreas SOD activity	[37]
Sprague–Dawley rats	15 and 30 mg/kg body weight/day; 2 weeks	• Decrease in glucose level • Decrease in creatinine level	• Decrease in Renal change • Decrease in Urine albumin level • Increase in Creatinine clearance • Decrease in lipid peroxidation Kidney: • Increase in SOD activity • Decrease in Malondialde-hyde (MDA)	[38]
Sprague-Dawley rats	50 mg/kg body weight/day; 6 weeks	• Increase in creatinine level • Decrease in Urea level	• Decrease in HSP-27 protein level • Increase in albumin level • Increase in Acetyl-histone H3 • Increase in phospho- histone H3	[39]
C57/BL6J mice	7.5 mg/kg body weight/day; 10 h before STZ	• Increase in insulin level • Decrease in glucose level • Decrease in IL-16 level • Decrease in TNF-α level	• Increase in glucose clearance • Increase in GLUT2 mRNA • Decrease in pancreatic IL-6 and TNF-α	[40]
Wistar rats	80 mg/kg body weight/day; 45 days	• Increase in insulin level • Decrease in glucose level	Kidney and liver: • Decrease in morphological change • Decrease in TBARS • Decrease in oxidative stress • Increase in SOD Activity • Increase in CAT activity • Increase in GPx activity	[41]
Swiss albino mice	10 mM; 10 μL/mouse i.p.; 28 days and 10^6 BMCs, single injection	• Decrease in glucose level • Decrease in TNF-α • Decrease in IL-1β • Increase in insulin level	• Increase in Islet regeneration. Pancreas: • Decrease in MDA level • Increase in catalase activity • Increase in SOD activity • Increase in GPx activity	[42]
Sprague–Dawley rats	100 mg/kg body weight/ day; 8 weeks	• Decrease in urea level • Decrease in glucose level • Decrease in creatinine level	Kidney: • Decrease in glomerular and tubular histological change • Decrease in Macrophage infiltration • Decrease in segmental sclerosis	[43]

administration. Curcumin treatment decreased blood triglyceride and phospholipid levels while increasing the ratio of polyunsaturated to saturated fatty acids ratio. In general, using curcumin, supplements reduce diabetic nephropathy.[34]

According to the studies mentioned above and included in Table 1, administering curcumin to STZ-induced diabetic animals increased islet cell regeneration, restored lipid and blood glucose levels, and decreased diabetic nephropathy. Antioxidant, anti-inflammatory, and enhanced mitochondrial qualities also came about as a result of its treatment.

Alloxan-induced Diabetes Model

Alloxan is an organic substance that is a urea derivative, cytotoxic glucose analog, carcinogen and is also known by its chemical name, 5,5-dihydroxyl pyrimidine-2,6-trione.[44] Alloxan is one of the most widely used diabetogenic agents, and it is used in diabetic investigations to evaluate the antidiabetic potential of both pure chemicals and plant extract.[45] Table 2 shows the results of administering curcumin to diabetic rats induced by alloxan. Curcumin (0.08 mg/kg body weight/day) and turmeric (1 mg/kg body weight/day) administration to alloxan-induced diabetic Wistar rats for 21 days significantly decreased serum glucose and hemoglobin A1c levels while increasing hemoglobin levels.[46] Curcumin or turmeric treatment decreased the levels of liver and serum thiobarbituric acid reactive substance level and sorbitol dehydrogenase activity while increasing GPx activity and glutathione levels, which are antioxidants. This implies that sorbitol conversion to fructose was inhibited by both curcumin and turmeric [Figures 2-4].[46]

Curcumin analogs were given to Wistar rats with alloxan-induced diabetes for 2 h and resulted in decreased blood glucose level, similar to levels achieved by treatment with the Glipizide (antidiabetic drug).[47] With intraperitoneal dosages of 150 mg/kg and less, there is often poor diabetogenicity and easy auto-reversal of alloxan-induced hyperglycemia.[48]

Comparing Alloxan with STZ as Diabetogenic Agent

In terms of a chemical agent, STZ has significant advantages over alloxan for the development of experimental diabetes and is frequently chosen over the latter (Alloxan). As an illustration, STZ has a longer half-life (15 min against

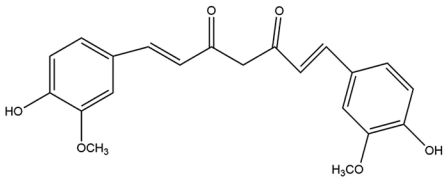

Figure 2: Chemical structure of curcumin

Figure 3: Turmeric plant

Figure 4: Turmeric

1.5 min of Alloxan).[49] It becomes more stable in solution as a result, both before and after injection into animals. Hyperglycemia caused by STZ is more persistent and often steadier (as much as 3 months compared to alloxan-induced hyperglycemia that can only be sustained for less than a month). In addition, the mechanism of STZ diabetogenicity has a lower level of cellular toxicity, which results in lower animal mortality. Alloxan, on the other hand, causes diabetes by a process that is characterized by occurrences of ketosis, reactive oxygen species toxicity, and a high death rate, which is especially a significant drawback in experimental diabetes investigations.[48] The fact that STZ is more specific to islet

Table 2: Evidence of antidiabetic effects of curcumin: *In vivo* alloxan-Induced diabetes animal studies

Animal	Concentration of curcumin	Serum effect	Other effect	References
Wistar rats	0.1 mg/kg body weight; 2 h	• Decrease in glucose Level	• No measured effect	[46]
Wistar rats	0.08 mg/kg body weight /day; 21 days	• Decrease in glucose level • Decrease in HbA1c level • Decrease in TBARS level • Increase in hemoglobin level	Liver: • Decreases in liver TBARS level • Increase in liver glutathione level	[47]

