

## Mini review

**CURCUMA LONGA AS MEDICINAL HERB IN THE TREATMENT OF DIABETIC COMPLICATIONS**KATARZYNA KARŁOWICZ-BODALSKA<sup>1\*</sup>, STANISŁAW HAN<sup>1</sup>, JULIA FREIER<sup>2</sup>,  
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**Abstract:** *Curcuma longa* L. (turmeric) of ginger family (*Zingiberaceae*) belongs to the group of oldest cultivated spice plants in the south-east Asian countries. For many years rhizome of this plant has been used also as a safe and active drug for the treatment of various chronic diseases, especially of diabetes mellitus (DM). The active substance of turmeric – curcumin (diferuloylmethane), possesses multiple therapeutic properties. In recent years, many detailed research (tests *in vitro* and *in vivo*) along with clinical trials have revealed its very valuable biological activities related to its anti-inflammatory, antioxidant and cancer preventive properties, which are presented in numerous publications (1-6). At the molecular level it has been stated that curcumin inhibits cell proliferation, metastasis creation and apoptosis. Currently, great attention has been focused on curcumin as a blocker of TNF-s, which are the principal mediators of most inflammation-related disturbances (7). The main cause of blocking the broadly extended pharmacological and clinical investigations of curcumin is its extremely low solubility in water and in organ fluids. This feature consequently limits its systemic bioavailability and makes use of curcumin as a therapeutic remedy (to date) difficult. The primary aim of presently conducted research is to achieve increased solubilization and bioavailability of this promising nontoxic agent.

**Keywords:** curcumin, diabetes mellitus, bioavailability, antioxidant

**Abbreviations:** AMPK – AMP-activated protein kinase (strong energy regulator, which controls whole-body glucose homeostasis in liver and key tissues in type 2-diabetes), COX-2 – cyclooxygenase 2, DM – diabetes mellitus, EPR – enhanced permeation and retention effect, FFA – free fatty acids, GSH – whole blood glutathione, HO-1 – heme oxygenase-1, iNOS – inducible nitric oxide synthase, LDL – low density lipoproteins, LOX – lipoxygenase, LPL – lipoprotein lipase, MCP-1 – monocyte chemoattractant protein 1, MMP-8 – neutrophil collagenase, NF-κB – nuclear factor-kappa B, NIDDM – non insulin dependent diabetes mellitus, Nrf2 – nuclear factor erythroid-2-related factor 2, responsible for phase 2 antioxidant and detoxification genes expression, PGE<sub>2</sub> – prostaglandin E<sub>2</sub>, PPAR-γ – peroxisome proliferator-activated receptor gamma, ROS – reactive oxygen species, SODC – superoxide dismutase and catalase, TMA – trimethylamine, TMAO – trimethylamine N-oxide, TNF-α – tumor necrosis factor-α

*Curcuma longa* L. (turmeric) (*Zingiberaceae*) has been known for centuries not only as one of the dietary spice plants of South-East Asia. Rhizome of this plant has also been used as a safe remedy against many ailments (mostly DM) in many countries, principally in China and India.

Recent investigations (2016) revealed hypolipidemic properties of ethanolic extract of turmeric which can be used in the treatment of hyperlipidemia. According to the authors “*India is the diabetic capital and leads the world with largest number of diabetic patients about 40.9 million in the year 2007 and probably to 69.9 million by the year 2025*” (8).

The active substance of turmeric forms yellow-orange powder (curcuminoids) with the main con-

stituent curcumin (77%) and its natural derivatives: demethoxycurcumin (DMC) (17%) and bisdemethoxycurcumin (BDMC) (6%) (9–11). In recent years, curcumin has gained great scientific attention because of its wide range of important pharmacological properties, including anti-inflammatory, antioxidant, antidiabetic, antiangiogenic, anti-mutagenic, anti-infective and anticancer activities. In the literature there are many publications describing the beneficial role of curcumin in the prevention and treatment of different chronic ailments (such as diabetes type 2, Alzheimer’s disease, multiple sclerosis, atherosclerosis, great variety of cancers) as well as in the improvement of its bioavailability in many organ disorders. Among them the reviews of teams led by M. Schaffer and B.B.

