British Journal of Medicine & Medical Research
17(6): 1-13, 2016, Article no.BJMMR.28370
ISSN: 2231-0614, NLM ID: 101570965

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Curcumin as a Bioactive Component

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Authors' contributions

This work was carried out in collaboration between both authors. Author SH wrote the manuscript and created the table. Author MLF edited the manuscript, agreed with the content and created figure 2. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/28370
Editor(s):
(1) Chan-Min Liu, School of Life Science, Xuzhou Normal University, Xuzhou City, China.
Reviewers:
(1) Obeagu,Emmanuel Ifeanyi, Michael Okpara University of Agriculture,Umudike,Abia State, Nigeria.
(2) Rajendra Nath, King George's Medical University, Lucknow (Up), India.
Complete Peer review History: http://www.sciencedomain.org/review-history/15809

Review Article

Received 16th July 2016
Accepted 10th August 2016
Published 20th August 2016

ABSTRACT

Curcumin, a bioactive polyphenol found in the plant Curcuma longa is a natural supplement available worldwide. Curcumin has been recognized for its anti-oxidant and anti-inflammatory properties for a number of years. Further, its therapeutic potential has been demonstrated in animal studies and clinical trials. Numerous reports exist on the mechanisms of action by which curcumin can protect against those chronic diseases associated with oxidative stress and inflammation. Several studies have addressed the effects of curcumin on Alzherimer's disease, type 2 diabetes, cardiovascular diseases and asthma. Although, curcumin has been shown to directly affect inflammatory pathways and production of inflammatory cytokines as well as to effectively scavenge free radicals and improve endothelial function, a number of clinical trials have failed to demonstrate efficiency due to its poor bioavailability, physicochemical instability and rapid metabolism. The use of nanoencapsulation to improve delivery of curcumin to target tissues suggests that nanodelivery could increase the healing efficiency of curcumin. In this review, the therapeutic potential of curcumin to protect against chronic disease and the underlying mechanisms will be discussed.

Keywords: Curcumin; availability; Alzheimer's disease; cardiovascular disease; type-2 diabetes; asthma.

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ABBREVIATIONS

Aβ: β-amyloid; AD: Alzheimer's disease; AGE: Advanced glycation end products; CMC: curcumin-carboxymethyl chitosan; CVD: cardiovascular disease; HO-1:Haem oxygenase-1; HbA1c:glycosylated hemoglobin; LOX-1: lectin-like oxidized LDL receptor-1; NFkβ:MCP-1:monocyte chemotactic protein-1: Nrf-2: Nuclear factor erythroid-2 related factor 2; NF kβ; Nuclear factor kβ; NO: nitric oxide; ROS: reactive oxygen species; VSMC: Vascular smooth muscle cell.

1. INTRODUCTION

Curcumin, a member of the ginger family is a bioactive polyphenol found in the rhizomes of turmeric (*Curcuma longa)*. In 1815, Vogel and Pelletier [1] isolated for the first time this bright yellow chemical from *Curcuma longa* and named it curcumin. Later in 1910, Vogel and Pellatier [2] identified the chemical structure of curcumin. Curcumin or 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione, is also represented by its condensed formula $C_{21}H_{20}O_6$ [3]. Commercially available curcumin powder commonly contains two curcuminoids: 17% demethoxycurcumin and 3% bisdemethoxycurcumin [4]. At room temperature, curcumin is a bright yellow-orange powder with a molecular weight of 368.39 g/mol. It is a hydrophobic compound capable to dissolve in organic solvents, including methanol, ethanol, acetone, and dimethyl sulfoxide. However, in alkaline aqueous solution, the curcumin molecule is deprotonated and its water solubility increases. Curcumin has three different pKa values of 8.54, 9.30 and 10.69, corresponding to the dissociation of protons in the enolic and the two phenolic groups [5]. Typically, curcumin has maximum absorption at 415–420 nm and 430 nm in the UV/visible absorption spectra when dissolved in methanol and acetone, respectively [6].