Table 3: Effects of curcumin: Human studies

Condition	Concentration in curcumin	Serum effect	Other effect	Reference
Type II DM dyslipidemia patients	200 mg/capsule/day; 12 weeks	• Increase in HDL level • Decrease in LDL level • Decrease in glucose level	• Decrease in BMI	[51]
Healthy individuals patient	6 g; 30 and 60 min	• Increase in insulin level	• No other effect	[50]
Type II DM patients	200 mg/day; 14 weeks	• Decrease in glucose level • Decrease in HbA1c level	• No other effect	[52]
Diabetic nephropathy	22.1 mg/day; 2 months	• Decrease in LDL level • Decrease in glucose level • Decrease in cholesterol level	• Decrease in Urinary IL-8 level • Decrease in proteinuria	[53]
Diabetic patients	200 mg/day; 4 weeks	• No measured effects	• Decrease in skin flux • Increase in PO_2 level • Increase in Venoarteriolar response	[54]
Pre- diabetic patients	150 mg/day; 9 months	• Decrease in insulin level • Decrease in C-peptide level • Decrease in glucose level	• Increase in β-cells function • Decrease in diabetes	[55]
Overweight diabetic patients	300 mg/kg; 3 months	• Increase in LPL level • Decrease in glucose level • Decrease in HbA1c level • Decrease in total fatty acid level	• Decrease in HOMA-IR	[56]
Obese patients	1 g/day; 30 days	• Decrease in triglyceride level	• No other effects	[57]
Metabolic syndrome patients	630 mg/thrice/day; 12 weeks	• Increase in HDL level • Decrease in LDL level	• No other effects	[58]
Fasting glucose impaired patients	125 mg/twice/day; 8 weeks	• Increase in HDL level • Decrease in fasting insulin level	• Decrease in HOMA-IR	[59]
Type II DM patients	1500 mg/thrice/day; 10 weeks	• Decrease in glucose level	• Decrease in mean weight • Decrease in BMI	[60]

HbA1c: Hemoglobin A1c

beta-cells than alloxan, which severely harms other cell types that express glucose transporter 2, is one explanation for this (systemic toxicity).[44]

BIOLOGICAL EFFECT OF CURCUMIN: HUMAN STUDIES

In Table 3, the biological effects of administering curcumin to healthy individuals and diabetic patients are compiled and explained. A 6 g dose of curcumin administered to healthy volunteers in a crossover trial led to a significant rise in serum insulin levels at 30 and 60 min in response to a 75 g oral glucose tolerance test.[50] Blood glucose levels were unaffected by curcumin consumption.[50] These data suggest that curcumin administration influences insulin secretion.

The clinical investigations in Table 3 show that giving curcumin to people with prediabetes and diabetes improved glucose and lipid homeostasis, enhanced beta-cell function, and slowed the course of diabetes. Curcumin treatment also enhanced antioxidant activity and kidney and liver function. These results imply that curcumin has potent diabetic-lowering properties. Further studies are required to determine the effective clinical dosage and temporal administration of curcumin.

CONCLUSION

Ayurvedic remedies have historically employed turmeric, which contains curcumin. It is efficient in treating numerous diseases and has numerous advantages. Curcumin, a naturally occurring anti-inflammatory and anti-diabetic substance, seems to be a safe and affordable substitute that is helpful for this condition, even though it is necessary to know its effective amount. Curcumin is a key component in the management of diabetes and in the prevention of the

disease and its complications. The major features of diabetes, such as insulin resistance, hyperlipidemia, hyperglycemia, and islet apoptosis and necrosis, may be impacted by Curcumin. *In vivo* animal studies examining the effect of curcumin indicate significant improved glucose and lipid homeostasis. Significant reductions were observed in serum lipid and glucose levels. Curcumin therapy reduced oxidative stress and lipid peroxidation while increasing antioxidant enzyme activity. Furthermore, mitochondrial biogenesis was improved with curcumin administration. Administration of curcumin to animal models of diabetic nephropathy resulted in improved kidney function.

The most prevalent form of diabetes among those who are younger in age is type I. Both wealthy and underdeveloped nations are seeing an increase in type I diabetes prevalence. Developing nations account for 85–95% of type II diabetes cases. According to estimates, 366 million people worldwide had diabetes in 2011; by 2030, this number will have to increase to million. About 80% of those with DM live in low- and middle-income nations. 4.6 million people perished in 2011 due of DM. The IDF estimates that 463 million people worldwide and 88 million individuals in Southeast Asia will have diabetes in 2020. India is home to 77 million of these 88 million individuals. According to the IDF, 8.9% of people have diabetes in this country. The number of children in India with type I diabetes is estimated by the IDF to be second only to that of children in the US. In the SEA region, it also accounts for the highest percentage of children who develop type I diabetes incidentally. About 2% of all deaths in India are attributable to diabetes, according to the World Health Organization.

In addition, numerous strategies are needed to overcome curcumin's poor bioavailability and restricted solubility. These include synthesis of curcuminoids and development of novel formulations of curcumin, such as nanoparticles, liposomal encapsulation, emulsions, and sustained released tablets. The development of a "super curcumin" is anticipated to result from curcumin improved bioavailability and convincing clinical trial findings, propelling this promising natural product to the forefront of therapeutic medicines for diabetes.

ACKNOWLEDGMENT

The authors would like to thank Principal and Management of college for their constant support and motivation.

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Source of Support: Nil. **Conflicts of Interest:** None declared.