IJP (2024), Vol. 11, Issue 1 **(Review Article)**

Received on 03 November 2023; received in revised form, 19 December 2023; accepted, 27 January 2024; published 31 January 2024

THE PHARMACOLOGICAL EFFECTS OF CURCUMIN IN DIABETES, CANCER, AND NEURODEGENERATIVE DISEASES: A REVIEW

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Keywords:

Curcumin, Anti-diabetic activity, Anti-oxidant activity, Neurodegenerative diseases, Anti-cancer activity

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ABSTRACT: Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione) is a hydrophobic polyphenol derived from the roots of the *Curcuma longa* and is also known as diferuloylmethane ($C_{12}H_{20}O_6$)**.** It shows various pharmacological effects like anti-inflammatory, anti-oxidant, anti-carcinogenic, chemo-preventive, anti-diabetic, anti-viral, and anti-bacterial in spite of these curcumin is still far away from the clinical uses due to their low bioavailability and in which is related by the poor absorption, quick metabolism, poor water solubility, and chemical instability as a diet-derived agent curcumin has been used traditionally in many forms for the treatment of inflammation and pain but most of the recent studies uncovered the role of curcumin as an antidiabetic, anti-carcinogenic, anti-infectious, antidepressant and antipsychotic agent. This dietary supplement has ability to block a number of cells signaling pathways at various levels underlies its diverse effect. By modulating cell cycles and interacting directly to molecular targets like glutathione peroxidase, nuclear factor kappa-B cells, cyclooxygenase-2, hepatic superoxide dismutase, reactive oxygen species tumor necrosis factors etc. curcumin can prevent the development of cancer. In this chapter, we demonstrated the therapeutic effects of curcumin in various cancers, neurodegenerative disorders, microbial infections and diabetes interconnected with its molecular pathways during preclinical trails.

INTRODUCTION: Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione) is a hydrophobic polyphenol derived from the roots of the *Curcuma longa* (Mudagal *et al.,* 2018) and is also known as diferuloylmethane ($C_{12}H_{20}O_6$) [17, 23]. It shows various pharmacological effects like anti-inflammatory, anti-oxidant, anti-carcinogenic, chemo-preventive, anti-diabetic, anti-viral, and anti-bacterial [2, 18, 24, 49] in spite of these curcumin is still far away from the clinical uses due to their low bioavailability and in which is related by the poor absorption, quick metabolism, poor water solubility, and chemical instability [18, 25,] Maheshwai *et al.,* 2006 [5, 6 48, 49].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.IJP.11(1).1-6

Article can be accessed online on:
www.ijpjournal.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.IJP.11(1).1-6

Curcumin's oral bioavailability is limited and frequently expected to poor absorption by the small intestine, diminutive and conjugative metabolism in the liver, and elimination by the gall bladder. Metabolism of curcumin happens to owe to phase-I and phase-II biotransformation. The primary site of the metabolism of curcumin is at liver and after that intestine and gut microbiota. In phase-I metabolism double bonds are reduced by the action of reductase

to form di, tetra, hexa, and octa hydro curcumin from curcumin [3, 40, 4, 12, 30]. Curcumin is a bis α, β - unsaturated diketone, and this manifests keto-enol tautomerism. Curcumin is special in structure with two isomers enol and beta-diketone in addition the enol structure has ionizable nucleons that have a close similarity to enolic and two phenolic groups [51]. *Curcuma longa* and specifically one of its active constituent curcumins possesses many pharmacological activities and in variety of preclinical trials of curcumin-related formulations and derivatives proves its uses in variety of diseases [27, 51, 15]. The current chapter provides an overview on the application of curcumin with multiple therapeutic effects in different animal's models. On the basis of these preclinical trials there is a possibility to introduce curcumin into further clinical studies to prevent many diseases in near future

Curcumin and its Applications on the Treatment of Different Diseases:

