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Review article

PHARMACOTHERAPEUTICS OF CURCUMA LONGA- A POTENT PATENT

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Abstract

Many herbal remedies individually or in combination have been recommended in various medical treatises for the cure of different diseases. The therapeutic value of *Curcuma longa* Linn. commonly known as Turmeric has been recognized in different systems of traditional medicine for the treatment of diseases and human ailments. It contains several phytoconstituents belonging to category of alkaloids, glycosides, triterpenoids, sterols and volatile oils. It has been reported to cure inflammation, wounds, infections and acts as a carminative. Several studies using modern techniques have authenticated its use as anti inflammatory, antimicrobial, anti-fertility, anticancer, anti diabetic, antioxidant, hypolipidemic, anti venom, anti hepato-toxic, nephroprotective, anticoagulant etc. Most importantly, the plant has shown to possess anti HIV activity which could be of great value to combat AIDS particularly in third world countries.

Keywords: Curcuma longa, Turmeric, Curcumin, anti-inflammatory activity, antimicrobial activity, anti fertility activity.

Introduction

Herbal drugs have a great growth potential in global market. Research work on chemistry of natural products, pharmacognosy, pharmaceutics, pharmacology and clinical therapeutics have been carried out on herbal drugs and most of the leading pharmaceutical corporations have revised their strategies in favour of natural products.

Plants have long been the principal tools of traditional medicinal systems. Despite convincing progress in synthetic Traditional or indigenous drugs used by different ethnic groups of the world for treatment of disease have special significance of having been tested on long time scale. This is attributed relatively safe nature, easily availability and provides economy to masses. Traditional drugs have given important lead in drug research, resulting in the discovery chemistry and biotechnology, plants are still important sources for preventive and curative medicinal products. of novel molecules. Artemisinine for the cure of multi drug resistant malaria, Theophylline for broncho-dialation, caffeine for CNS stimulation, Glycyretinic Acid for peptic ulcer treatment, Silymarin for hepatoprotection and Vincristine and Vinblastine for certain cancers have already been isolated from plants and sincere efforts for curing immunity related problems, AIDS, Alzheimer's and Diabetes are on the way.

For variety of reasons, popularity of complimentary medicines is on increase. Traditional plant therapies coupled with dietary measures as prescribed Ayurvedic and other indigenous systems of medicines has proven results in a number of health disorders. In Australia and U.S., a sizeable number of populations use at least one form of unconventional therapy including herbal medicines [1,2]. This review focuses on certain pharmacological potentials about turmeric so that some other chemical moieties may be designed for some other disorders and can give a boost on research on this plant. This plant needs much attention because turmeric powder being part of diet carries a greater compliance value for the patients. So it needs more pharmacological exploration.

Curcuma longa L., a perennial herb which is known as turmeric, is a member of the *Zingiberaceae*. It is a sterile plant and does not produce any seeds. The plant grows up to 3-5 ft tall and has dull yellow flowers. The underground rhizomes or roots of the plant are used for medicinal and food preparation. The rhizome is an underground stem that is thick and fleshy ringed with the bases of old leaves. Rhizomes are boiled and then dried and ground to make the distinctive bright yellow spice, turmeric. The plant has oblong, pointed leaves with funnel-shaped yellow flowers [3,4].

Turmeric was described as *C. longa* by Linnaeus and its taxonomic position is as follows:

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Class Liliopsida
Subclass Commelinids
Order Zingiberales
Family Zingiberaceae
Genus *Curcuma*
Species *Curcuma longa*

Traditional Uses

Turmeric has a long history of medicinal use in South Asia and was widely used in Ayurvedic, Siddha and Unani systems. It possesses antiseptic, anti-inflammatory and detoxifying properties [4]. It is also used to treat gastrointestinal upsets, arthritis pain, and "low energy." In traditional Indian Ayurvedic medicine, turmeric has been used as a tonic for the digestive system and the liver; to dispel worms, strengthen the body, and dissolve gallstones; and for menstrual irregularity and arthritis. In old Hindu texts it is described as an aromatic, stimulant, and carminative. Mixed with slaked (hydrated) lime, turmeric is a well known household remedy for sprains and swellings caused by injury [5].

