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Molecular mechanisms underlying chemopreventive potential of curcumin: Current challenges and future perspectives

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ABSTRACT

In recent years, natural compounds have received considerable attention in preventing and curing most dreadful diseases including cancer. The reason behind the use of natural compounds in chemoprevention is associated with fewer numbers of side effects than conventional chemotherapeutics. Curcumin (diferuloylmethane, PubMed CID: 969516), a naturally occurring polyphenol, is derived from turmeric, which is used as a common Indian spice. It governs numerous intracellular targets, including proteins involved in antioxidant response, immune response, apoptosis, cell cycle regulation and tumor progression. A huge mass of available studies strongly supports the use of Curcumin as a chemopreventive drug. However, the main challenge encountered is the low bioavailability of Curcumin. This extensive review covers various therapeutic interactions of Curcumin with its recognized cellular targets involved in cancer treatment, strategies to overcome the bioavailability issue and adverse effects associated with Curcumin consumption.

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1. Introduction

Since the ancient times, plant derived bioactive molecules are being used to treat most dreadful diseases like cancer. Among these, polyphenols have received much attention in disease prevention due to their various pharmacological properties [1, 2]. Curcumin comes under one of the most widely studied bioactive polyphenol. It is low molecular weight hydrophobic compound, which is widely used in the form of consumable spice, turmeric [3]. The active ingredient of Curcumin is diferuloylmethane, which imparts Curcumin a characteristic yellow color. Chemically, it is bis-α, β-unsaturated β-diketone in which two oxy-substituted aryl moieties are linked together through a seven carbon chain (Fig. 1). The aryl rings may be substituted by many hydroxyl or methoxy groups, symmetrically or asymmetrically; to obtain a number of Curcumin analogs [4]. After ingestion, Curcumin undergoes metabolic *O*-conjugation to Curcumin glucuronide and Curcumin sulfate and bio-reduction to tetrahydroCurcumin, hexahydroCurcumin, and hexahydroCurcuminol and finally metabolized to dihydroferulic acid together with traces of ferulic acid derivatives [5–9]. *In vivo*, oral Curcumin is poorly absorbed, improperly metabolized and shows poor systemic bioavailability [6, 9]. It has been suggested that the liver and intestinal tract play an important role in the metabolic biotransformation of Curcumin [10]. Studies have shown that Curcumin can modulate a variety of cancer related targets or pathways, including induction of phase II enzymes via activation of NF-E2 related factor-2 (Nrf 2), induction of apoptosis, modulation of cell cycle regulators, inhibition of nuclear factor kappa B (NF-κB), inhibition of angiogenesis, inhibition of microtubule polymerization and other pathways involved in chemoprevention [10–16]. These strategies may open a new therapeutic approach from cancer prevention to cancer treatment. This review is focused on the cellular pathways governed by Curcumin in prevention and cure of cancer, strategies to improve its bioavailability and the adverse effects associated with Curcumin consumption.

2. Molecular pathways governed by curcumin

2.1. Modulation of aryl hydrocarbon receptor (Ahr)

Many carcinogens require bio-transformation via phase I enzymes like cytochrome P450 (CYP), to be destructive towards DNA or other cellular molecules [17]. Earlier studies have suggested the involvement of AhR dependent mechanisms in Curcumin mediated modulation of CYP enzymes [18]. Previously, dose and time dependent Curcumin mediated down-regulation of CYP3A2, CYP2E1 and CYP1A have been demonstrated in *in vivo* study with rat and mouse models [19, 20]. Furthermore, in a variety of cells, Choi et al., (2008) also reported Curcumin mediated attenuation in the induction of CYP1A1 and CYP1B1, as a consequence of degradation of AhR [21]. Similarly, an *in vivo* study with mouse also demonstrated Curcumin mediated inhibitory effects on B[*a*]*P*-induced AhR activation, its nuclear translocation and DNA binding, thereby decrease in catalytic activity of CYP1A and reduced expression and catalytic activity of CYP1A1/1A2 [22]. In contrast, Rinaldi et al., (2002) reported Curcumin mediated up-regulation in nuclear translocation of AhR followed by increased expression of CYP1A1 and CYP1B1 in a variety of cells [23]. Moreover, one other study also revealed Curcumin mediated activation of AhR, followed by increase in the activity of CYP1A1 [24]. Due to conflicting outcomes of Curcumin in context of modulation of AhR and CYP enzyme, the use of Curcumin as a dietary supplement in order to prevent cancer is worthy of further research.

