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Curcumin: The miraculous golden ingredient of Indian saffron

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Abstract

Background: Indian Saffron (*Curcuma longa)* also called turmeric; has been consumed for centuries by people as a dietary component and used in the traditional medicine as a household remedy for various diseases in India, China and South East Asia. Curcumin (*diferuloyl methane*), the main yellow bioactive pigment in turmeric has been shown to have a broad spectrum of biological activities. Purpose of study: The present review was performed to evaluate the molecular mechanism of action and role of Curcumin in health and disease. Sources of evidence: The literature search was conducted using Sciencedirect, Medline, Scopus data bases, 26 studies were included in this review. Main arguement: Animal studies with curcumin exhibited its digestive and anti-ulcer role through its excess production of mucin, bile, and digestive enzymes. Curcumin is effective in preventing cognitive impairment in Alzheimer Disease, Parkinson Disease and other oxidative stress related pathologies due to its antioxidative, anti-inflammatory roles. It has been suggested that the ability of curcumin to quench free radicals and reactive oxygen species (ROS) results in its protective role towards neuronal tissues against toxic chemicals as *Manganese.* Anticancer effect is mainly mediated through apoptosis of cancer cell lines. Clinically curcumin is used to reduce post-operative inflammation. Conclusions: Safety evaluation studies indicate that both turmeric and curcumin are well tolerated at a high dose without any toxic effects and therefore, have the potential for the development of modern medicine in the treatment of various diseases.
Key words: Curcumin, antioxidant, anticancer, anti-inflammatory.

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1. Introduction

1.1. Curcumin and its Traditional Uses

Curcumin has been used as a spice, ingredients in cosmetics, colouring agents and as a traditional remedy for a number of diseases in India and also the Asian subcontinent [1]. Powdered turmeric taken with boiled milk for respiratory ailments , application of turmeric paste to treat cuts, wounds, burns and various skin infections, use of turmeric in the treatment of dental health, and for digestive disorders such as dyspepsia and acidity, indigestion, flatulence and ulcers has been practised for centuries [2, 3].

However, systematic studies to understand the molecular basis of therapeutic properties of curcumin began to appear in the scientific literature only during the last three decades. Curcumin has also been shown to exert anti-inflammatory, antioxidant, antibacterial, anti-atherosclerotic properties in animal models as well as human subjects. Safety evaluation studies indicate that both turmeric and curcumin are well tolerated at a high dose without any toxic effects [4] and therefore, have the potential for the development of modern medicine in the treatment of various diseases. Curcumin is effective in preventing cognitive impairment in Alzheimer Disease, Parkinson Disease and oxidative stress related pathologies due to its antioxidative, anti-inflammatory roles [2].

Due to the great deal of interest that continues to grow regarding health benefits of Curcumin and the extensive research that is being performed in this field, the present study reviews and evaluates the major health benefits of Curcumin - the miraculous ingredient of turmeric, also called Indian saffron.

2. Sources of Evidence: Literature Search Methods

The literature search was conducted using the Sciencedirect, Medline, Pub-Med and Scopus data bases. The key words used for the search engine was as follows: “Turmeric” or “Curcumin” AND “Cancer” OR “Alzheimer’s disease” OR “Cardiovascular Heart Diseases” OR “Arthiritis” OR “degenerative diseases”. More than 45 original research and review articles in English language dated within last 14 years were scanned, 26 of which were selected and used for this overview.

3. Curcumin

3.1. Chemistry and bioavailability

Indian saffron or turmeric owes its bright golden colour to its active ingredient the curcuminoids, including curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%). Other ingredients include various volatile oils, including tumerone, atlantone, and zingiberone, sugars, proteins, and resins [5]. Curcumin (*diferuloyl methane*) is a polyphenol that constitutes approximately 3-4% by weight of the turmeric and has several biological functions [3]. Curcumin has been reported to exhibit poor bioavailability. The major reasons attributed to the low bioavailability of curcumin are poor absorption, rapid metabolism, and rapid systemic elimination. Although, a comprehensive pharmacokinetic data does not exist, pilot studies indicate that low systemic bioavailability in humans following oral doses. In a clinical study performed on 25 patients with pre-malignant lesions, a dose of 500 mg/day was given initially, the dose was then escalated in the order of 1000, 2000, 4000, 8000, and 12,000 mg/day. The researchers noticed no treatment-related toxicity up to 8 g/day but the bulky volume of the drug was unacceptable to the patients beyond 8 g/day. The serum concentration of curcumin usually peaked at 1–2 h after oral intake of curcumin and gradually declined within 12 hours [6]. In another study, curcumin in the serum samples were detected only in those individuals, who took 10 -12 g curcumin/day [7]. The systemic elimination of curcumin is another contributing factor for low bioavailability of curcumin. Studies conducted on rats reported that after oral administration

of 1 g/kg curcumin, more than 75% of curcumin was excreted in feces and negligible amount was detected in urine. Combining curcumin with piperine was shown to increase the bioavailability in rats and in human subjects upto several hundred times [8]. Other ways to improve the bioavailability of curcumin was to administer in the form of nanoparticles as liposomes, micelles and phoshoplipid complexes. The possible advantages attributed to such formulations were (a) longer circulation; (b) increasing the cellular permeability and (c) inducing resistance to metabolic processes [8].