Chemical Constituents

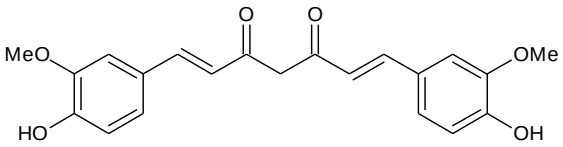
Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). Phenolic diketone, curcumin (diferuloylmethane) (3–4%) is responsible for the yellow colour, and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%). Other phenolic diketones demethoxycurcumin and bis-demethoxycurcumin have also been isolated from the rhizomes of *Curcuma longa* (Chattopadhyay et. al., 2004). Presence of tumerones (a and b), curdione, curzerenone, mono- and di-demethoxycurcumin have been reported in the rhizomes. The essential oil (5.8%) obtained by steam distillation of rhizomes has *a*-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%) [6].

The essential oils of leaves of *C. longa* have been analyzed by GLC (Perkin–Elmer auto-system fitted with capillary column carbowax 20 m of 50 m length flux ionization detector) and reported to contain *α*-pinene, *β*-pinene, sabinene, myrcene, *a*-phellandrene, 1,8-cineole, *p*-cymene, C_8-aldehyde, linalool, caryophyllene, geraniol and methyl heptanone [7].

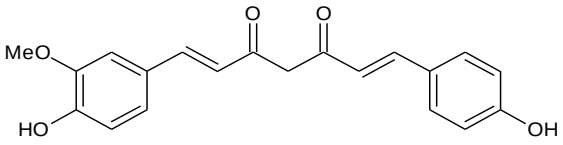
One novel sesquiterpene with new skeleton, (6S)-2-methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one, two new bisabolane sesquiterpenes, (6S)-2-methyl-6-(4-hydroxyphenyl)-2-hepten-4-one, (6S)-2-methyl-6-(4-formylphenyl)-2-hepten-4-one, and two calebin derivatives, 4''-(4'''-hydroxyphenyl-3'''-methoxy)-2''-oxo-3''-butenyl-3-(4'-hydroxyphenyl)-propenoate and 4''-(4'''-hydroxyphenyl)-2''-oxo-3''-butenyl-3-(4'-hydroxyphenyl-3'-methoxy)-propenoate were isolated along with five known bisabolane sesquiterpenes from *C. longa*. The structures have been elucidated by spectral methods [8].

Structures

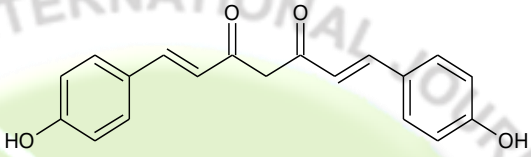
Curcumin I



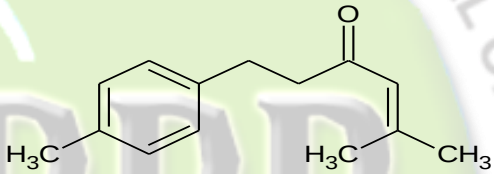
Curcumin II



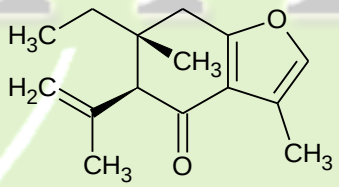
Curcumin III



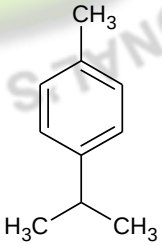
Ar-tumerone



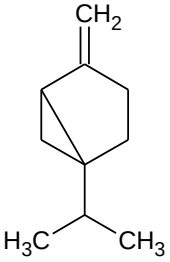
Curzerone



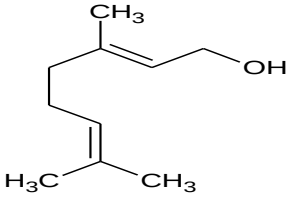
α-phellandrene



Sabinene



Geraniol



Pharmacological Activities

Anti inflammatory activity

The petroleum ether extract of the rhizomes of *Curcuma longa* (turmeric) showed significant anti-inflammatory activity (AIA) and was effective in delayed hypersensitivity. In granuloma pouch method, the water extract was the most potent with activity comparable to Indomethacin [9,10]. Curcumin, a constituent of turmeric, chemically, known as diferuloylmethane has been known to be effective [11]. It is as potent as Phenylbutazone in the carrageenan induced oedema test but half as potent in chronic tests. In subacute inflammation models in rats, it is found to be a stabilizer of lysosomal membrane (more potent than Ibuprofen) and as an uncoupler of oxidative phosphorylation [12]. Two naturally occurring curcumin–related analogues, feruloyl-4-hydroxycinnamoylmethane and bis (4– hydroxycinnamoyl) methane, have shown AIA. Water soluble sodium curcuminate showed better AIA than curcumin in albino rats. The potencies of the curcumin analogues and Phenylbutazone in the carrageenan oedema, cotton pellet granuloma tests were in the order: sodium curcuminate > tetrahydrocurcumin > curcumin > phenylbutazone > triethylcurcumin [13].