The natural source of curcumin, turmeric, has been used as an herbal medicine and as a food colorant in Asian countries for centuries. Nowadays, as a safe natural supplement, curcumin is available worldwide. According to the Joint FAO/WHO Expert Committee on Food Additives, daily consumption of 0.1–3 mg/kg has been established as an acceptable dose for curcumin [7]. Curcumin has been granted Generally Recognized as Safe (GRAS) status by the Food and Drug Administration. Abundant research findings support that curcumin may have favorable anti-oxidant, anti-inflammatory, antimicrobial and antifungal properties [8-11]. Curcumin may exhibit its antimicrobial and antifungal properties by suppressing the growth of pathogens and activating immune responses of the host, including M1 macrophage activation [9,10]. Further, during the past three decades, numerous clinical trials have provided evidence of therapeutic potentials from this phytochemical against a wide range of human chronic diseases, including type 2 diabetes [12], autoimmune diseases, asthma [13], inflammatory bowel disease [14], rheumatoid arthritis [15], cardiovascular diseases [16], and cancer [17,18]. Thus curcumin could be considered as a safe therapeutic option for chronic diseases. The following paragraphs will provide an updated review of the beneficial effects of curcumin on a variety of chronic diseases, including Alzheimer's disease (AD), type 2 diabetes and cardiovascular diseases (CVD) as well as the underlying mechanisms.

2. ANTI-OXIDANT PROPERTIES OF CURCUMIN

The antioxidant properties of curcumin have been recognized since 1948, when it was first reported that curcumin was partly responsible for the antioxidant properties of vegetable oils [19]. Curcumin has been demonstrated to inhibit reactive oxygen species (ROS), nitric oxide (NO) formation and scavenge free radicals in a number of *in vitro* studies [20-22]. Curcumin molecules have been reported to quench excited superoxide radicals by donating protons to those superoxides [23]. Basically, two major sites in the curcumin molecules are responsible for proton donation: The first one is the central methylene group, which is adjacent to the two highly activated carbonyl groups in the feruloyl-methane skeleton. In the redox reaction, massive delocalization of the unpaired electron on the adjacent oxygen atoms will induce breakdown of C–H bonds in the methylene group, providing protons to free radicals. The second one is the hydroxyl groups located on phenolic rings of curcumin molecules. At the beginning, one phenolic hydroxyl group is able to donate protons and thus turns the curcumin molecule into a phenoxyl radical. The ability for this phenoxyl radical to scavenge oxidizing free radicals is dramatically higher than the original molecule by donating the second hydrogen atom to free radicals from the other phenolic hydroxyl group,