Curcumin in Anxiety and Depression: In studies using animal models, curcumin has demonstrated having potent antidepressant effects. It works by preventing the monoamine oxidase-A (MAO-A)and monoamine oxidase-B (MAO-B) enzymes from being expressed, which raises the amounts of norepinephrine, serotonin, and dopamine. The mouse amygdala's increased expression of the brain-derived neurotrophic factor (BDNF) is controlled by extracellular signal-regulated kinase (ERK) and contributes to curcumin's antidepressant effects. Curiously, in a rodent model of chronic stress, curcumin was shown to support hippocampal neurogenesis and raise the BDNF levels. According to the reports, curcumin has anxiolytic-like effects that may be related to its ability to reduce pro-inflammatory mediator levels, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) messenger ribonucleic acid (mRNA) by activating the nuclear factor kappa-B (NF-$_K$B) signaling pathway. Its anti-inflammatory action in depression is confirmed by the inhibition of proinflammatory cytokines interleukin-1 (IL-1) via the NF-$_K$B pathway [**8**, 7, 21, 29, 54].

Curcumin in Presenile Dementia: Presenile Dementia or Alzheimer's disease (AD) is a long-term neurodegenerative condition marked by selective neuronal death, neurofibrillary tangles made of hyperphosphorylated tau protein, and memory and cognitive decline that worsens over time. Beta-amyloid (Ab) plaques are deposited extracellularly in the hippocampus, which is a molecular pathogenesis of Alzheimer's disease. Curcumin has been shown to decrease the pathology of Alzheimer's disease may be because of its anti-aggregatory properties. Curcumin administration (1 or 4 gm, 6 months trial) substantially increased levels of antioxidant vitamin E in human neuroblastoma SH-SY5Y cells without causing any negative side effects in patients with AD due to its diverse benefits, including antioxidant and anti-inflammatory properties, metal chelation, and reduction ofβ-amyloid levels [38, 22, 19].

Curcumin in Parkinson`s Disease: One of the most common neurodegenerative illnesses Parkinson's diseases (PD) is characterized by the progressive loss of dopaminergic neurons in the substantia nigra compacta (SNpc), the deposition of synuclein and the presence of Lewy bodies [8, 31, 47]**.** Parkinson's disease is a specific form of movement disorder linked to a lack of the brain chemical dopamine. Chronic curcumin administration (50, 100, or 200 mg/kg, p.o., for 3 weeks) substantially improved behavioral alterations in the rodent Parkinson's disease model, including locomotor activity and motor coordination. Similar research found that curcumin supplementation decreases acetylcholinesterase (ACE) activity, oxidative stress, and mitochondrial dysfunction in brain homogenate [28, 38].

Curcumin Having Antioxidant Activity: Curcumin is considered as an antioxidant because the β-diketone group in its structure enables it to support the majority of its biological functions by suppressing superoxide radicals, hydrogen peroxide, and nitric oxide radicals. Curcumin may also increase the activity of many antioxidant enzymes, such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase, and heme oxygenase-1 (OH-1). These methods reduce lipid peroxidation, which in turn reduces liver damage. Additionally, curcumin can boost the activity of xenobiotic detoxification enzymes in the liver and kidneys, preventing the processes that lead to cancer. According to other research, 200 mg/kg of

curcumin increased the superoxide dismutase (SOD) and catalase activities as well as the liver's total antioxidant capacity in rats with thallium acetate induced liver damage [42, 39, 1, 41].

Curcumin in Diabetes: Diabetes is a common hyperglycemic disorder that damages the liver, heart, brain, and kidneys. Type 2 diabetes is thought to develop primarily due to inflammation, transcription factors, a variety of inflammatory cytokines, and Enzymes that are crucial to the development and progression of diabetes.

Activating peroxisome proliferator-activated receptor gamma and improving the antioxidant status of pancreatic β-cells are two mechanisms through which curcumin`s treatment has been proven to lower blood glucose levels in diabetics peroxisome proliferator-activated receptor (PPAR-γ) [37, 11, 55].