It has been found that curcumin regulates numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation [14]. Administration of curcuminoids 50 mg/kg body weight orally daily for 3 weeks decreased MDA (gastric mucosal lipid peroxidation), gastrin, and NO, and normalized mucosal GSH (gastric mucosal glutathione) but failed to affect serum pepsinogen level [15]. A number of studies have been conducted that support curcumin-mediated regulation of COX and LOX pathways, which is an important mechanism by which curcumin prevents a number of disease processes, including the cancer. The specific regulation of 5-LOX and COX-2 by curcumin is not fully established; however, existing evidence indicates that curcumin regulates LOX and COX-2 predominately at the transcriptional level and, to a certain extent, the posttranslational level. Thus, the curcumin-selective transcriptional regulatory action of COX-2, and dual COX/LOX inhibitory potential of this naturally occurring agent provides distinctive advantages over synthetic COX/LOX inhibitors, such as non steroidal anti-inflammatory drugs [16]. It has been found that in inhibiting the granulomatous tissue formation, maximum activity was observed with triethyl curcumin whereas curcumin, sodium curcuminate and phenylbutazone were almost half as effective as triethyl curcumin. It is thought that the anti-inflammatory action of sodium curcuminate is not mediated through release of steroids from the adrenal cortex or inhibition of the biosynthesis of prostaglandins from arachidonic acid [17]. Curcumin, demethoxycurcumin (DMC),bisdemethoxycurcumin (BDMC), tetrahydrocurcumin (THC) and turmerones, have been reported to exhibit chemopreventive activity by modulating inflammatory signaling and cell proliferation signaling. The relative potency for suppression of tumor necrosis factor (TNF)-induced nuclear factor-kappa B (NF-kappa B) activation was Cur > DMC > BDMC; thus suggesting the critical role of methoxy groups on the phenyl ring. THC, which lacks the conjugated bonds in the central seven-carbon chain, was completely inactive for suppression of the transcription factor. Turmerones also failed to inhibit TNF-induced NF-kappa B activation. The suppression of NF-kappa B activity correlated with inhibition of NF-kappa B reporter activity and with down-regulation of cyclooxygenase-2, cyclin D1 and vascular endothelial growth factor, all regulated by NF-kappa B. In contrast to NF-kappa B activity, the suppression of proliferation of various tumor cell lines by Cur, DMC and BDMC was found to be comparable; indicating the methoxy groups play minimum role in the growth-modulatory effects of curcumin. THC and turmerones were also found to be active in suppression of cell growth but to a much lesser extent than curcumin, DMC and BDMC [18]. Curcumin (50-100 mg/kg, p.o.) significantly attenuated the damage and caused substantial reductions of the rise in MPO (myeloperoxidase activity) activity and tumour necrosis factor alpha (TNF)-alpha. Also curcumin was able to reduce nitrites colonic levels and induced down-regulation of COX-2 and iNOS (inducible nitric oxide synthase) expression, and a reduction in the activation of p38 MAPKs (Mitogen-activated protein kinases). However, no changes in the activation of JNK (c-Jun N-terminal kinase) were observed. In conclusion, it is suggested that inhibition of p38 MAPK signaling by curcumin could explain the reduced COX-2 and iNOS immunosignals and the nitrite production in colonic mucosa reducing the development of chronic experimental colitis [19]. In a study it has been shown that crude organic extracts of turmeric were capable of inhibiting LPS-induced TNF-alpha (IC50 value = 15.2 microg/ml) and PGE2 (IC50 value = 0.92 microg/ml) production. Purified curcumin was more active than either demethoxy- or bisdemethoxycurcumin. A combination of several of the fractions that contain the turmeric oils was more effective than the curcuminoids at inhibiting PGE2. While curcumin inhibited COX-2 expression, turmeric oils had no effect on levels of COX-2 mRNA [20].