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Aggarwal are worthy special attention (6, 7, 10, 12–19). Publications from the recent years describe the activity of curcumin as a biologically available blocker of pro-inflammatory factors, being able to stimulate appearance of different diseases, first of all induced on the pro-inflammatory base or by oxidative stress (7). Currently used inflammatory blockers from TNF- $\alpha$  cytokine group (Infliximab, Humira, Enbrel), apart from their high costs are also related to the occurrence of side effects that often exceed the benefits of treatment. Curcumin is a natural substance inhibiting pro-inflammatory markers, which is highly safe, non-toxic (even in 8 g *pro die* dose), easily available, and side-effect-free (20). The chemical structure of curcumin was established over 100 years ago by a group of Polish researchers (Kostanecki, Lampe and Miłobędzka) who also confirmed it later by total synthesis (9, 19). A lot of detailed investigations are connected with biomedical turmeric application into the treatment of diabetes and diabetes-related complications (10) and also with the elaboration of active nanotechnological formulations of this natural product in order to enhance its solubility and bioavailability (2). The researchers and practitioners are concerned about difficulties to use curcumin beneficial properties in practice. In this context several formulations have been proposed, such as the encapsulation of curcumin in liposomes or in polymeric micelles, complex formations with cyclodextrin, polymer-curcumin conjugates and others to ameliorate its physical and biological properties. A parallel increase in liposomal curcumin solubility and its activity is observed. (2, 21). This present review shortly synthesizes results from several latest reviews and the investigation data (from June 2015 till February 2016), indicating the opportunities of application of curcumin in the traditional medicine in spite of its adverse physicochemical properties (mainly of hydrophobic nature), biological instability (poor absorption, rapid metabolism in the gastro-intestinal tract) and consequently limited bioavailability.

#### Physico-chemical properties of curcumin

Curcumin – yellow-orange substance, chemical formula  $C_{21}H_{20}O_6$ , 1.7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1.6-diene-3.5-dione; m.w. 368.39 g/mol, m. p. 187-188°C, poorly soluble in water (0.6  $\mu\text{g/mL}$ ) and most organic solvents, appears in nature in two tautomeric: keto and enol forms; the enol form is more stable in the solid state and in solution. Maximum absorption ( $\lambda_{\text{max}}$  in methanol) at 430 nm. (2, 9, 23).

Extraction of curcumin from its natural source (*Curcuma longa* rhizoma) involves neither difficulties nor significant costs. Its main obstacle in

conducting both clinical and chemical studies is – in the opposition to other TNF inhibitors – its low bioavailability. Numerous research reported that curcumin is poorly absorbed from gastrointestinal tract, metabolized (*via* glucuronidation and sulfation) and eliminated rapidly. Only the small amount of curcumin is distributed from blood to tissue. Mostly, the concentration level of curcumin in tissues remains under the detection limit. Therefore, numerous formulations were created in order to improve bioavailability of this compound. Although nanotechnology gives an opportunity to increase hydrophobic drugs absorption, little research was conducted on curcumin nanoparticles (20). Liposomes can carry hydrophobic and lipophobic particles due to its amphiphilic properties. Liposome-encapsulated curcumin is now being developed to be introduced into clinical trials as it has a more potent growth-inhibitory effect on colorectal cancer in *in vivo* trial than oxaliplatin (24). Another approach to improve curcumin absorption includes the modification of its chemical structure to create analogues with more favorable properties.

#### Curcuminoids

The name curcuminoids refers both to the natural diferuloylmetane derivatives (curcumin, DMC, BDMC) and synthetic curcumin analogs, among which tetrahydrocurcumin (THC), bis-o-hydroxycinnamoylmethane, bis-1.7-(2-hydroxyphenyl)-hepta-1.6-diene-3.5-dione (BDMC) analogs and two new curcumin derivatives C66 and B06 have been studied (10). All above-mentioned (mainly synthetic) curcuminoids have better solubility and bioavailability than curcumin.

