PHARMACOLOGICAL PROFILE OF CURCUMIN: A REVIEW

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ABSTRACT

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a natural product, which possesses various pharmacological activities like antioxidant, anti-inflammatory, and anti-tumor activity etc. Curcumin is a low molecular weight polyphenol. Curcumin is a member of curcuminoids isolated from Curcuma longa(turmeric). Currently, it is one of the investigational new drug substances that have great clinical potential and several groups from all over the world worked on its pharmacology. This review article highlights different pharmacological profile of curcumin.

Keywords: Curcumin, Chemical properties & pharmacological activities

No: of Figures: 5 **No: Of References: 19**

INTRODUCTION

Curcumin is a yellow coloured polyphenolic pigment obtained from powdered rhizomes of Curcuma *longa belonging to* family-Zingiberaceae (Fig: 1), commonly known as turmeric, a medicinal plant widely used in traditional Indian and Chinese medicine [1]. Chemically curcumin is 1,7 - bis (4-hydroxy-3-methoxy phenyl) - 1,6-heptadiene - 3,5 - dione (Fig: 2). Molecular weight and molecular formula of curcumin is $C_{12}H_{20}O_6$ and 368.385g/mol[2]. Curcumin is one of the major curcuminoids present in *curcuma longa*. The other two curcuminoids are des- methoxycurcumin(16%) and bis–des methoxycurcumin (8%). It can exist in Two tautomeric forms, keto and enol. The enol form is more energetically stable in the solid phase and in solution. It can be used for boron quantification in the so-called curcumin method. It reacts with boric acid forming a red coloured compound, known as rosocyanine. Curcumin is brightly yellow coloured compound and widely used as a food colouring agent.

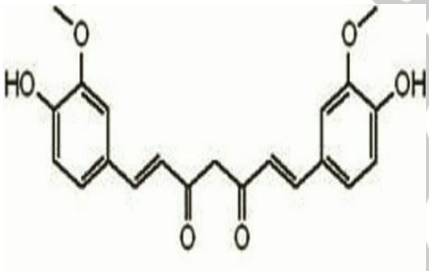

Fig: 1 *Curcuma longa* rhizomes and powder

Fig: 2 Chemical Structure of curcumin

SIGNIFICANCE OF CURCUMIN IN AYURVEDA

Curcuma longa has a 25 years(is it only 25 years) old medical history. Ayurveda, Siddha, Unani and Chinese systems of medicine recommend curcumin for large number of diseases and disorders (Fig: 3). Traditional Indian systems of medicine use the powder against disorders like diabetic wound, cough, hepatic disorders, rheumatic disorders etc.Traditional Chinese medicine uses curcuma in diseases associated with abdominal pain, amenorrhea, dysmenorrhea, distending or pricking pain in the chest and abdomen. It is also applied topically for ulcers, wounds, eczema, and inflammations [3].