Antidiabetic and Antioxidant activity

Combination of *Curcuma longa* and *Abroma augusta* have been screened for their protective effect against reactive oxygen species induced lipid peroxidation. They have been found to be efficient antioxidant when administered in combination in sterptozotocin induced diabetic rats. The administration of an aqueous extract of turmeric and abromine powder resulted in a significant reduction in blood glucose and an increase in total haemoglobin, decrease in free radical formation, thiobarbituric acid reactive substances (TBARS) and increase in reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) clearly. It suggested that the mixture of the two plants have shown antidiabetic activity and also reduced oxidative stress in diabetes [21].

Reports are there which indicate that the active components of *Curcuma longa* such as curcumin and tetrahydrocurcumin (THC) possess antidiabetic activity. The effect of THC on glycoproteins was carried out in normal and streptozotocin-nicotinamide induced type 2 hyperglycaemic rats for 45 days. Oral administration of THC to diabetic rats showed a decrease in the level of blood glucose and plasma glycoproteins. The levels of plasma insulin and tissue sialic acid were increased where as the levels of tissue hexose, hexosamine and fucose were near normal in diabetic rats treated with THC. The study indicated that the THC possesses a significant beneficial effect on glycoprotein moiety in addition to its antidiabetic effect. The effect of THC is more prominent than curcumin [22].

The turmeric ethanolic extract (E-ext) containig both curcuminoids and sesquiterpenoids, hexane extract (H-ext) containig sesquiterpenoids, and ethanol extraction from hexane-extraction residue (HE-ext) containig curcuminoids were tested for antidiabetic activity.

Although blood glucose levels in the control group significantly increased ($P < 0.01$) after 4 weeks but feeding of 0.2 or 1.0 g of E-ext, 0.5 g of H-ext, and 0.5 g of HE-ext/100 g of diet suppressed the significant increase in blood glucose levels. E-ext also stimulated human adipocyte differentiation, and these turmeric extracts had human peroxisome proliferator-activated receptor-γ (PPAR- γ) ligand-binding activity in a GAL4-PPAR- γ chimera assay. Also, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone had PPAR- γ ligand-binding activity. These results indicated that both curcuminoids and sesquiterpenoids in turmeric exhibit hypoglycemic effects via PPAR- γ activation as one of the mechanisms, and suggest that E-ext including curcuminoids and sesquiterpenoids has the additive or synergistic effects of both components [23].

Free radical scavenging activity of dry powder of turmeric has been investigated using a stable radical DPPH [24]. A study has been done to test individual curcuminoids, such as curcumin, bisdemethoxycurcumin and demethoxycurcumin, for their antioxidant activities by in vitro model systems, such as the phosphomolybdenum and linoleic acid peroxidation methods. Antioxidant capacities of the extracts, as ascorbic acid equivalent (μmol/g) were in the order: curcumin > demethoxycurcumin > bisdemethoxycurcumin. In comparison with butylated hydroxyl toluene (BHT), at 100 ppm, the antioxidant activity, by linoleic acid peroxidation, was found to be highest with curcumin, followed by demethoxycurcumin and bisdemethoxycurcumin. The data obtained by the in vitro models clearly establish the antioxidant potencies of individual curcuminoids. This is the first report on antioxidant activity of individual curcuminoids using the phosphomolybdenum method and linoleic acid peroxidation method [25]. A study has been performed on female Swiss mice in which control group was fed the standard diet and other group received 4 mg/Kg /day of hydroalcoholic extract of turmeric along with food (equivalent to 0.4 mg/Kg/day curcumin). The effects of the treatment were determined weekly by measuring food intake, body weight and muscular and CNS function (evaluating performance of mice subjected to string and T-maze tests). After four weeks of treatment there was a decrease in the level of both plasma and liver lipid peroxides [26].

Curcuma longa along with *Emblica officianalis* and *Salacia oblonga* is used in a marketed ayurvedic preparation, *Rajanyamalakadi* for the treatment of Type II diabetes mellitus [27].