#### Biological activity

##### Anti-inflammatory

Numerous *in vivo* and *in vitro* trials conducted by Aggarwal's team (7) have shown that curcumin inhibits the activity of pro-inflammatory agents related to the occurrence of many above-mentioned chronic diseases. In a comprehensive review (including 263 literature positions) authors have ascertained that curcumin binds directly to TNF, blocking both its synthesis and activity, which makes this substance an important factor in the prevention and treatment of many civilisation diseases like DM, cancer and skeletal system disorders. The authors report that there is no sufficient evidence nowadays which could confirm the curcumin's inhibitory action on the TNF- $\alpha$  production in human organism. However, its properties preventing tumor invasion and metastasis have been stated (*in vitro* in

anticancer models). Several studies in the past also showed that curcumin enhances apoptosis activity and that it is one of the main mechanisms of tumor inhibition induced by this substance, and that treatment using curcumin cause a rapid increase in ROSs and a decrease in mitochondrial membrane potential events, leading to apoptosis activation (7, 13, 19). Curcumin inflects TNF- $\alpha$  synthesis by specific acetyltransferase inhibition, which causes histone-nonhistone protein acetylation decrease and – as a

result – the inhibition of the transcription factor (25). The modulation of TNF- $\alpha$  expression by curcumin may also occur by the inhibition of this biomarker’s methylation model (26). Curcumin also alternates the activity of hepatic enzymes, connected with glycolysis, gluconeogenesis and lipid metabolism. It acts protectively (in dose-dependent manner) in hypoxia, restrains toxic effect in adipocytes by lowering the level of pro-inflammatory cytokines and also protects liver and kidneys in paracetamol poi-

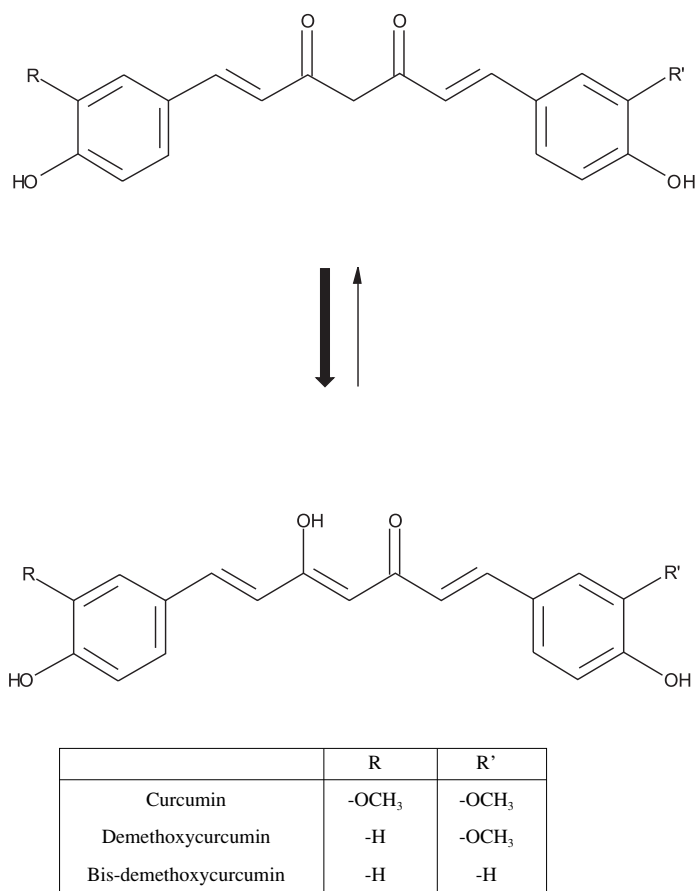


Figure 1. Curcumin (keto and enol form), demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC)

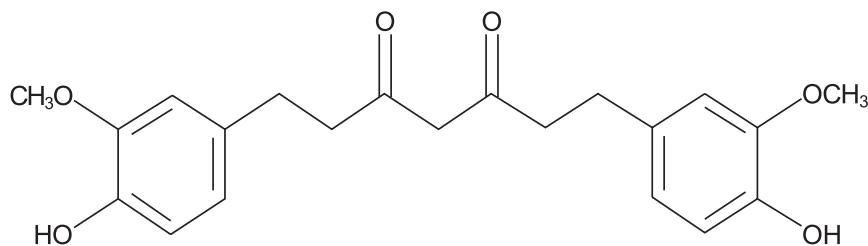


Figure 2. Tetrahydrocurcumin

soning by reducing MMP-8, IL-1, IL-8, TNF- $\alpha$  and acute phase protein secretion (27). Curcumin ameliorates inflammatory responses associated with asthma by its ability to upregulate Nrf2/HO-1 and regulate of TNF- $\alpha$ , (IL-1 $\beta$ ) and IL-6 production (11, 28, 29). Newly synthesized curcumin analogues reduce TNF- $\alpha$ , NO synthesis, lower mRNA IL-1 $\beta$ , TNF- $\kappa$ , IL-6, IL-12, COX-2 and iNOS levels. Similarly, a new standardized preparation of curcuminoids (NCB-02) has been shown to possess in clinical trials the profitable effect on endothelial dysfunction attributed to its antioxidant and anti-inflammatory mechanisms (10).