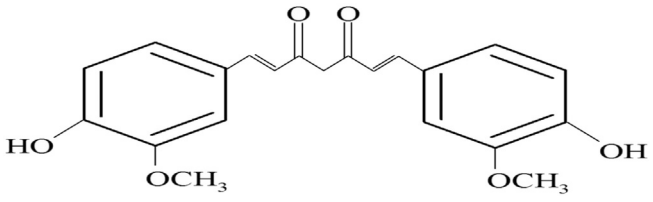

Fig. 1. Molecular structure of Curcumin. Curcumin comes under most widely studied chemopreventive compounds and has been used in common food consumables since ancient times.

2.2. Induction of Nrf2

The induction of phase II enzymes, including heme oxygenase-1 (HO-1), UDP-glucuronosyl transferase (UGT), glutathione *S*-transferase (GST), and quinone oxidoreductase (NQOR) can suppress or inhibit carcinogenesis. The genes coding for these enzymes contain antioxidant response element (ARE), which is under the strict regulation of Nrf2, a transcription factor, which is associated with another repressor, Kelch-like ECH-associated protein 1 (Keap1). Apart from acting as a repressor, Keap1 also promotes ubiquitin mediated degradation of Nrf2 [17]. Curcumin and other inducers of Nrf2, are known to break Nrf2-Keap I complex, leading to translocation of Nrf2 to the nucleus, where it binds over ARE, and activates the transcription of phase II enzymes (Fig. 2) [25]. In an *in vivo* study with mice, dietary dose of Curcumin was responsible for nuclear translocation of Nrf2, and subsequent induction of NQOR, GST and their isoforms [12]. Curcumin (50 mg/kg and 200 mg/kg of body weight, diet) mediated nuclear translocation of Nrf2, followed by induction of HO-1, was also reported in *in vivo* studies with mice and rats, respectively [25, 26]. Similarly, a group of researchers also reported Curcumin (1 g/kg diet) mediated increase in HO-1 levels in their *in vivo* experiments with rats [27]. Recently, elevation in levels of Nrf2 dependent HO-1 was also reported in Curcumin treated lung tissue of mouse and RAW264.7 mouse macrophages [28]. In addition, one another study with cerebellar granule neurons of rats, showed Curcumin (5–30 μM) mediated neuro-protection against hemin, the oxidized form of heme, induced damage *via* Nrf2 dependent HO-1 expression [29]. Moreover, Nrf2 dependent induction of paraoxonase 1 was reported in hepatocytes treated with Curcumin and its degraded products [30].

Till now the exact biochemical mechanism by which Curcumin activates Nrf2 cascade is unclear. However, increasing number of evidences suggest the involvement of mitogen-activated protein kinase (MAPK) signaling pathways in Curcumin mediated induction of Nrf2. Previously, p38/MAPK and NF-κB dependent induction of Nrf2, followed by HO-1 expression, was reported in Curcumin (5–40 μM) treated HBL-100 and MDA-MB468 human breast cancer cells [31]. Moreover, Kou et al. also reviewed protein kinase C (PKC)-δ and p38/MAPK dependent Nrf2 mediated expression of antioxidant defense genes in Curcumin treated human monocytes [32]. Curcumin mediated activation of Nrf2 *via* MAPK pathway has also been suggested by Alrawaiq and Abdullah [33]. In addition, a group of authors reported the role of Akt pathway in Curcumin mediated increase in Nrf2-DNA binding and subsequent induction of NQOR1 in their study with primary culture of cortical neurons [34]. Similarly, Kim et al. also suggested the role of phosphatidylinositol-3-kinase (PI3K)/Akt pathway in Curcumin mediated modulation of Nrf2 activity [35]. Whereas, Khor et al. revealed Curcumin (5 and 10 μM) mediated reduction in methylation (by 27% and 57.6%, respectively) of CpGs in Nrf2 promoter, followed by increase in NQOR1 expression at both mRNA and protein level in TRAMP *C*1 prostate cancer cells [36]. Thus, Curcumin governs a number of mechanisms in regulating Nrf2 mediated gene expression.

2.3. Induction of cell death by apoptosis and autophagy

Apoptosis, also known as programmed cell death, has been known as one of the most potent strategies to counter the cancerous growth. A number of *in vitro* and *in vivo* studies have reported Curcumin mediated apoptosis, as a consequence of modulation in expression of proteins involved in apoptosis [17,37–39]. Previously, Curcumin (1–10 μM) mediated increased levels of p27, p53, caspase-3 and pro-

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