Anticancer/ Antitumour/ Antiproliferative effects

The antiproliferative effects of curcumin against several breast tumor cell lines, including hormone-dependent and -independent and multidrug-resistant (MDR) lines have been examined. All the cell lines tested, including the MDR-positive ones, were highly sensitive to curcumin. The growth inhibitory effect of curcumin was time- and dose-dependent, and correlated with its inhibition of ornithine decarboxylase activity. Curcumin preferentially arrested cells in the G2/S phase of the cell cycle. Curcumin-induced cell death was neither due to apoptosis nor to any significant change in the expression of apoptosis-related genes, including Bcl-2, p53, cyclin B and transglutaminase [28]. Studies have exhibited that Ar-turmerone treatment inhibited U937 cell viability in a concentration dependent fashion, with inhibition exceeding 84%. Moreover, the treatment produced nucleosomal DNA fragmentation and the percentage of sub-diploid cells increased in a concentration-dependent manner; both are hallmarks of apoptosis. The apoptotic effect of ar-turmerone was associated with the induction of Bax and p53 proteins, rather than Bcl-2 and p21. Activation of mitochondrial cytochrome *c* and caspase-3 demonstrated that the activation of caspases accompanied the apoptotic effect of ar-turmerone, which mediated cell death. It was suggestivfe that the apoptotic effect of ar-turmerone on U937 cells may involve caspase-3 activation through the induction of Bax and p53, rather than Bcl-2 and p21 [29]. The antiproliferative capacity of both

oxaliplatin and curcumin was compared in HCEC (normal-derived), HT29 (p53 mutant adenocarcinoma) and HCT116 (p53wt adenocarcinoma) colorectal cell lines to determine whether effects were cell-type specific at pharmacologically achievable doses, and whether the combination resulted in enhanced efficacy. Both oxaliplatin and curcumin displayed marked antiproliferative capacity at therapeutic concentrations in the two tumor cell lines. Order of sensitivity to oxaliplatin was HCT116>HT29>HCEC, whereas order of sensitivity to curcumin was HT29>HCT116>HCEC. HCT116 cells underwent induction of G2/M arrest in response to both oxaliplatin (irreversible) and curcumin (reversible). Apoptosis was induced by both agents, and up to 16-fold induction of p53 protein was observed in response to the combination. Antiproliferative effects in HT29 cells were largely cell cycle independent, and were mediated by induction of apoptosis. Effects were greatly enhanced in both cell lines when agents were combined. There is a strong evidence that curcumin may be of use in therapeutic regimes directed against colorectal cancer, and suggests that in combination with oxaliplatin it may enhance efficacy of the latter in both p53wt and p53 mutant colorectal tumors [30]. Studies have indicated that curcumin can sensitize pancreatic cancer to gemcitabine *in vitro* and *in vivo*. *In vitro*, curcumin inhibited the proliferation of various pancreatic cancer cell lines, potentiated the apoptosis induced by gemcitabine, and inhibited constitutive NF-κB activation in the cells. *In vivo*, tumors from nude mice injected with pancreatic cancer cells and treated with a combination of curcumin and gemcitabine showed significant reductions in volume (P = 0.008 versus control; P = 0.036 versus gemcitabine alone), Ki-67 proliferation index (P = 0.030 versus control), NF-κB activation, and expression of NF-κB–regulated gene products (cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, cyclooxygenase-2, matrix metalloproteinase, and vascular endothelial growth factor) compared with tumors from control mice treated with olive oil only. The combination treatment was also highly effective in suppressing angiogenesis as indicated by a decrease in $CD31^+$ microvessel density (P = 0.018 versus control) [31]. It has been demonstrated curcumin-induced apoptosis in the breast cancer cell line MCF-7, in which expression of wild-type p53 could be induced. Apoptosis was accompanied by an increase in p53 level as well as its DNA-binding activity followed by Bax expression at the protein level [32]. It has been shown that curcumin induces chemoprotective anti-inflammatory activity in prostate cells by Map kinase phosphate-5 [33]. Curcumin, the yellow pigment in the spice turmeric, has profound anti-inflammatory activity and exhibits chemopreventive and tumor growth inhibitory activity. In the present study, we investigated whether curcumin sensitizes malignant glioma cell lines U251MG and U87MG to TRAIL-induced apoptosis. Treatment with low concentrations (5-20 microM) of curcumin alone had no effect on the viability of either cell line. At low concentration (5 ng/ml) TRAIL induced cytotoxicity in U251MG cells but not in U87MG cells. Whereas curcumin at subtoxic concentration sensitized U87MG cells to TRAIL-induced cytotoxicity, it had no effect on TRAIL-mediated cytotoxicity in U251MG cells. The combined curcumin and TRAIL treatment enhanced accumulation of hypo-diploid U87MG cells in sub G1 cell cycle phase and induced the cleavage of procaspases-3, -8, -9 and release of cytochrome c from mitochondria [34]. Curcumin treatment resulted an increase in the protein levels of both Bax and Bak, and mitochondrial translocation and activation of Bax in MEFs to trigger drop in mitochondrial membrane potential, cytosolic release of apoptogenic molecules [cytochrome c and second mitochondria-derived activator of caspases (Smac)/direct inhibitor of apoptosis protein-binding protein with low isoelectric point], activation of caspase-9 and caspase-3 and ultimately apoptosis [35]. polymeric nanoparticle encapsulated formulation of curcumin – nanocurcumin – utilizing the micellar aggregates of cross-linked and random copolymers of N-isopropylacrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly(ethyleneglycol)monoacrylate (PEG-A). Physico-chemical characterization of the polymeric nanoparticles by dynamic laser light scattering and transmission electron microscopy confirms a narrow size distribution in the 50 nm range. Nanocurcumin, unlike free curcumin, is readily dispersed in aqueous media. Nanocurcumin demonstrates comparable *in vitro* therapeutic efficacy to free curcumin against a panel of human pancreatic cancer cell lines, as assessed by cell viability and clonogenicity assays in soft agar. Further, nanocurcumin's mechanisms of action on pancreatic cancer cells mirror that of free curcumin, including induction of cellular apoptosis, blockade of nuclear factor kappa B (NFκB) activation, and downregulation of steady state levels of multiple pro-inflammatory cytokines (IL-6, IL-8, and TNFα) [36].