Figure 1. Curcuma longa plant and the rhizome

4. Anti-oxidative activity of Curcumin

Oxidative damage is believed to be one of the mechanisms behind ageing and many diseases. The damage involves free radicals which are highly reactive molecules with unpaired electrons, that tend to react with important organic substances, such as fatty acids, proteins or DNA. The free radical-scavenging mechanism of curcumin was reported to be enhanced by the phenolic hydrogens present in the curcumin molecule which played a major role in the anti-oxidant activity as compared to the –CH2 hydrogen, against lipid peroxidation and free radical scavenging activities [5]. Daily intake of curcumin or turmeric was reported to have delayed the onset of cataracts. Oxidative damage to the constituents of the eye lens is considered to be a major mechanism in the initiation and progression of various types ofcataracts, including diabetic cataracts. Diabetes causes increased oxidative stress in various tissues, as evidenced by increased levels of oxidized DNA, proteins, and lipids, which are thought to play an important role in the pathogenesis of various diabetic complications. Curcumin also played a major role in inhibiting lipid peroxidation (LPO), thereby providing protection against cardiovascular heart diseases and some forms of cancer [1, 5].

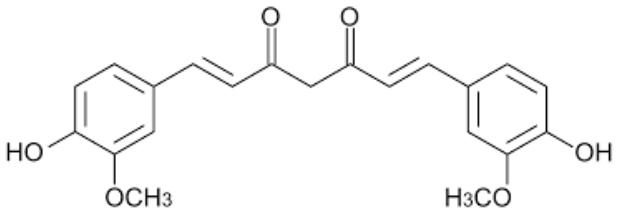

Figure 2. Chemical structure of Curcumin

5. Anti-Inflammatory Effects

It is now believed that chronic, low-level inflammation plays a major role in almost every chronic, degererative disease including cardiovascular heart disease, cancer, metabolic syndrome, Alzheimer's and various degenerative conditions. The volatile oils and curcumin of Curcuma longa exhibited potent anti-inflammatory effects. Oral administration of curcumin in instances of acute inflammation was found to be as effective as cortisone or phenylbutazone, and one-half as effective in cases of chronic inflammation. Curcumin may also be applied topically to counteract inflammation and irritation associated with inflammatory skin conditions and allergies. Curcumin's anti-inflammatory properties may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins from arachidonic acid, and neutrophil function during inflammatory states [4].

Epidemiological studies have shown that chronic inflammation predisposes individuals to various types of cancer [9]. Inflammation is also considered to be a critical initial step in the development of atherosclerosis [10]. Curcumin raises interest as an agent of potential use in therapy of many diseases other than cancer, with inflammation constituents including cardiovascular diseases, Alzheimer's disease, rheumatoid arthritis and metabolic syndrome. Curcumin blocks NF-kB, a molecule that travels into the nuclei of cells and turns on genes related to inflammation. NF-kB is believed to play a major role in many chronic diseases [9]. Curcumin has also been shown to inhibit the production of other pro-inflammatory factors as monocyte / macrophage-derived cytokines; interleukin- 8 (IL-8), monocyte inflammatory protein-1 (MIP-1), monocyte chemotactic protein-1 (MCP-1), interleukin-1b (IL-1b), and tumor necrosis factor-a (TNF- a) [3].

6. Curcumin's Effect on Chronic Inflammatory Diseases

6.1 Cardiovascular Heart Diseases:

Endothelial function is a key determinant of vessel wall and myocardial function in health and disease. During ischemia and other stress states, the endothelium becomes activated and later on dysfunctional producing reduced amounts of antioxidants and anti-inflammatory molecules. Inflammation plays a powerful etiologic role in the determination of myocardial infarct size after coronary artery occlusion [11]. The inflammatory cascade begins soon after ischemia and involves release of large amounts of reactive oxygen species (ROS) and activation of pro-inflammatory proteins and transcription factors particularly nuclear factor kB (NF-kB) and and activating protein-1(AP-1). The release of ROS and the inflammatory state also regulate Ca++ movement across the sarcoplasmic reticulum and regulate myocardial contractility. Curcumin was shown to provide protection against the adverse effect of tumor necrosis factor (TNF)-a and activate the inflammatory factors as intracellular cell adhesion molecule-1, monocyte chemoattractant protein (MCP)-1, and interleukin (IL)-8 at mRNA and protein levels [12].