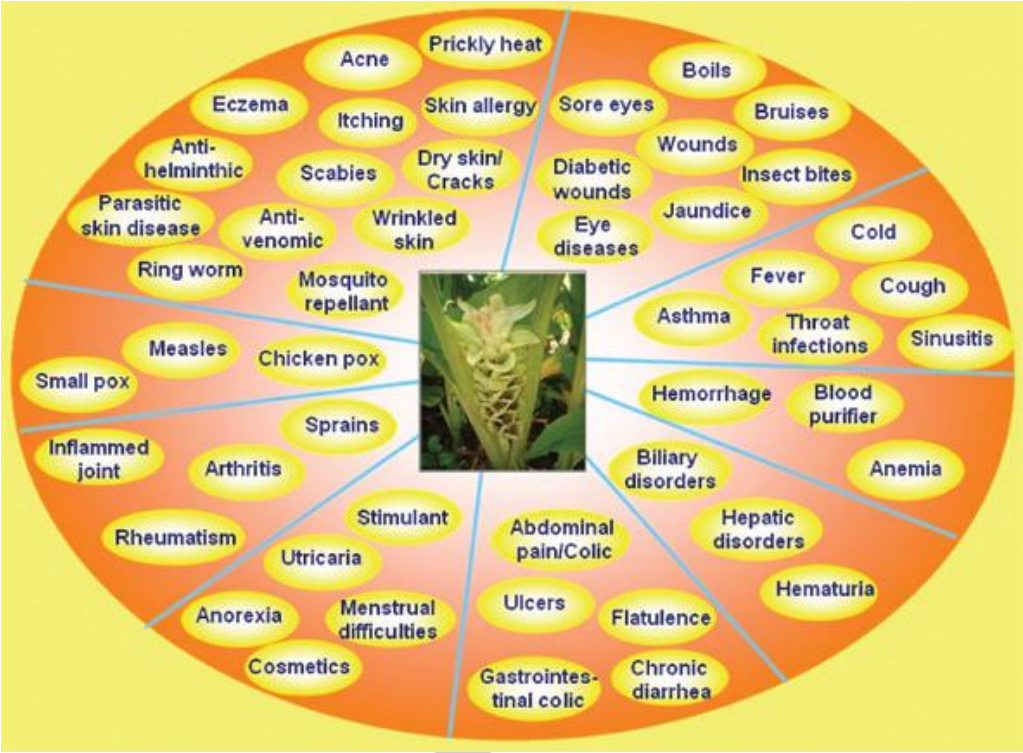

Fig: 3. Traditional uses of curcumin

PHARMACOKINETICS AND PHARMACODYNAMICS OF CURCUMIN

Preclinical data from animal models and phase I clinical studies performed with human volunteers and patients with cancer have demonstrated low systemic bioavailability with oral dosing. It is because of the first pass metabolism and some degree of intestinal metabolism, particularly glucuronidation and sulfation of curcumin. A daily oral dose of 3.6 g of curcumin is compatible with detectable levels of the parent compound in colorectal tissue from patients with cancer. The levels demonstrated might be sufficient to exert pharmacological activity [4].

Curcumin shows poor aqueous solubility, preventing its administration by the intravenous route. When administrated orally, the majority of curcumin is secreted in the faeces and only negligible amounts in the urine, indicating that this drug is poorly absorbed from the gut. Pharmacokinetic studies have indicated that curcumin is rapidly metabolized in the liver, undergoing extensive reduction via alcohol dehydrogenase [5].

CHEMICAL PROPERTIES OF CURCUMIN

Curcumin is the one of major curcuminoid present in turmeric. The yellow colour of the turmeric is due to the presence of curcumin. Molecular formula of Curcumin is $C_{21}H_{20}O_6$. Chemically curcumin is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It is practically insoluble in water. Curcumin is a bis-*α*-*β*-unsaturated *β*-diketone; under acidic and neutral conditions, the bis-keto form of the compound predominates, and at pH above 8, the enolate formed. Hence at

pH 3–7, it acts as an extraordinarily potent H-atom donor and above pH 8, it acts mainly as an electron donor, a mechanism more suitable to the scavenging or antioxidant properties of curcumin. Curcumin is quite unstable at basic pH and degrades within 30 minutes. Human blood or antioxidants such as ascorbic acid, or the presence of 10% bovine serum in the culture media prevents this degradation . Curcumin has a molecular weight of 368.7 and the commercial grade curcumin contains curcuminoids, 10–20% des methoxy curcumin and less than 5% bis desmethoxy curcumin[6] .

MECHANISM OF ACTION

The unique physical, chemical, biological properties and chemical structure of curcumin is responsible for it's various pharmacological actions. Curcumin is 1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione,containing two ferulic acid residues joined by a methylene bridge. It has three important functionalities: an aromatic o-methoxy phenolic group, alpha, beta-unsturated beta-diketo moiety and seven carbon linker. The o-methoxy phenol group and methylenic hydrogen are responsible for the antioxidant activity of curcumin (curcumin donates electron/hydrogen atom to reactive oxygen species).Curcumin interacts with a number of biomolecules through non-covalent and covalent binding.The hydrogen bonding and hydrophobicity of curcumin, arising from the aromatic and tautomeric structure along with the flexibility of linker group are responsible for the non-covalent interactions. The alpha, beta-unsaturated beta-diketone moiety covalently interacts with protein thiols, through Michael reaction. The beta diketo group present in compound chelates with transition metals, hence it reduce metal induced toxicity. Some of the metal complexes show improved antioxidant activity. Nowadays researchers are trying to functional group modification of curcumin to improve the pharmacological activities [7].

PHARMACOLOGICAL ACTIVITYS OF CURCUMIN

Various pharmacological actions of curcumin have been studied by various researchers worldwide (Fig: 4.). Curcumin has been shown to possess several pharmacological actions including anti-inflammatory, anticancer, antioxidant andantimicrobial effects. Curcumin has demonstrated chemo preventive properties, suppressing the tumorigenic activity of a wide variety of carcinogens in several kinds of cancer. In culture cell and animal studies, curcumin has been shown to exhibit antiproliferative, anti-invasive, and anti angiogenic properties. Curcumin has also demonstrated its usefulness for the treatment of other diseases such as Diabetes, Alzheimer's disease, Parkinson's disease, and Arthritis [8].