Neuroprotective and anti ageing effects

It has been reported that curcumin is used in the treatment of Alzheimer's disease as it can decrease beta-amyloid plaques, delay degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decrease microglia formation and this results in the overall memory in patients with Alzheimer's disease gets improved [4]. It has been investigated that curcumin on chronically administration can influence normal ageing-related parameters: lipid peroxidation, lipofuscin concentration and intraneuronal lipofuscin accumulation, activities of the enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx), and Na^+, K^+, -adenosine triphosphatase (Na^+, K^+, -ATPase) in different brain regions (cerebral cortex, hippocampus, cerebellum and medulla) of 6- and 24-month-old rats. Chronic curcumin treatment of both 6 and 24 months old rats resulted in significant decreases in lipid peroxide and the lipofuscin contents in brain regions, the activities of SOD, GPx and Na^+, K^+, -ATPase however, showed significant increase in various brain regions [37]. Studies have shown that curcumin improves memory in mice and has neuroprotective effect of curcumin *in vitro* and *in vivo* [38]. Chronic treatment with curcumin (10, 20 and 50 mg/kg, p.o.) once daily for a period of 8 days beginning 4 days prior to 3-NP administration dose-dependently improved the 3-nitorpropionic acid (3-NP)-induced motor and cognitive impairment. Biochemical analysis revealed that curcumin administration significantly attenuated 3-NP-induced oxidative stress (lipid peroxidation estimation, reduced glutathione and nitrite activity) in the brains of rats. It also significantly restored the decreased succinate dehydrogenase activity. The results of the present study

clearly indicate that curcumin by its antioxidant activity showed neuroprotection against 3-NP-induced behavioral and biochemical alteration [39].

Hepatoprotective effect

Turmeric ingestion decreased hepatocyte peroxidation in both well-nourished (42%) and malnourished rats (33%) and was able to avoid the acetaminophen pro-oxidant effect in both well-nourished and malnourished animals. Turmeric ingestion played a beneficial role to the organism and, therefore, can be considered a functional food [40]. It has been found out that turmeric together with its sesquiterpenes and curcuminoids fractions has hepatoprotective effect on D-galactosamine induced liver injury in rats. The turmeric extract, the curcuminoids fraction, and the sesquiterpenes fraction suppressed the increase of LDH, ALT, and AST levels caused by D-GalN treatment [41]. This study aims to evaluate the hepatoprotective effect of the standard extracts from *Curcuma longa* and *Andrographis paniculata* (Turmeric and AP-extracts). It has been revealed that oral administration of the turmeric extract exhibited hepatoprotective activities against CCl_4 induced hepatotoxicity but not against acetaminophen induced hepatotoxicity [42].