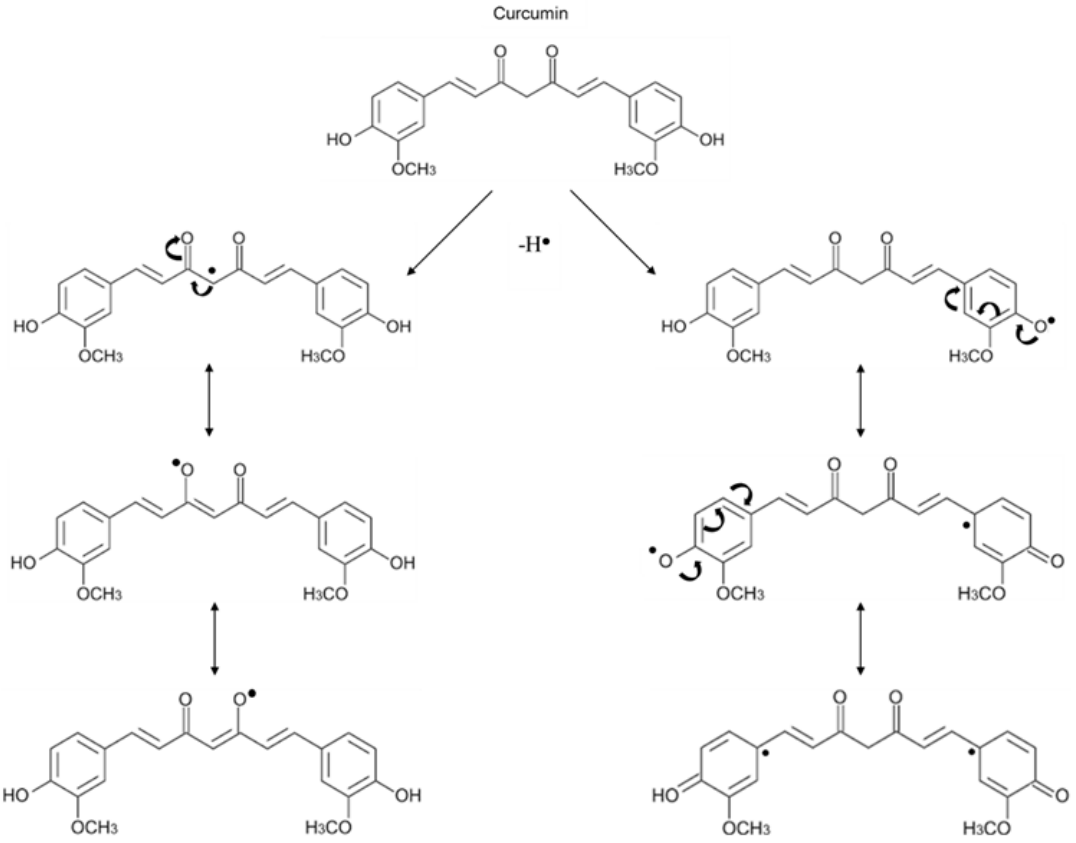

Fig. 1. Sites for proton donation for the curcumin molecule

thereby forming a diradical. This diradical may be further degraded into smaller phenols such as ferulic acid, vanillic acid and feruloylmethane or converted into stable compounds like quinones [3]. The sites for proton donation in the curcumin molecule are represented in Fig. 1 above.

3. ANTI-INFLAMMATORY PROPERTIES OF CURCUMIN

Many studies have indicated curcumin is able to modulate the nuclear factor Kappa β (NF-κβ) pathway [24-26], which has close links to both oxidative stress and the inflammatory response. Curcumin inhibits the NF-κβ pathway by chelating and scavenging ROS, the stimulus for the NF-κB pathway activation [27,28]. Moreover, curcumin can also suppress NF-κB activation through inhibiting the degradation of inhibitor kβ (IkB) and modifying the NF-κB/IκB complex, in order to retain NF-κB in the inactive form [27]. Subsequently, curcumin suppresses a variety of NF-κB dependent pro-inflammatory factors by blocking this pathway. For instance, in an alcoholic liver disease study, Nanji et al. [29] reported curcumin suppressed the expression of tumor necrosis factor-α (TNF-α), interleukin (IL)-12, monocyte chemotactic protein-1 (MCP-1), and cyclooxygenase-2 both *in vitro* and *in vivo*. They also observed curcumin reduced the binding activity of NF-κB to downstream genes[22].

Curcumin also modulates Nuclear factor erythroid-2 related factor 2 (Nrf2), a pathway that is closely associated with oxidative stress and inflammation. By binding and cooperating with target genes, Nrf2 regulates the innate immune system and represses pro-inflammatory gene inductions [30]. By activating the Nrf2/Haem oxygenase-1 (HO-1) pathway, curcumin has been shown to ameliorate expression of TNF-α, IL-1β and IL-6 and the inflammatory responses in asthma [31]. Later, Li and colleagues [32] revealed curcumin lowered both serum and liver TNF-α and IL-6 level in a rat model via activation and modulation of the Nrf2–Keap1 signaling pathway. They suggested curcumin enhanced Nrf2 expression at both transcriptional and translational levels.

4. CURCUMIN AND CHRONIC DISEASES

4.1 Curcumin and Alzheimer's Disease

Alzheimer's disease (AD) is considered as a progressive neurodegenerative disease. It is characterized by progressively deteriorated cognition along with challenging behavior. According to a recent report, approximately 5.2 million Americans are suffering from AD. Further, during the period 2000 to 2010, the proportion of deaths resulting from AD increased by 68% in the US [33]. Ng et al. [34] reported that regular curcumin consumption resulted in better cognitive performance in the elderly, indicating curcumin may be a possible choice for AD treatment.

Abnormal extracellular deposition of β-amyloid (Aβ) peptides is hypothesized as the fundamental cause of AD and modulation of amyloid peptides clearance is one of the therapeutic effects of curcumin against this disease. Yang and colleagues [35] revealed that low-dose and chronic oral consumption of curcumin dramatically inhibited amyloid level and plaque burden in transgenic mice. They demonstrated that curcumin directly binds small Aβ fragments, thus blocking their aggregation both *in vitro* and *in vivo* via binding to the N terminus of Aβ monomers [36]. Interestingly, a recent report indicated curcumin reduced the toxicity of β-amyloid aggregates by encouraging the formation of nontoxic soluble oligomers and prefibrillar aggregates instead of inhibiting the aggregation of Aβ [37].