6.2 Cancer

Cancer is a hyper-proliferative disorder where a normal cell loses its cellular homeostasis and a plethora of genes, involved in cell cycle, invasion, survival, metastasis, and angiogenesis, are activated. Curcumin has been found to suppress initiation, progression, and metastasis of a variety of tumors. The anti-cancer effects of curcumin are predominantly mediated through its negative regulation of various transcription factors, growth factors, pro- inflammatory cytokines like TNF-a and NF-kB, inflammatory enzymes like Inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), lipooxygenase (LOX), protein kinases, and other oncogenic molecules. It also abrogates proliferation of cancer cells by arresting them at different phases of the cell cycle and/or by inducing their apoptosis [9]. Various *in vitro* as well as *in vivo* studies demonstrated that curcumin can inhibit the growth of various cancer cells from different organs including, blood, brain, breast, gastrointestinal system, head and neck, liver, pancreas, colon, prostate, ovary and skin cancers. Dietary curcumin significantly suppressed azoxymethane-induced colonic preneoplastic lesions, colon tumor incidence and multiplicity, radiation-initiated mammary tumorigenesis and effectively inhibited implantation and growth of bladder tumor cells in mice [8]. Angiogenesis, a fundamental process by which new blood vessels are formed from existing vessels, is essential in reproduction, development, and wound healing as well as tumour growth and metastasis. Curcumin has been shown to interfere with many of the processes involved in angiogenesis as inhibition of growth factors, angiogenic receptor activities, regulation of intracellular, vascular, endothelial leukocyte adhesion molecules and cell surface proteins involved in tumor metastasis [3].

6.3. Neurogenerative disorders

Curcumin has been proposed as a potential remedy against brain ageing and neurodegenerative disorders. It exhibits activity against various neurologic diseases, including Alzheimers disease (AD), multiple sclerosis, Parkinson's disease, epilepsy, cerebral injury, age-associated neurodegeneration, schizopherenia, spongiform encephalopathies, neuropathic pain and depression (13, 14). AD is a neuro-degenerative disease that involves inflammation, oxidative damage, and amyloid beta plaques accumulation in the brain. Abeta can efficiently generate ROS in the presence of the transition metals (Cu and Fe) causing functional impairment of neurones. Curcumin reduced levels of amyloid and oxidized proteins and prevented cognitive deficits. Metals can induce Abeta aggregation and toxicity and are concentrated in AD brain. Thus chelation of metals can reduce amyloid aggregation and oxidative neurotoxicity. Each Cu2+ or Fe2+ ion can bind at least two curcumin molecules (8). *In vivo* studies with mice showed that, injected curcumin could cross the blood brain barrier and bind to the abeta amyloid plaques and reduced amyloid levels, plaque formation and aggregation. Curcumin was also found to enhance the uptake of abeta molecules by macrophages for the clearance of amyloid plaqes [15]. Manganese (Mn) is an essential ubiquitous trace element that is required for normal growth, development and cellular homeostasis. However, overexposure to high Mn levels causes a clinical disease characterized by extrapyramidal symptoms resembling idiopathic Parkinson's disease [16]. In a study performed by Nigam et al on rat brain cells exposed to high Mn levels in the form of $MnCl_2$ (8 mg/kg /orally day) the group receiving curcumin in the form of turmeric (1g/body weight/orally day) had significantly lower levels of reactive oxygen species, lipid peroxidation potential, conjugated dienes, glutathione reductase and glutathione peroxidase as compared to the other groups. The study suggests that turmeric exhibits neuroprotection against free radical-mediated neurotoxicity of Mn [17].

6.4. Diabetes and Glucose metabolism

Diabetes is a disorder of glucose metabolism that affects the brain, kidney, heart, liver, and other organs. Several reports have suggested that curcumin might be of value in treatment of diabetes. Curcumin lowered blood glucose in streptozotocin-treated rats [18], and has been reported to

markedly improve blood glucose and insulin sensitivityin mouse models of diabetes [19]. Inflammation has been shown to play a major role in development of type II diabetes. Activation of various inflammatory cytokines and transcription factors (such as TNF-a, NF-kB) have been linked to insulin resistance. One of the mechanism by which curcumin improves this situation may be by its hypocholesterolemic influence, antioxidant nature, and free-radical scavenging property. Obesity is a major risk factor for type 2 diabetes and curcumin has been reported to cause a significant reduction in blood glucose and serum cholesterol levels in rats. Glucose production through gluconeogenesis and glycogenolysis was inhibited upto 45% in isolated rat hepotocytes on 120 min exposure to 25 mM curcumin by affecting the funcioning of some of the enzymes of the pathways [20]. Curcumin was also reported to have increased insulin production by the islet cells of the pancreas by protecting the organ tissues against ROS. In a study performed by Greene et al, on rat adipocytes, curcumin was found to inhibit insulin signaling and translocation of GLUT4 to the cell surface of adipocytes but had no effect on insulin inhibition of lipolysis [21].