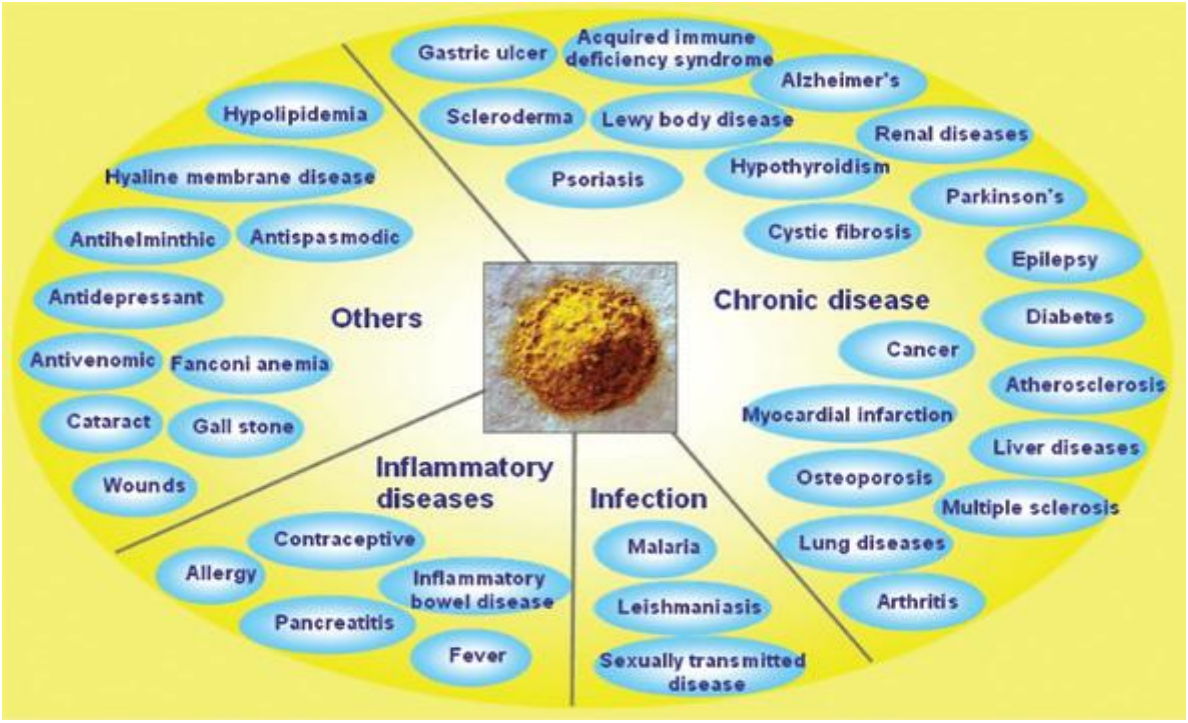

Fig: 4. Potential uses of curcumin based on scientific research

ANTI-INFLAMMATORY EFFECT

Several studies show that curcumin has anti-inflammatory effect. A study shows that curcumin has beneficial effects in sepsis. Male sparaque Dawley rates are used for the study with bolus intravenous injection of curcumin (0.2micro mol) followed by a continuous infusion of 0.24 micro mil/day for 3 day. After that rates were subjected to sepsis. After 20hrs, the rats were killed and blood and tissue samples were collected and analysed.

Study shown that peroxisome proliferator-activated receptor gamma(PPAR- $_{\gamma}$) has been associated with anti-inflammatory effects. By binding with ligand PPAR- $_{\gamma}$ forms hetro dimers with the retinoid receptor and bind to a peroxisome proliferation response element in a gene leading to regulation of gene transcription[9].

ANTI-OXIDANT ACTIVITY

Antioxidant and free radical scavenging abilities of curcumin were evaluated using in vitromodels such as, reducing potential, 1,1-diphenyl-2-picryl-hydrazil (DPPH), superoxide (O^{2-}), hydrogen peroxide (H_2O_2) and nitric oxide (NO) radical scavenging. Curcumin could efficiently scavenged DPPH, H_2O_2, NO , ferric reducing antioxidant power assay (FRAP) and superoxide anion radicals in a dose-dependent manner. Ex vivomodels like erythrocyte lipid peroxidation and erythrocyte haemolysis were also studied. Curcumin could efficiently scavenged the peroxy radicals which can induce haemolysis in erythrocytes and inhibit the erythrocyte membrane lipid peroxidation. The presence of antioxidants was confirmed by comparing with natural antioxidant ascorbic acid. Based on the various in vitro and ex vivo assays, it can be concluded that the curcumin possesses strong antioxidant activity as evidenced

by the free radical scavenging property[10].