### **Antioxidant**

The antioxidant action of curcumin determines its chemical structure as keto-enol form of the molecule. Produced after some transformations, the metabolic phenoxyl-radical form of curcumin is able to scavenge the ROS. The antioxidant, chelating and anti-free radical activities of curcumin are available mainly in the poisonings of many organs (mainly liver) by the heavy metals or other toxins (30). Dall'Acqua et al. inform, that the study of *in vivo* antioxidant activity cannot be realized "due to the complex multiple targets of purified natural products or extracts possessing this effect" (11). Current studies of antioxidant phytochemicals are conducted with individual compounds and their effects support the limited number of markers.

### **Curcumin in DM treatment**

DM is a chronic, metabolic disease which mainly affects pancreas and its symptoms are the lack or deficiency of insulin and permanent high sugar level in blood. Two types of diabetes are characterized: type 1 (insulin-dependent) – which often affects young people and is caused by impairment and total inability to synthesize insulin by pancreas and needs permanent insulin taking; and type 2 (insulin independent) in which pancreas synthesizes insulin but cells become insulin resistant. This status leads to three diabetes characteristic serious complications: *polyuria*, *polyphagia*, *polydipsia*. A patient should be treated immediately and be under constant physician supervision. A beneficial role of turmeric in diabetes treatment has been known and practiced in Ayurveda medicine for thousands years. Scientists paid great attention to curcumin and after many research results prove that this compound lowered the level of glucose in blood in patients with diabetes type 2. During only one year about 200 turmeric-related studies were published. Most of them referred to curcumin usage as a glucose

level controlling agent in rodent models (mostly rats). Commonly used models were alloxan-, streptozotocin-, streptozotocin with nicotinamide-induced diabetes. Curcumin was administered to all diabetic animals orally in different time intervals. The reduction of glucose, hemoglobin (Hb) and glycosylated hemoglobin (HbA1C) levels in blood and the increase of sensitivity to insulin was observed in all examined models.

The mechanisms of positive curcumin effects on diabetes can be explained by e.g., the modulation of signaling molecules function, the level of transcription factors (like TNF- $\alpha$ ) and free fatty acid lowering, activity of NF- $\kappa$ B, lipid peroxidase and lysosomal enzymes inhibition (10).

Curcumin also shows an ability to increase the level of insulin in plasma and the sensitisation of lipoprotein lipase. A suppressing effect on glucose-6-phosphatase and phosphoenolpyruvate carboxylase activity leads to downregulation of blood glucose concentration (31). Curcumin acts as anti-diabetic agent due to its anti-inflammatory and anti-oxidative properties, which can not only affect blood enzymes and factors activity, but also increase  $\beta$ -islets glutathione level and therefore, lower its damage caused by oxidative stress (32). Curcuminoids performed antidiabetic activity, caused lipid profile improvement by lowering their oxidation in pancreas, liver and aorta as well as post-diabetic brain complications improvement in diabetic rats by the stimulation of anti-oxidative defensive mechanisms and the reduction of mitochondrial dysfunction (33). However, the most potent anticancer, cardioprotective, neuroprotective and antidiabetic action among these three natural curcuminoids (curcumin, DMC, BDMC) is performed by the first compound (19). New synthetic curcumin analogues (C66 and B06) reduce TNF- $\alpha$  and NO synthesis and lower mRNA levels of IL-1 $\beta$ , TNF- $\kappa$ , IL-6, IL-12, COX-2 and iNOS (34).