In addition to the direct interaction with Aβ molecules, curcumin may also modulate the innate immune system thereby promoting the clearance of Aβ deposits by utilizing its anti-inflammatory properties. In AD mice models, the Aβ-binding ability and phagocytosis capacity of microglia are impaired, as a result of chronic inflammation [38]. He and colleagues [39] reported curcumin ameliorated defective microglial phagocytosis by restoring the expression of milk fat globule-EGF factor-8 protein, suppressing the expression of NF-κB p65 and phospho-signal transduced and activator of transcription-3.

Metal ions like Cu^{+2} and Zn^{+2} are widely distributed in the brain and closely related to Aβ plaque formation. Dysregulation of the homeostasis of these ions encourages their binding with Aβ and subsequent Aβ aggregation, contributing to progression of AD [40]. By reducing Cu^{+2} to Cu^{+1}, Aβ releases ROS, resulting in oxidative damage to neural cells [41]. As an efficient metal chelator, curcumin is able to bind to copper, zinc and iron ions [42]. Therefore this property can also potentially contribute to the protective effects of curcumin against AD. In addition, a microscopic study revealed curcumin significantly compromised the formation of β-sheet of the Aβ peptide, which is promoted by metal ions such as Cu^{+2} and Zn^{+2} in a time dependent manner. It is known that β-sheet structure facilitates aggregation of Aβ [43].

Recently, Kochi et al. [44] studied the reactivity of curcumin and its derivatives with Aβ particles with/without metal association. According to the results, compared to free curcumin and Cur-S (a water-soluble form of curcumin), Gd-Cur (curcumin conjugated to a potential Aβ imaging agent) was superior in regulating copper-induced Aβ aggregation. Thus Gd-Cur could be considered a possible diagnostic agent for AD. Another study used magnetic resonance imaging for Aβ plaque detection with the assistance of biocompatible curcumin conjugated magnetic nanoparticles (Cur-MNPs). The results showed Cur-MNPs were specifically co-localized with amyloid plaques, providing a new alternative diagnostic method for AD [45]. Both studies indicated the possibility of using modified curcumin molecules for diagnosis of AD.

4.2 Curcumin and Type 2 Diabetes

Diabetes mellitus is considered as a serious threat for public health. Among all three categories of diabetes: type 2 diabetes is the most common type, accounting for approximately 90% of cases [46]. Type 2 diabetes is characterized by insulin resistance, which is associated with impaired insulin secretion [47]. It is known that oxidative stress and chronic low-level inflammation have significant roles in the initiation and progression of type 2 diabetes [48].

As curcumin possesses both antioxidant and anti-inflammatory properties, it is a promising therapeutic option for type 2 diabetes. The first study on curcumin and diabetes can be dated back to 1972, in a study in which curcumin showed blood glucose lowering effect in a diabetic patient [49]. Later on, research on murine models reported both short term (5 d) and long term (28 wk) curcumin oral consumption improved insulin resistance [50,51]. Recent double-blinded and placebo-controlled clinical trials further provided evidence for the glucose-lowering effect of curcumin [12,52]. According to Na et al. [52], curcumin supplementation

significantly reduced fasting blood glucose, glycosylated hemoglobin (HbA1c), and insulin resistance index in type 2 diabetic patients. The anti-diabetic effects of curcumin may be a result of the following plausible mechanisms: curcumin is able to modulate activation of multiple cell signaling pathways related to inflammatory responses (including PI3K/Akt, Nrf2 and NF-κB) [53-55] and the level of bioactive molecules in the circulation system, thereby improving insulin sensitivity,. Curcumin treatment has been shown to increase the antioxidant status of pancreatic β-cells and suppress blood glucose levels by activating peroxisome proliferator-activated receptor gamma [56,57]. Curcumin is also involved in the inhibition of sterol regulatory element-binding protein, a transcription factor involved in the regulations of genes associated with biosynthesis of lipids, in order to ameliorate obesity and insulin sensitivity [58]. Na and colleagues [12] suggested curcumin may exert anti-diabetic effects partly by reducing serum adipocyte-fatty acid binding protein levels and serum free fatty acids In addition, a recent study indicated curcumin improved β-cell function and proliferation both *in vitro* and *in vivo* by functioning as a proteasome inhibitor [59].