IMMUNOMODULATING ACTIVITY

Curcumin is recognized as a potent modulator of the immune system exerting immunomodulatory effects on several cells and organs of the immune system.

Studies showed that curcumin can modulate the proliferation and activation of T- cells. It reduces the proliferation of T-cells induced by compound concanavalin A (Con A)[11]. Lymphoma B-cell proliferation is inhibited by curcumin via down-regulation of c-MYC, BCL-XL and NFκB activities[12]. Further curcumin is shown to modulate macrophage activities and inhibit generation of ROS in macrophages [13].

Curcumin is also effective against natural killer T- cell, where it promotes apoptosis by regulating the NFκB pathway and blockage of BCL-XL, Cyclin D_1[14] . Curcumin can suppress expression of CD_{80}, CD_{86} and class-II antigens by dendritic cells and blocks the release of inflammatory cytokines like $IL_{1\beta}$, IL_6 and TNFa from LPS-stimulated dendritic cells. Curcumin was shown to modulate phosphorylation of MAPK and nuclear translocation of NFκB in dendritic cells [15].

ANTI-CANCER ACTIVITY

Recently curcumin has been found to have anti-cancer properties that affect a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, angiogenesis and metastasis (Fig:5). Several studies were conducted to explore the anti-cancer properties of curcumin and it was shown that curcumin modulates multiple cell signalling pathways which include cell proliferation (Cyclin D_1, c-MYC), cell survival (BCL-2, BCL-XL, FLIP, XIAP, C-IAP1), apoptosis or cell death (Caspase-8, 3, 9), as well as controls tumour suppressor pathway (p53, p21) death receptor pathway (DR_4, DR_5), mitochondrial pathways, and protein kinase pathway (MAPK, JNK, AKT, and AMPK), thereby affecting tumour cell growth .The anticarcinogenic effects of turmeric and curcumin are due to direct antioxidant and free-radical scavenging activities[16].

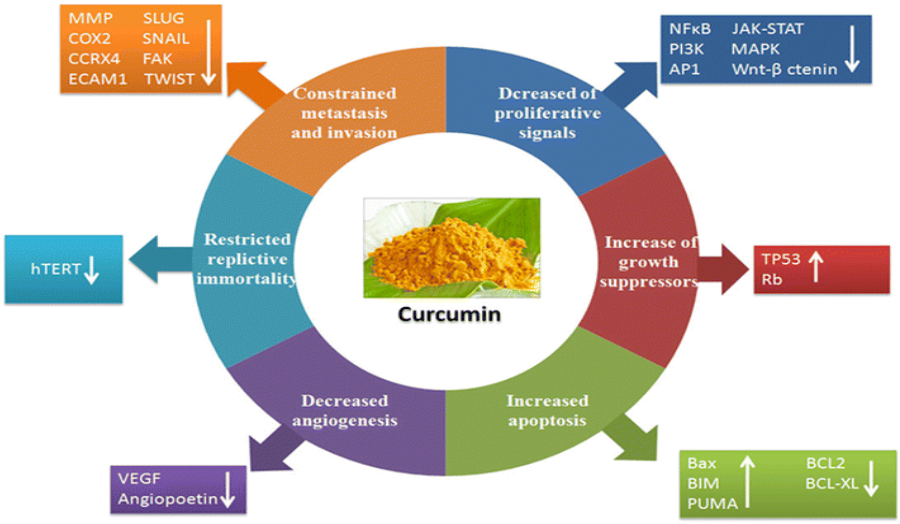

Fig: 5. Action of curcumin on cancer cells

ANTIMICROBIAL ACTIVITY

Antimicrobial activities for curcumin and rhizome extract of *C. longa* against different bacteria, viruses, fungi, and parasites have been reported. The antibacterial study on aqueous extract of curcuma longa rhizome demonstrated the MIC (minimum inhibitory concentration) value of 4 to 16 g/L and MBC (minimum bactericidal concentration) value of 16 to 32 g/L against *S. epidermis* ATCC 12228, *Staph. aureus* ATCC 25923, *Klebsiella pneumonia* ATCC 10031, and *E. coli* ATCC 25922 .Curcumin as a plant derivative has a wide range of antiviral activity against different viruses. Inosine monophosphate dehydrogenase (IMPDH) enzyme due to rate-limiting activity in the de novo synthesis of guanine nucleotides is suggested as a therapeutic target for antiviral and anticancer compounds. Among the 15 different polyphenols, curcumin through inhibitory activity against IMPDH effect in either non-competitive or competitive manner is suggested as a potent antiviral compound via this process.

