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Invited review

The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update

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ABSTRACT

The concept of using phytochemicals has ushered in a new revolution in pharmaceuticals. Naturally occurring polyphenols (like curcumin, morin, resveratrol, etc.) have gained importance because of their minimal side effects, low cost and abundance. Curcumin (diferuloylmethane) is a component of turmeric isolated from the rhizome of *Curcuma longa*. Research for more than two decades has revealed the pleiotropic nature of the biological effects of this molecule. More than 7000 published articles have shed light on the various aspects of curcumin including its antioxidant, hypoglycemic, anti-inflammatory and anti-cancer activities. Apart from these well-known activities, this natural polyphenolic compound also exerts its beneficial effects by modulating different signalling molecules including transcription factors, chemokines, cytokines, tumour suppressor genes, adhesion molecules, microRNAs, etc. Oxidative stress and inflammation play a pivotal role in various diseases like diabetes, cancer, arthritis, Alzheimer's disease and cardiovascular diseases. Curcumin, therefore, could be a therapeutic option for the treatment of these diseases, provided limitations in its oral bioavailability can be overcome. The current review provides an updated overview of the metabolism and mechanism of action of curcumin in various organ pathophysiologies. The review also discusses the potential for multifunctional therapeutic application of curcumin and its recent progress in clinical biology.

1. Introduction

Curcumin is the active ingredient of the dietary spice turmeric and is extracted from the rhizomes of *Curcuma longa*, a plant in the ginger family. It was first discovered about two centuries ago when Vogel and Pelletier reported the isolation of a "yellow coloring-matter" from the rhizomes of Curcuma longa (turmeric) and named it curcumin (Vogel and Pelletier, 1815). Milobedzka and Lampe first showed the chemical structure of curcumin (Milobedzka et al., 1910). Turmeric, the common source of curcumin, has been used for medicinal purposes for years, mostly in Asian countries as the different beneficial properties of curcumin are well known. Therefore, in this review the focus is on some aspects of curcumin including its effect on anti-inflammatory diaseases, diabetes and Alzheimer's disease (AD). Its modulating activities on cellullar signalling molecules involved in pathophysiology in various organs and tissues, along with some current clinical reports are also discussed.

2. Physical and molecular properties of curcumin

The chemical name of curcumin is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione, defining the chemical formula as $C_{21}H_{20}O_6$. Its pKa value is 8.54. Curcumin predominately resides in its keto form in acidic and neutral conditions and also in

Abbreviations: ROS, Reactive Oxygen Species; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); Aβ, Amyloid beta; IL-1β, Interleukin 1beta; ICAM, intracellular cell adhesion molecule1; VCAM, vascular cell adhesion molecule; LPS, lipopoly saccharide; MCP1, Monocyte chemo attractant protein 1; PGE_2, Prostaglandin E2; iNOS, inducible nitric oxide synthase; TNFα, Tumour necrosis factor alpha; TLR, Toll like receptor; BACE1, Beta-site AAP cleaving enzyme 1; IL-12, 8, 5, 18, interleukin 12, 8, 5, 18; MIP1α, Monocyte inflammatory protein 1 alpha; COX-2, Cyclooxygenase 2; AMPK, 5′ adenosine monophosphate-activated protein kinase; ELAM1, endothelial-leukocyte adhesion molecule1; LOX, lipooxygenase; HUVEC, Human umbilical vein endothelial cells; NO, nitric oxide; COX, cyclooxygenase1; VEGF, vascular endothelial growth factor; TGFβ1, Transforming growth factor β1; CRP, C-reactive protein; VSMC, Vascular smooth muscle cells; SOCS1, suppressor of cytokine signalling proteins; PARP, poly (ADP-ribose) polymerase 1; HIF, Hypoxia inducing factor1; AIF, Apoptosis inducing factor; ATF4, Activating transcription factor 1; XBP1, X-box binding protein 1; PERK, PKR like ER kinase; GADD153, Growth arrest and DNA damage inducible.

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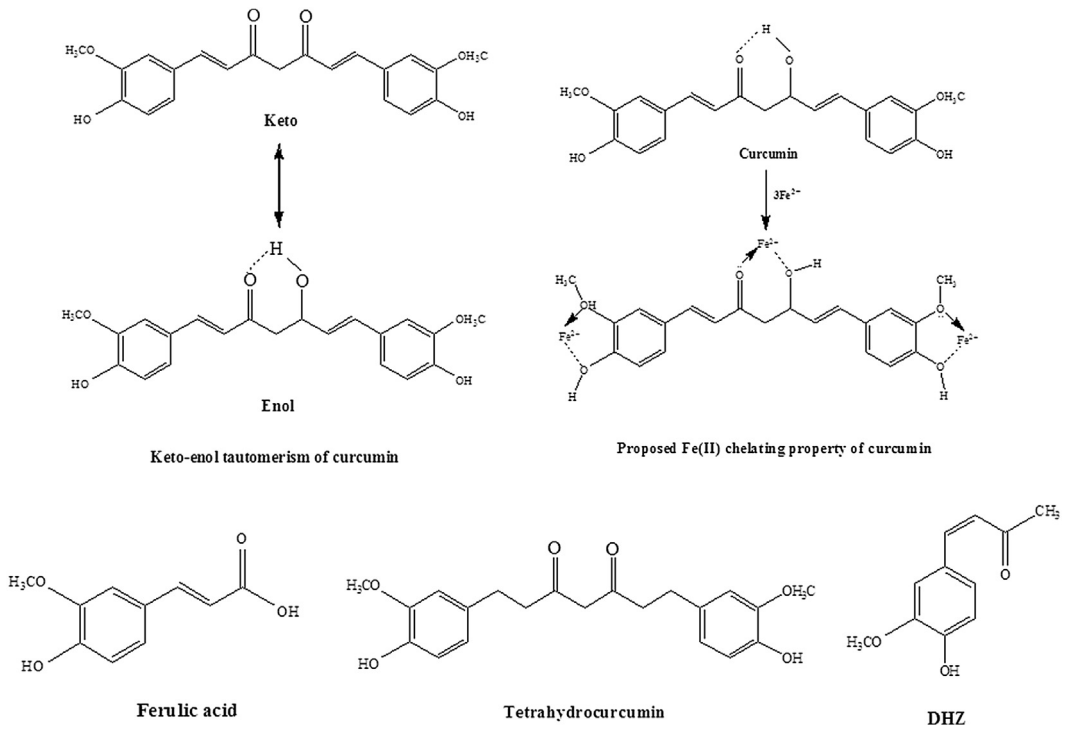

