Molecular Biology: Open Access
ISSN: 2168-9547

Tyagi and Prasad, Mol Biol 2014, 4:1
DOI: 10.4172/2168-9547.1000e123

Editorial Open Access

Molecular Targets of Curcumin: A Potential Magic Bullet for Health

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Editorial

Curcumin (diferuloyl methane) is the active ingredient (nutraceuticals) of the dietary spice turmeric found in the rhizomes of *Curcuma longa* and has been used for medicinal purposes for thousands of years in Asian countries. Extensive research over the past few decades has shown that it can modulate multiple cell signaling pathways as well as directly interact with numerous signaling biomolecules, and thus has therapeutic potential against a wide range of human diseases. Promising effects of curcumin have been observed in the patients with various pro-inflammatory diseases including cancer, arthritis, uveitis, ulcerative proctitis, cardiovascular disease, Crohn's disease, ulcerative colitis, irritable bowel disease, tropicalpancreatitis, gastric inflammation, gastric ulcer, peptic ulcer, idiopathic orbital inflammatory pseudotumor, oral lichen planus, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, diabetic nephropathy, diabetic microangiopathy, lupus nephritis, renal conditions, acquired immunodeficiency syndrome, β-thalassemia, biliary dyskinesia, Dejerine-Sottas disease, cholecystitis, and chronic bacterial prostatitis. Hepatic conditions, chronic arsenic exposure, and alcohol intoxication has also been protected by curcumin [1]. The safety,efficacy and tolerability of curcumin at different doses have been well established by human clinical trials. In these clinical trials, curcumin was used either alone or in combination with other agents such as lactoferrin, piperine, docetaxel, gemcitabine, soy isoflavones, acetylcysteine, prednisone, bioperine, quercetin, mesalamine, sulfasalazine, and pantoprazole [2]. Based on these observation, the U.S. Food and Drug Administration has approved curcumin as a "generally regarded as safe" (GRAS) compound in clinical trials.

Researchers have been studied varioushealth beneficial effects of this single molecule. Numerous lines of evidence indicated curcumin's ability to modulate multiple cell signaling molecules such as inflammatory cytokines (Tumor Necrosis Factor [TNF]-α, [TNF]-β), Interleukin([IL]-1, IL-2, IL-6, IL-12), chemokines (monocyte chemo-attractant protein 1, IL-8), pro-inflammatory transcription factors (NF-kappaB, STAT3), pro-inflammatory enzymes (COX-2, 5-LOX, 12-LOX, MMPs), apoptotic proteins, IKKβ, endothelin-1, Malondialdehyde (MDA), adhesion molecules (Intercellular Adhesion Molecule [ICAM-1], Vascular Cell Adhesion Molecule [VCAM]-1, Endothelial-Leukocute Adhesion Molecule [ELAM]-1), Vascular Endothelial Growth Factor (VEGF), and TWIST. prostaglandin E2, Prostate-Specific Antigen (PSA), C-reactive protein, GST, glutathione (GSH), pepsinogen, phosphorylase kinase (PhK), transferrin receptor, triglyceride, total cholesterol, Transforming Growth Factor (TGF)-β, creatinine, HO-1, antioxidants, AST, and ALT, in human participants [3]. Structurally, the hydroxyphenyl unit in curcumin has showncrucial for its anti-inflammatory activity.

Duringthepast30years,ourlaboratoryandothershavedemonstrated that curcumin has chemopreventive and a chemotherapeutic potential against cancer. The chemopreventive efficacy of curcumin has been reported against cancer of esophageal, oral, breast, lung, kidney, liver, bladder, stomach, leukemia, small intestine, pancreatic, skin, brain, and prostate. Most of these studies have used *in vitro* or rodent models. Diverse effects of curcumin have also been reported for treatment of different types of cancers includingpancreatic, hepatocellular, cholangiocarcinoma, lymphoma, melanoma, prostate, colorectal, breast, ovarian, and bladder cancers along with reduction in cancer-associated symptoms such as neuropathic pain, fatigue, and cognitive deficit [4]. Curcumin acts at several stages of cancer development. It blocks transformation, tumor initiation, tumor promotion, invasion, angiogenesis, and metastasis. Curcumin modulates growth of tumor cells through cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), apoptosis pathway (PARP) tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, inflammatory pathway (NF-kB, STAT3), and protein kinase pathway (JNK, Akt, and AMPK) [5].