4.3 Curcumin and Cardiovascular Diseases

Cardiovascular diseases including coronary artery diseases, stroke and atherosclerosis, are the main cause of deaths globally [60]. Quite a few clinical trials and *in vitro* studies have shown oxidative stress, chronic inflammation and subsequent endothelial dysfunction play significant roles in the pathophysiology of CVD [61]. Furthermore, bioactive molecules including pro-inflammatory cytokines, adhesion molecules and vasoactive factors are all closely related to CVD [62]. Over the past decade, polyphenols have been used as a therapeutic agent for CVD, including olive oil, tea and soy derived polyphenols to successfully improve oxidative stress, arterial stiffness and endothelial function [63].

As a polyphenolic compound, curcumin has also shown beneficial effects against CVD from multiple aspects, such as inhibiting lipoprotein oxidation, impairing smooth muscle cell migration, and restoring endothelial cell function [64]. The oxidation and macrophage uptake of LDL contributes to inflammatory responses in the intimal space, foam cell formation and subsequent thrombotic events playing a key role in the initiation and progression of atherosclerosis [65]. In 1999, Ramírez-Tortosa and colleagues [66] revealed curcumin could prevent oxidized LDL formation in an atherosclerosis study with a rabbit model. As an anti-oxidant, curcumin could directly protect LDL by donating hydrogen-atom from its phenolic group [67]. Later, Kou et al. [68] reported curcumin ameliorated LDL oxidation and macrophage uptake by inducing HO-1 expression and inhibiting cluster of differentiation-36 in macrophages. Furthermore, a recent *in vivo* study demonstrated curcumin treatment significantly enhanced serum paraoxonase-1 activity thereby reducing the susceptibility of LDL to oxidation [69].

Vascular smooth muscle cell (VSMC) migration and proliferation are pivotal steps in the progression of CVD. Curcumin was found to be responsible for blocking the platelet-derived growth factor (PDGF)-Erk/Akt signaling pathways, which induces VSMC migration and proliferation [70]. On the other hand, curcumin is also able to impair VSMC proliferation by reducing cyclinD1 and E2F activities and activating the caveolin-1/ mitogen activated protein kinase signaling pathway [71]. Yu et al. [72] suggested curcumin prevented VSMC migration via inhibition of TNF-α induced matrix metalloproteinase-9 expression. According to a recent report, curcumin may inhibit VSMC proliferation via down-regulation of sirtuin7 levels, inducing rRNA gene promoter hypermethylation and therefore inhibiting rRNA synthesis. This inhibition may also result from p53/p21 induced cell cycle arrest [73].

Endothelial dysfunction is another significant component in the pathophysiology of CVD. It is involved in the reduction and in the production/bioavailability of NO and in the imbalance between relaxing and contracting factors released by endothelial cells [74]. As reported by Ramaswami and colleagues [75], curcumin restored endothelium-dependent vasorelaxation, recovered endothelial nitric oxide synthase activity and inhibited superoxide anion production Later Fang et al. [76] indicated the effect of curcumin against endothelial dysfunction could be the result of increases in HO-1 activity, followed by activation of the guanylate cyclase-–cGMP signaling system What's more, by suppressing the expression of lectin-like oxidized LDL receptor-1 and inhibiting the NF-κB pathway, curcumin increased NO production while reduced the synthesis of adhesion molecules in endothelial cells [77]. Subsequently, Fleenor et al. [78] observed curcumin ameliorated endothelial dysfunction in an aged murine model and

reduced advanced glycation end product (AGE) formation. Therefore it could be hypothesized that curcumin improved endothelial dysfunction by inhibiting AGE formation. This hypothesis was later confirmed [79]. In addition, curcumin protects against lipopolysaccharide-induced endothelial dysfunction in a rat model via suppressing the expression of thrombospondin-1 and transforming growth factor-β1 [80].