Nephroprotective effects

According to a study *Curcuma longa* has revealed the nephroprotective activity against acetaminophen induced nephrotoxicity in mice. The protective mechanism may be due to direct binding with acetaminophen toxic metabolites and decreasing the attraction of acetaminophen metabolites for other cellular GSH. Additionally it has been reported that *Curcuma longa* treatment increased the concentration of hepatic GSH and maintained a high level activity of GSTase (glutathione-S-transferase) which led to increase in the excretion of toxic acetaminophen metabolites [43].

Antiparasitic effects

The methanolic extract of Rhizomes of *C. longa* was found to possess antimicrobial activity against *Bacillus subtilis, Staphylococcus aureus, Listeria monocytogenes* and *Proteus vulgaris* [44]. The antimicrobial efficacy of turmeric (*Curcuma longa*) has been evaluated against five strains of *Listeria monocytogenes* and four strains of *Salmonella enterica* ssp. *enterica* sero var. Typhimurium DT104. Antimicrobial activity was investigated in microbiological media by using an agar dilution assay and enumeration over time and a model food system, apple juice, by monitoring growth over time. In the agar dilution assay, water extracts and 50% ethanolic extracts of the turmeric had no effect on *L. monocytogenes.* Essential oils (EO) of turmeric inhibited all *L. monocytogenes* at $\leq$10% [45]. The oil obtained from *Curcuma longa* has known to show antimicrobial activity by pour plate method against *Bacillus cereus, Bacillus coagulans, Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*. Fractionation and the analysis of the oil by GC-MS yielded *ar*-Turmerone, turmerone, and curlone were found to be the major compounds present in these fractions along with other oxygenated compounds [46]. Antibacterial activity of ionic, oil, ethanolic and resin was checked against both gram positive and gram negative urinary tract isolates. Sixty-five bacterial strains were isolated and identified by conventional methods. Ionic, resin and ethanolic fractions were found to be active against *Staphylococcus, Enterobacter* and *Bacillus* species while oil fraction did not show any activity against these organisms [47].

C. longa due to presence of curcumin has also been found to have mild activity against *Plasmodium falciparum* and *Leishmania major* [48].

Antifungal activities of turmeric oil against *Penicillium chrysogenum* has been investigated. The broth dilution method was employed to determine the minimal inhibitory concentration (MIC) and minimal fungicidal concentration (MFC) using the concentration of essential oils between 10-250 µL/mL. Inhibitory effects of the essential oils against mould were also examined by means of the dip treatment. It was found that the MIC and MFC values for each treatment were identical for all conditions examined. The MIC and MFC of turmeric oil against *Penicillium chrysogenum* were 100 µL/mL and 200 µL/mL, respcetively. In addition, tumeric oil at MIC and MFC provided a protection from mold growth on rubberwood for at least 8 weeks at the storage condition of 30°C with 100%RH [49].

Curcumin has been known to have antiviral activity [50]. It acts as an efficient inhibitor of Epstein-Barr virus (EBV) key activator Bam H fragment z left frame 1 (BZLF1) protein transcription in Raji DR-LUC cells. EBV inducers such as 12-0 tetradecanoylphorbol-13-acetate, sodium butyrate and transforming growth factor-beta increase the level of BZLF1 m-RNA at 12–48 h after treatment in these cells, which is effectively blocked by curcumin [51]. Most importantly, curcumin also shows anti-HIV (human immunodeficiency virus) activity by inhibiting the HIV-1 integrase needed for viral replication [52,53]. It also inhibits UV light induced HIV gene expression [54].

Gastrointestinal Effects

Constituents of *Curcuma longa* exert several protective effects on the gastrointestinal tract. A salt of curcumin, sodium curcuminate, was found to inhibit intestinal spasm, and p-tolymethylcarbinol, a turmeric component, was found capable of increasing gastrin, secretin, bicarbonate, and pancreatic enzyme secretion [5]. Turmeric has also been shown in rats to inhibit ulcer formation caused by stress, alcohol, indomethacin, pyloric ligation, and reserpine. This study demonstrated turmeric extract significantly increased the gastric wall mucus in rats subjected to these gastrointestinal insults [55]. The crude extract of turmeric (Cl.Cr) has been found to relax the spontaneous and K^+ (80 mM)-induced contractions in isolated rabbit jejunum as well as shifted the $CaCl_2$ concentration-response curves. In rabbit