6.5 Digestive Diseases

Curcumin has been reported to exert several protective effects on the gastrointestinal tract. Curcumin has been shown to stimulate secretion of bile with higher amount of bile acids which play a major role in digestion and absorption of dietary lipids. 40 mg oral curcumin incresed bile production by 50% [5]. In a study performed by Prakash et al, dietary ginger (0.05%), piperine (0.02%), capsaicin (0.015%), and curcumin (0.5%) were examined for their influence on bile secretion, digestive enzymes of pancreas and absorption of dietary fat in high-fat (30%) fed Wistar rats for 8 weeks. These spices enhanced the activity of pancreatic lipase, amylase, trypsin and chymotrypsin by 22-57%, 32-51%, 63-81% and 12-38%, respectively. Dietary intake of spices along with high-fat enhanced fat absorption [22]. Besides, sodium curcuminate, a turmeric component, increased gastrin, secretin, bicarbonate, and pancreatic enzyme secretion [4]. Turmeric was also shown to inhibit ulcer formation caused by stress, alcohol, indomethacin, pyloric ligation, and reserpine, significantly increasing gastric wall mucus in rats [4]. Akram et al, in his study reported that Curcumin inhibits the growth of Helicobacter pylori, which causes gastric ulcers and has been linked with gastric cancers. Curcumin can chelate various metal ions to form metallo-complexes of curcumin which show greater effects than curcumin alone. Zn(II)–curcumin complex showed significant gastroprotective and antidepressant effects compared with curcumin alone via a synergistic effect between curcumin and zinc [23]. Curcumin has also been suggested as a remedy for digestive diseases such as inflammatory bowel diseases (IBD), a chronic immune disorder affecting the gastrointestinal tract. Mechanism of action for the use of curcumin in the treatment of IBD is unknown, but there is abundant evidence proving its effects on pro-inflammatory pathways in the intestinal mucosa [23].

7. Other Effects

Anti-inflammatory properties of Curcumin has been shown to relieve the aches and pains associated with arthiritis. Curcumin has been used for the chemoprevention and treatment of various skin diseases like scleroderma, psoriasis and skin cancer. Curcumin protects skin by quenching free radicals and reducing inflammation through NF-κB pathway inhibition. The herb's volatile oils functions as external antibiotics, preventing bacterial infection in wounds. Curcumin also modulates the detoxification enzymes which are crucial in detoxification reactions and for protection against oxidative stress [5, 24]. Turmeric has been found to have a hepatoprotective property against carbon tetrachloride (CCl_4), galactosamine, acetaminophen (paracetamol), and Aspergillus aflatoxin. Curcumin has also been shown to reduce the hepatotoxicity induced by heavy metals as arsenic, cadmium, chromium, copper, lead and mercury, prevents histological injury, lipid peroxidation and glutathione (GSH) depletion, maintains the liver antioxidant enzyme status and protects against mitochondrial dysfunction [25]. Turmeric's hepatoprotective effect is mainly a result of its scavenging

and chelating properties, as well as its ability to decrease the formation of pro-inflammatory cytokines [25]. Curcumin has been shown to enhance immunity in general. Scientisits have documented increased antibodies and more immune action in mice given curcumin [4]. Apart from local immunity, curcumin has been suggested to be a candidate for treatment of autoimmune neuropathies in a study performed by Han et al, where T-cell mediated experimental neuritis – an autoimmune disease in rats were controlled by curcumin administration. Curcumin modulated T-cell differentriation and reduced inflammation [26].

8. Conclusions

The extensive research and numerous investigations that has been performed over the past four decades suggest that curcumin has great potential in the prevention and cure of many diseases. Curcumin modulates several biochemical pathways and numerous targets involved in cancers. Orally administered curcumin has poor bioavailability and tissue accumulation, however, metallo-complexes of curcumin have been found to be more bio-available and effective. Toxic or side effects of curcumins are not known. Overall, the biological safety, combined with its cost and efficacy and thousands of years of experimentation and use in India and Asian countries probably justify calling curcumin as the miraculous golden ingredient of turmeric.

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