4.4 Curcumin and Asthma

Asthma is one of the most prevalent chronic respiratory diseases worldwide, especially among young-age groups, imposing abundant direct and indirect economic costs [81]. Airway inflammation has been found to be a significant component in the pathophysiology of asthma, therefore current treatments mainly employ anti-inflammatory drugs such as inhaled corticosteroids [82]. In 1997, Kobayashi et al. [83] reported curcumin inhibited proliferation, production of interleukins, and release of granulocyte macrophage colony-stimulating factor in lymphocytes isolated from asthmatic patients, indicating curcumin may have a potential effect on controlling asthma. Then another in-vitro study suggested curcumin induced a significant decrease in human airway smooth muscle cell derived chemokine level, including eotaxin, MCP-1 and MCP-3 [84]. Further, curcumin inhibited the secretion of pro-inflammatory cytokines (TNF-α and IL-1β), anti-inflammatory cytokine IL-10 and adhesion molecule ICAM-1 in activated eosinophils and bronchial epithelial cells, probably via inhibition of the NF-κB and AP-1 pathways [85]. Later, Ram and colleagues [86] conducted an *in vivo* study with guinea pigs in which they demonstrated oral curcumin consumption ameliorated allergen-induced airway constriction and airway hyper-reactivity A recent study suggested that curcumin activates the Nrf2/HO-1 pathway and alleviates airway inflammation and goblet cell hyperplasia in asthmatic mice. In addition to oral treatment, nasal-delivered curcumin successfully lowered bronchial prostaglandin level thereby attenuating airway hyper-reactivity and inflammation [86]. Curcumin also suppressed the activation of mitogen-activated protein kinases, which are responsible for expression and activation of asthmatic inflammatory factors [87].

The effects of curcumin in the regulation of pathways associated with chronic disease are presented in Fig. 2.

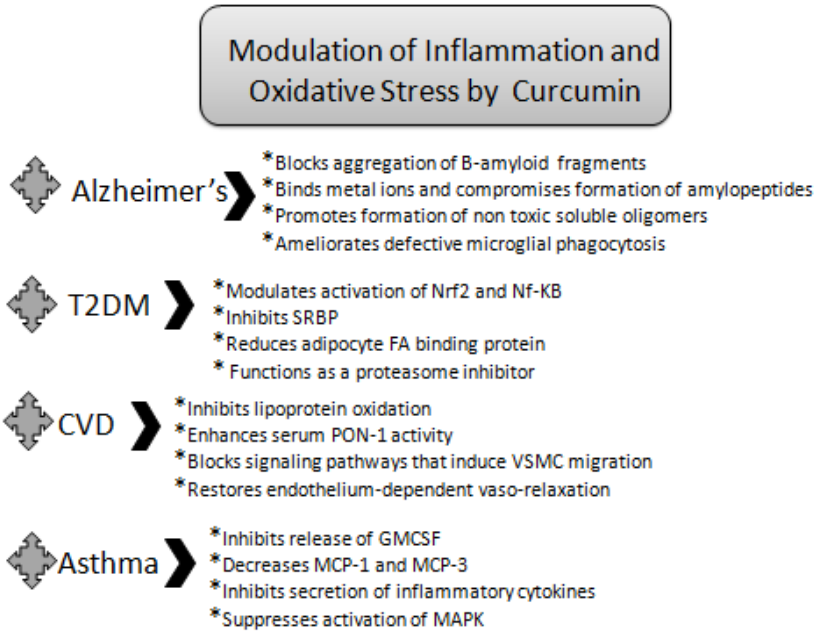

Fig. 2. Modulation of inflammatory pathways and oxidative stress by Curcumin, which result in protection against chronic disease: Alzheimer's, type-2 diabetes (T2DM), cardiovascular disease (CVD) and Asthma

Abbreviations used: Nfr-2: Nuclear factor erythroid-2 related factor 2; NF-kb: nuclear factor: kB; SRBP: sterol regulatory binding protein; PON-1: paraoxonase 1; GMCSF: granulocyte macrophage colony stimulating factor; MCP: monocyte chemotactic protein MAPK: mitogen activated protein kinases