Curcumin in Esophageal Cancer`s: Due to its reduction of inflammatory mediators like nuclear factor kappa-B (NF-$_K$B) curcumin is regarded as a promising candidate for the treatment and prevention of esophageal cancer. In addition to inhibiting NF-$_K$B, curcumin also causes enhanced drug accumulation and death in esophageal cancer cells. Moreover, curcumin therapy prevented bile acid-induced cyclooxygenase-2 (COX-2) activation and sodium dismutase-1 gene expression, suppression in the rat esophageal HET-1A epithelium suggesting chemoprevention during in vivo studies. Curcumin administration to rodents during the pre- and post-cancer phases decreased the probability of esophageal carcinogenesis by 27 and 33%, respectively [37, 20, 9, 44].

Curcumin in Breast Cancer: Many studies have shown that curcumin suppresses the development of certain breast cancer cells. Curcumin's potential anticancer activities were largely reversed in an animal trial where it has been used to treat tumor exosome-mediated natural killer cell (NK-cell) suppression. According to the othe *in-vivo* studies, curcumin also showed anti-metastatic effects in breast cancer by inhibiting cytochrome P450 cells [50, 36, 46, 5, 6].

Curcumin in Kidney Cancer: Renal cell carcinoma (RCC) another name for kidney cancer, generally appears in the kidneys' tiny tubes. A 50 µM dose of curcumin has been demonstrated to cause deoxyribonucleic acid (DNA) breakage which results in apoptosis in Caki-1 cells. In the same cell line, curcumin promotes the upregulation of the death receptor 5 (DR5) at the messenger ribonucleic acid (mRNA) and protein levels by generating reactive oxygen species (ROS). According to this study, curcumin inhibited the growth of metastases (18% vs. 0%; P 14 0.01) and decreased the incidence of tumors (15% vs. 0%; P 14 0.025) [37, 26, 16].

Curcumin in Liver Cancer: Despite being less prevalent than other types of tumors, hepatic tumors are very interesting. In this area, research is constantly expanding and significant advancements in diagnosis and therapy are being made. One of the most prevalent such malignancies and a major consequence in those with cirrhosis or chronic liver disease brought on by hepatitis B or C virus infection is hepatocellular carcinoma.

Hepatoblastoma is an uncommon childhood cancer with low incidence rates and is challenging to research. Nevertheless, other hepatoblastoma types and subtypes have been discovered. The biliary tract epithelium is impacted by cholangiocarcinoma which can develop in intrahepatic or extrahepatic bile ducts. Both its prevalence and diagnostic methods have grown in recent years. A tumor that originates from vascular endothelial cells is primary hepatic angiosarcoma.

This barely accounts for 1.8% of all hepatic diseases. hence it has not received as much research attention as other hepatic illnesses. In the carbon tetra chloride (CCl_4) induced liver injury by intraperitoneal injection, by reacting the impaired activity of vital antioxidant enzyme i.e., hepatic superoxide dismutase (SOD), reducing lipid peroxidation and serum aminotransferase curcumin has been reported to improve acute liver injuries [53, 23, 10, 14, 52, 13].

Anti-microbial: In numerous animal studies, curcumin has shown antibacterial, antiprotozoal, antiviral and antifungal effects. In Swiss mice infected by intraperitoneal injection of P. berghei, oral curcumin led to a 90% reduction in parasitemia with a 29% increase in overall survival rate.

Curcumin's impact may be linked to its ability to promote cell death and prevent cell growth [15].

CONCLUSIONS: As curcumin has been a staple of the South Asian diet for millennia it is highly well tolerated, bioactive, and nontoxic although the genotoxic and long-term effects of curcumin administration have not been well studied, it has been suggested that the large doses used in clinical trials still warrant significant concern. Moreover, there are infrequent anecdotal accounts of the negative effects caused by curcumin in humans like urticaria and allergic contact dermatitis in high doses.

The information in this review shows that the curcumin modulates numerous cellular signaling pathways and interacts with a wide range of molecular targets, including transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. The outcomes of these studies are a collection that verifies the efficacy and uses of curcumin in the treatment of various neurodegenerative condition and cancers.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

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How to cite this article:
Hassanpour SH: The pharmacological effects of Curcumin in diabetes, cancer, and neurodegenerative diseases: a review. Int J Pharmacognosy 2024; 11(1): 1-6. doi link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.11(1).1-6.