Fig. 1. Curcumin and its analogues.

solid phase (Fig. 1). The chemical structure makes it much less soluble in water at acidic and neutral pH but soluble in methanol, ethanol, dimethyl sulfoxide (DMSO) and acetone. It is reported that the maximum absorption (λ_{max}) of curcumin in methanol occurs at 430 nm (Aggarwal et al., 2003; Goel et al., 2008).

3. Metabolism of curcumin and its bioavailability

A number of studies showed that curcumin undergoes metabolism upon oral administration in animals and almost each and every metabolite produced has some beneficial effect apart from their antioxidant property. Firstly, curcumin becomes O-conjugated to form curcumin glucuronide and curcumin sulphate, then undergoes bio-reduction into tetrahydrocurcumin, hexahydrocurcumin, octahydrocurcumin, and hexahydrocurcuminol [Fig 2] in rats, mice and humans *in vivo*, as well as in rat hepatocytes in culture (Asai and Miyazawa, 2000; Ireson et al., 2001; Sharma et al., 2001). Reduced curcumin then undergoes glucuronidation to be converted into curcumin glucuronide, dihydro-curcumin-glucuronide, tetrahydrocurcumin-glucuronide, and curcumin sulphate (Holder et al., 1978).

Numerous evidences indicate that curcumin is potentially effective and safe. U.S. Food and Drug Administration has approved curcumin as a "Generally Regarded As Safe" compound and the daily intake of curcumin at a dose of 0.1–3 mg/kg-BW has been considered as an acceptable dose by the Joint FAO/WHO Expert Committee on Food Additives, 1996 (Clinical development plan: curcumin, 1996). In spite of this, the use of curcumin is mainly limited because of its poor pharmacokinetic and pharmacodynamic profile, i.e., poor absorption, short half-life and rapid metabolism in the GI tract. Studies on the uptake and bio-distribution of dietary curcumin in rodents showed that after oral ingestion, peak serum levels of curcumin are very low (Anand et al., 2007). The dose of 2 g/kg resulted in 1.35 g/mL peak serum levels (Shoba et al., 1998) and in humans, a daily dose of 4–8 g resulted in peak serum levels of 0.4–3.6 μM after 1 h. Phase I clinical trials have indicated that curcumin is safe even at a dose of 12 g/day in humans but exhibits relatively poor bioavailability (Anand et al., 2007).

Recently, several strategies have been taken to improve the bioavailability of curcumin. Among them, conjugation is getting much attention. Several structural modifications of curcumin (i.e. conjugation) have been tested including chitosan-coated curcumin, liposome encapsulated curcumin, nanocurcumin, polylactic-co-glycolic acid encapsulated curcumin and cyclodextrin encapsulated curcumin etc. In one of such studies, amorphous curcumin nanosuspensions were designed using the anti-solvent precipitation method with β-lactoglobulin (β-lg) as a stabilizer which enhanced ~35-fold solubility of the amorphous curcumin nanosuspension due to the reduced size and lower crystallinity. Bioavailability was also enhanced significantly as observed from an in vitro study using Caco-2 cell lines (Aditya et al., 2015). A significant increase in its bioaccessibility was also obtained by excipient food emulsions technique (Zou et al., 2015) and nanotized curcumin (Nehra et al., 2015).

Encapsulation within lipid particles is also a solution to improve the bioavailability of curcumin. In a recent study, its uptake was improved significantly by piperine addition only in the case of oil-in-water emulsions stabilized by Poloxamer 407 (Gulseren et al., 2014).In addition, enhanced solubility and bioavailability of curcumin was reported by a new curcumin dripping pills (Cur-DPs) formulation (Hu et al., 2015).

A recent study also suggested that curcumin loaded PLGA-poloxamer blend of nanoparticle induces a persistent block in G0/G1 phase of mesothelioma cells up to 72 h, thereby overcoming the drug tolerance phenomenon, normally evidenced with free curcumin (Mayol et al., 2015).

Curcumin conjugated nano liposome could directly interact with amyloid plaque and partly inhibited Aβ induced cell death