### **Most common diabetes complications**

#### ***Hepatic steatosis***

Hepatic steatosis is the most frequently observed disease in diabetic patients. M. Prentki et al. (35) have proven that curcumin administration to STZ-induced diabetic rats leads to the decrease of liver weight and the level of lipid peroxidation products in plasma and urine. P.S. Babu et al. have confirmed those observations (36, 37) and stated that the beneficial role of curcumin can be seen observing animals' weight or glycemia and that STZ-diabetic rats fed with curcumin diet for 8 weeks excreted less protein, urea and inorganic phosphorus. The

tendency of lowering total cholesterol and LDL was shown in a clinical trial with the participation of 63 people with acute coronary syndrome. The patients administered 45 mg of curcumin daily for two months (38). Similar effects were obtained by M.I. Yousef et al. (39). Curcumin administered orally to rats with sodium arsenite-induced liver impairments caused total amount of lipid, cholesterol, TG and LDL-c level decrease. Diabetes type 2 may trigger changes in adiponectin secretion. Adipose tissue has an essential impact on the maintenance of proper glucose level in the whole body (40).

### **Nephropathy**

Diabetes nephropathy is a dangerous complication connected with diabetes type 2 that manifests itself with constant proteinuria, progressive decrease of glomerular filtration rate and the increase of blood pressure. Curcumin acts supportively by the increase of urea nitrogen blood level and creatine clearance, and the decrease of albuminuria and enzymuria (N-acetyl-D-glucosaminidase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase and alkaline / acid phosphatases) (10). According to A.T. Reutens, diabetic nephropathy is the main cause of chronic kidney disease and one of the most significant long-lasting complications that sometimes lead to death (41). Curcumin treatment is beneficial and may lead to improvement because of mechanisms mentioned above. Clinical trials confirmed a significant role of curcumin in the last stage of disease (kidney integration reconstruction by glutathione, antioxidant enzymes – e.g., peroxide dismutase, superoxide dismutase and catalase, glucose 6-phosphate dehydrogenase, LDH, aldose reductase, transaminase level normalization).

### **Diabetic vascular disease (1)**

According to studies, an inflammation is the main factor responsible for the occurrence of cardiovascular disease. Renal failure, which often afflicts diabetics can also lead to cardiovascular disorders. Curcumin administration lowers oxidative stress by increasing eNOS expression (endothelial nitric oxide synthase) and decreasing superoxide production (42). Curcumin's ability to reduce COX-2 activity and normalize prostanoid products ratio (PGI<sub>2</sub>/TXA<sub>2</sub>) was proven on STZ-induced diabetes rat model. High glucose in blood may lead to serious damage in erythrocytes. Curcumin acts protectively by the regulation of aldose reductase and red blood cell membrane enzymes. Turmeric also accelerates wound healing in rats and guinea pigs through the improvement of neovascularization and reepithelialization.

### **Diabetic neuropathic disease**

Curcumin (as it has been presented above) has many biological activities, shown mostly through its antioxidant and anti-inflammatory properties. Because of microvascular injury neuropathy disorders also belong to the DM-associated complications. Research has shown the neuroprotective action of aqueous extract of turmeric combined with metformin and proved that *Curcuma* delays the occurrence of diabetes-induced neurodegenerative complications (43).

## **CONCLUSIONS**

A dietary spice – rhizomes of *Curcuma longa* L. (turmeric) from the ginger family (Zingiberaceae) have been used for years in India and in China as a beneficial remedy against many chronic ailments (mostly diabetes). As it has been shown, curcumin (diferuloilmethane), the active substance of turmeric, possesses significant anti-oxidative, anti-inflammatory and anticancer properties. The research (*in vitro* and *in vivo*) has proved that curcumin can also suppress the activity of some signaling molecules (such as transcription factors, various enzymes, for example protein kinases) and this way can modulate the inflammation process, gene expression and potentially control the effectiveness of curcumin treatment of many organ disorders, principally diabetes mellitus and its complications. However, in almost all papers quoted in this review, very poor bioavailability of curcumin is emphasized. In connection with its rapid metabolism as well as extremely low serum levels after oral administration it makes up to date use of curcumin as a therapeutic agent quite impossible. In spite of these difficulties, recent research has aroused the great interest of scientists all over the world to valuable biological properties of turmeric, particularly of curcumin and confirmed its important role in the prevention and treatment of many disturbances especially related to its antioxidant, anti-inflammatory and cancer preventive activities. In the era of the increase of diabetes incidence, it is important to support the treatment of its complications as it lowers the total costs of patients' therapy and improves their quality of life.

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