High-risk human papilloma viruses (HPVs) infection via the expression of E6 and E7 viral oncoproteins has a critical role for development of cervical carcinoma. Curcumin showed the inhibitory activity against the expression of E_6 and E_7 genes of HPV-16 and HPV-18 as two main highly oncogenic human papilloma viruses.

Curcumin showed the anti-influenza activity against influenza viruses PR8, H_1N_1, and H_6N_1. The results showed more than 90% reduction in virus yield in cell culture using 30 µM of curcumin. The plaque reduction test elicited the approximate EC_{50} of 0.47 µM for curcumin against influenza viruses. In H_1N_1 and also H_6N_1 subtypes, the inhibition of haem agglutinin interaction reflected the direct effect of curcumin on infectivity of viral particles and this has proved by time of drug addiction experiment. Additionally, unlike amantadine, viruses developed no resistance to curcumin. The methoxyl derivatives of curcumin also did not show noteworthy role in the haem agglutination .These results proved the significant potential of curcumin for inhibition of influenza.The methanol extract of turmeric demonstrated antifungal activity against *Cryptococcus neoformans* and *Candida albicans* with MIC values of 128 and 256 µg/mL, respectively. The study of hexane extract of *C. longa* at 1000 mg/L demonstrated antifungal effect against *Rhizoctoniasolani*, *Phytophthora infestans* , and *Erysi phegraminis*[17].

HEPATO PROTECTIVE EFFECTS

Some studies shows that curcumin has hepatoprotective activity. The hepatoprotective effect of ethanolic extract of curcuma longa was measured in rat model of thioacetamide induced liver cirrhosis over 8weeks. Hepatic cytochrome p450 2E1 and serum levels of TGF-β_1 and TNF-a1 were evaluated. Oxidative stress was measured by malondialdehyde, urinary 8-hydroxyguanosine and nitrotyrosine levels. The protective activity of CLRE-free-radical scavenging mechanisms were evaluated through antioxidant enzymes. Protein expression of pro-apoptotic Bax and anti-apoptotic BCl-2 protein in animal blood serum was

studied and confirmed by immunohistochemistry of Bax and BCl-2 protein and proliferating cell nuclear antigen. The observations shows that histopathology, immunohistochemistry and liver biochemistry were significantly lower in the curcuma longa treated groupwhen compared with controls. The study shows that it inhibit hepatocyte proliferation but has no effect on hepatic CYP2E1 levels.

The mechanism of action of curcumin against liver cirrhosis is mainly by anti-oxidant and anti-inflammatory activity of curcumin[18].

RENOPROTECTIVE ACTIVITY

Oral administration of curcumin (100mg/wt) shows nephroprotective activity. The study shows that curcumin has ability to protect against the nephrotoxicity induced by APAP (Acetaminophen). The capacity of curcumin to protect the kidney is correlated with it's ability to suppress APAP-induced NO (nitric oxide) over production, depletion of intracellular GSH (glutathione), inhibition of SOD (superoxide dismutase) and GP_x (glutathione peroxidase) activities and increases of LPO level. Hence, the protective effect of curcumin against APAP-induced renal damage may due to inhibition of NO and ROS over production and maintenance of cellular ant-oxidant defence mechanism via down regulation of iNOS (inducible nitric oxide synthase) and CYP2E1 gene expression that is due to anti-oxidant and anti-inflammatory activities of curcumin[19].

CONCLUSION

It can be concluded that curcumin is wonder molecule with a wide range of biological activities which can be used for the preparation of various formulations for the treatment of inflammation, wound and microbial infections, tumour and cancerous growth. Moreover, it is a promising molecule withyears of traditional practice updated with anti-oxidative and free radical scavenging profile added with anti-inflammatory and anti-tumour activity. Hence it provides a wide area for research into the detail pharmacological actionsof this drug which has not been explored much compared to its utility.

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