5. BIOAVAILABILITY OF CURCUMIN

Although curcumin has promising potentials for treatment of a wide range of chronic diseases, its clinical practices have been limited due to physiochemical instability, rapid metabolism, and low oral bioavailability [88]. Curcumin showed no significant effect in a number of human trials possibly due to its bioavailability problems [13,16]. Table 1 presents the positive and negative results of clinical trials conducted with Curcumin. Previous studies have shown the extremely low bioavailability of curcumin in both murine and human subjects. Research in this area could be tracked back to 1978, in a report where orally administrated curcumin at a high dose of 1 g/kg to rats, showed that plasma curcumin levels were only trace amounts, while most curcumin was lost in the feces, indicating that curcumin was barely absorbed in the intestine [89]. Then in a later study, an oral administration at a dose of 2 g/kg curcumin, resulted in serum curcumin levels of only 1.35 ± 0.23 μg/m in Wistar rats after 1 hour, whereas in human subjects, the serum curcumin levels were barely detectable [90]. Therefore, to further apply curcumin in therapeutics, its bioavailability should be improved. In recent years, nanoencapsulation has been employed to improve the gastrointestinal absorption of curcumin, resulting in a higher blood level and lower kinetic elimination and thereby improving the bioavailability of this polyphenol. A pharmacokinetic study conducted by Ray and colleagues [91] could be a good example. In this study, despite having a lower dose,

Table 1. Randomized clinical trials with curcumin and health outcomes

Study	Population	Disease	Health outcome
[11]	45 male post-surgery patients, ages 15-68, 6 d	Patients with post-operative inflammation	Post–surgery inflammation, pain and tenderness were ameliorated
[34]	1,010 elderly Asian subjects, ages 60–93	Cognitive function	Subjects with higher consumption level had better cognitive performance
[49]	1 patient with type 2 diabetes, 5 mg, diet	Type 2 diabetes	Blood glucose level was reduced
[12]	100 patients with type 2 diabetes, ages ~55, 3 mths	Type 2 diabetes	Oxidative stress, inflammatory biomarkers were reduced
[52]	100 patients with type 2 diabetes, ages ~55, 3 mths	Type 2 diabetes	Glycemic profiles improved; serum lipid profile and LPL activity also improved
[13]	15 patients with asthma, ages 18-60, 6 mths	Asthma	Symptoms not significantly ameliorated
[16]	33 patients with coronary artery disease, ages ~60, 2 mths	Cardiovascular risk factors	Triglycerides, LDL-cholesterol and VLDL-cholesterol profile improved, other lipid profiles and inflammatory condition were not significantly changed
[15]	45 Indian patients with rheumatoid arthritis, ages 18-65, 8 wks	Rheumatoid arthritis	C-reactive protein level significantly decrease, achieved the highest percentage of improvement in Disease Activity and American College of Rheumatology scores among groups
[14]	82 Japanese patients with ulcerative colitis, ages 13-65, 6 mths	Ulcerative colitis	Curcumin treatment improved Clinical activity index and endoscopic index of patients, recurrence rates also lower than the placebo group
[18]	41 patients with rectal aberrant crypt foci, ages 42-70, 30 d	Rectal aberrant crypt foci	Aberrant crypt foci number reduced by 40% in the 4 g consumption group

curcumin-carboxymethyl chitosan (CMC) nanoparticles (5 mg/kg) appeared to have a higher cardiac bioavailability compared to free curcumin (35 mg/kg) in a rat model. Moreover, nanoencapsulation in CMC dramatically increased the efficacy of curcumin on regressing cardiac hypertrophy [92]. These results indicate that nanoencapsulation could significantly increase both bioavailability and therapeutic potential of curcumin even at a lower dose.

6. CONCLUSIONS

Curcumin has been shown to exhibit therapeutic potential for various chronic diseases, mainly by exploiting its anti-oxidant and anti-inflammatory properties. Both *in vitro* and *in vivo* studies suggest curcumin is able to modulate multiple bioactive molecules, including transcription factors, protein kinases and cell-cycle regulators, thereby controlling gene expression, cell proliferation and immune responses, which have been identified as having close associations with the pathophysiology of chronic diseases. However, as reported in some studies, the therapeutic use of curcumin is still limited due to its poor absorption, rapid metabolism, and low oral bioavailability. Those problems need to be improved before it can be widely utilized in clinical practice.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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http://sciencedomain.org/review-history/15809