tracheal preparation, Cl.Cr inhibited carbachol and K^+-induced contractions. In anesthetized rats, Cl.Cr produced variable responses on blood pressure with a mixture of weak hypertensive and hypotensive actions. In rabbit aorta, Cl.Cr caused a weak vasoconstrictor and a vasodilator effect on K^+ and phenylephrine-induced contractions. In guinea-pig atria, Cl.Cr inhibited spontaneous rate and force of contractions at 14–24 times higher concentrations. Activity directed fractionation revealed that the vasodilator and vasoconstrictor activities are widely distributed in the plant with no clear separation into the polar or non-polar fractions. When used for comparison, both curcumin and verapamil caused similar inhibitory effects in all smooth muscle preparations with relatively more effect against K^+-induced contractions and that both were devoid of any vasoconstrictor effect and curcumin had no effect on atria. These data suggest that the inhibitory effects of Cl.Cr are mediated primarily through calcium channel blockade, though additional mechanism cannot be ruled out [56].

Cardiovascular and Hypolipidemic effects

Turmeric causes lowering of cholesterol and triglyceride levels by decreasing susceptibility of low density lipoprotein (LDL) to lipid peroxidation, [57] and decreases platelet aggregation [58]. Turmeric has also been known to decrease cholesterol levels by decreasing cholesterol uptake in the intestines and increased conversion of cholesterol into bile acids [59]. *C. longa* is believed to increase prostaglandin synthesis and inhibits thromboxane synthesis due to which it causes decreased platelet aggregation [58]. The hypocholesterolemic and antioxidant potency of both raw and pressure-cooked turmeric and was evaluated in experimental rats that were rendered hypercholesterolemic by feeding 0.5% cholesterol enriched diet and maintained for 8 weeks on 5% spice diet. Turmeric either raw or heat processed significantly countered the extent of hypercholesterolemia. Serum total cholesterol was 31 and 32% lower as a result of feeding raw and heat processed turmeric. The reduction in blood cholesterol brought about by turmeric was predominantly in the LDL-cholesterol fraction. Turmeric significantly countered the increase in hepatic triglyceride level in hypercholesterolemic rats. Total thiols in serum were slightly but significantly increased by raw turmeric both in basal and in hypercholesterolemic rats. Serum α-tocopherol was significantly enhanced (81 - 113%) by turmeric in hyper-cholesterolemic animals. Hepatic lipid peroxides were significantly lowered (9 - 15%) as a result of turmeric in hypercholesterolemic situation [60].

Immunostimulant Activity

Researchers have isolated a lipopolysaccharide from the root of *Curcuma* that is an immunostimulant. Turmeric has been found to increase the mitogenic response of lymphocytes in rats. Dietary curcumin (40 mg/kg) given to rats for five weeks was found to enhance levels of IgG, a protein important for protecting mucosal surfaces from invasion by pathogenic bacteria and viruses [61].

Anticoagulant activity

Curcumin shows anticoagulant activity by inhibiting collagen and adrenaline-induced platelet aggregation *in vitro* as well as *in vivo* in rat thoracic aorta [62].

Antifertility activity

Petroleum ether and aqueous extracts of turmeric rhizomes showed 100% antifertility effect in rats when fed orally43. Implantation was completely inhibited by these extracts [63].

Curcumin found to inhibit 5*a*-reductase, which converts testosterone to 5*a*-dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster [64]. Curcumin also inhibited human sperm motility and has the potential for the development of a novel intravaginal contraceptive [65].

Antivenom effect

Ar-turmerone, isolated from *C. longa*, neutralizes both haemorrhagic activity of *Bothrops* venom and 70% lethal effect of *Crotalus* venom in mice [50]. It acts as an enzymatic inhibitor of venom enzymes with proteolytic activities [66].

Conclusion

From the times immemorial, plants have been used as curative agents for variety of ailments. *Curcuma longa* preparations are widely available and employed by practitioners of natural health for treatment of infections, pain, wound healing, inflammation and as carminative. Although the studies of *Curcuma longa* have proved its efficacy in several complications but the detailed research work on isolation of bio actives through clinical trials followed by standardization is seriously required. Recently some synthetic analogues such as sodium curcumin, and tetrahydrocurcuin (THC) has shown some better anti-inflammatory activity and antioxidant activities than curcumin. There have been reports on the clinical uses of *C. longa* which have shown promising results as the plant *C. longa* has a wide array of pharmacological activities, many isolated compounds and synthetic analogs of *C. longa* lack study on their pharmacological activity.

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