Other than its anticancer efficacy, curcumin has potential as a cardioprotective agent by a significant reduction in circulating C-reactive protein levels, which is a strong predictor and independent risk factor of cardiovascular disease and activation of SIRT1[6]. Curcumin has also been shown to be effective against atherosclerosis and myocardial infarction.Curcumin treatment attenuated ischemia or reperfusion through the modulation of the JAK/STAT3 signaling pathway, which transmits a survival signal to the myocardium. Curcumin was also reported for the protection of myocardial I/R injury through the activation of pro-survival kinases (PI3K-Akt, ERK1/2, and GSK-3β), and attenuation of p38 and JNK. Level of biomarker enzymes like LDH and CPK and biochemical parameters (AST, ALT and ALP) was also regulated by curcumin.The effect of curcumin against various skin diseases such as dermatitis, scleroderma, psoriasis, and skin carcinogenesis has been reported in various studies. Skin protective effect of curcumin was mainly by modulating the protein kinase C (PKC) pathway. Curcumin act as an anti-diabetic agent and shown to improve the symptoms associated with diabetes. It also exhibits anti-hyperglycemic effect and improves insulin sensitivity. Curcumin appears to be a potent glucose-lowering agent in type 2 diabetes mellitus (T2DM) mice [4].

Curcumin was found to be safe and effective for the rheumatoid arthritis (RA) treatment. Antirheumatic and antiarthritic effects of curcumin were most likely throughthe inhibition of inflammatory molecules (NF-kB, AP-1 and Egr-1, COX2, LOX, NOS, MMP-9, uPA, TNF and chemokines). It was also reported that curcumin inhibits collagen and Freund's complete adjuvant-induced arthritis by suppression of IFNγ-induced BAFF expression, STAT1 phosphorylation and nuclear translocation thereby attenuated the progression and severity of RA in animals. The therapeutic benefits of curcumin for neurodegenerative diseases such as Alzheimer diseases appear through the suppression of oxidative damage, inflammation,

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Received December 28, 2014; **Accepted** December 30, 2014; **Published** December 31, 2014

Citation: Tyagi AK, Prasad S (2014) Molecular Targets of Curcumin: A Potential Magic Bullet for Health. Mol Biol 4: e123. doi:10.4172/2168-9547.1000e123

cognitive deficits, amyloid accumulation and inhibition of Aβ fibril formation [7]. Curcumin treatment decreases colon injury and effective in preventing and treating inflammatory bowel disease (IBD), which is associated with, decreased inflammatory reactions, apoptotic cell death, lipid peroxidation, modulating p38- and JNK-MAPK-ERKpathways, inhibition of free radicals, and inhibitingmyeloperoxidase, COX-1, COX-2, LOX, TNF-α, IFN-γ, iNOS. Curcumin was also reported as a sarcoplasmic/endoplasmic reticulum calcium (SERCA) pump inhibitor and may prevent cystic fibrosis transmembrane conductance regulator gene (CFTR) mutation, which subsequently protect the cystic fibrosis [2].

Curcumin has been shown to be effective against several other diseases. It exhibits inhibitory effect against HIV-1, dengue virus type 2, selenite-induced cataractogenesis, and cyclophosphamide-induced early lung injury. Thus, it is clear that curcumin is multitargetted unique molecule that acts against wide varieties of human diseases. Curcumin contains a number of functional groups that are involved in target modulation. Since this molecule is safe and cost effective, further more clinical trials are needed to reach this molecule for human use. Besides these, several questions have been raised against its bioavailability. Several studies have shown that curcumin is sufficiently bioavailable and even its metabolite tetrahydrocurcumin is comparably active as curcumin [8]. In spite of these, designing formulations of the curcumin is also very much desired. These formulations can enhance the biological activity of curcumin.

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