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Biological activities of curcumin

¹V.Divya Teja* ,²Dr.R.Govindharajan

¹II/II M.Pharmacy, M.Pharmacy,Ph.D.Professor&HOD,

Department of pharmaceutical chemistry,

Hindu college of pharmacy, Amaravathi Road ,Guntur-522002,Andra Pradesh,India

Abstract: In recent years, several drugs have been developed deriving from traditional products & current drug research is actively investigating the possible therapeutic roles of many Ayurvedic and Traditional Indian medicinal therapies. commonly used spice are well documented for its medicinal properties in Indian and Chinese systems of medicine. It has been widely used for treatment of several diseases. Epidemiological observations, though in conclusive, are suggestive that curcumin consumption may reduce the risk of some form of cancers and render other protective biological effects in humans. Its most important active ingredient is curcuminoids. Curcuminoids are phenolic compounds commonly used as a spice, pigment and additive also utilized as a therapeutic agent used in several foods. Some of them were obtained by reaction of substitution involving the two phenolic OH groups of curcumin while the analogues with a substituent at C-4 was prepared following an original procedure that regards the condensation of benzene sulfenic acid on to the nucleophilic central carbon of the curcumin skeleton. Various pre clinical cell culture and animals studies suggest that curcuminoids have extensive biological activity as an antioxidant, neuroprotective, antitumor, anti-inflammatory, anti-acidogenic, radioprotective and arthritis. Different clinical trials are suggest a potential therapeutic role for curcuminoids in numerous chronic diseases like colon cancer, lung cancer, breast cancer, inflammatory bowel diseases. As a result of extensive epidemiological, clinical, and animal studies several molecular mechanisms are emerging that elucidate multiple biological effects of curcumin. The above review is summerized the most interesting in vitro and in vivo studies on the biological effect of curcumin.

Key words: curcumin, Antioxidant, Neuroprotective Antitumor, Antiinflammatory, Anti-acidogenic, Radioprotective and Arthritis.

I. INTRODUCTION

II. From human kind, natural products have been widely used for medicine for the management of a wide range of diseases that affected the human health⁽³⁾. Natural product are mainly refers to any chemical substance that has been collected, extracted or isolated from living organisms⁽⁴⁾.

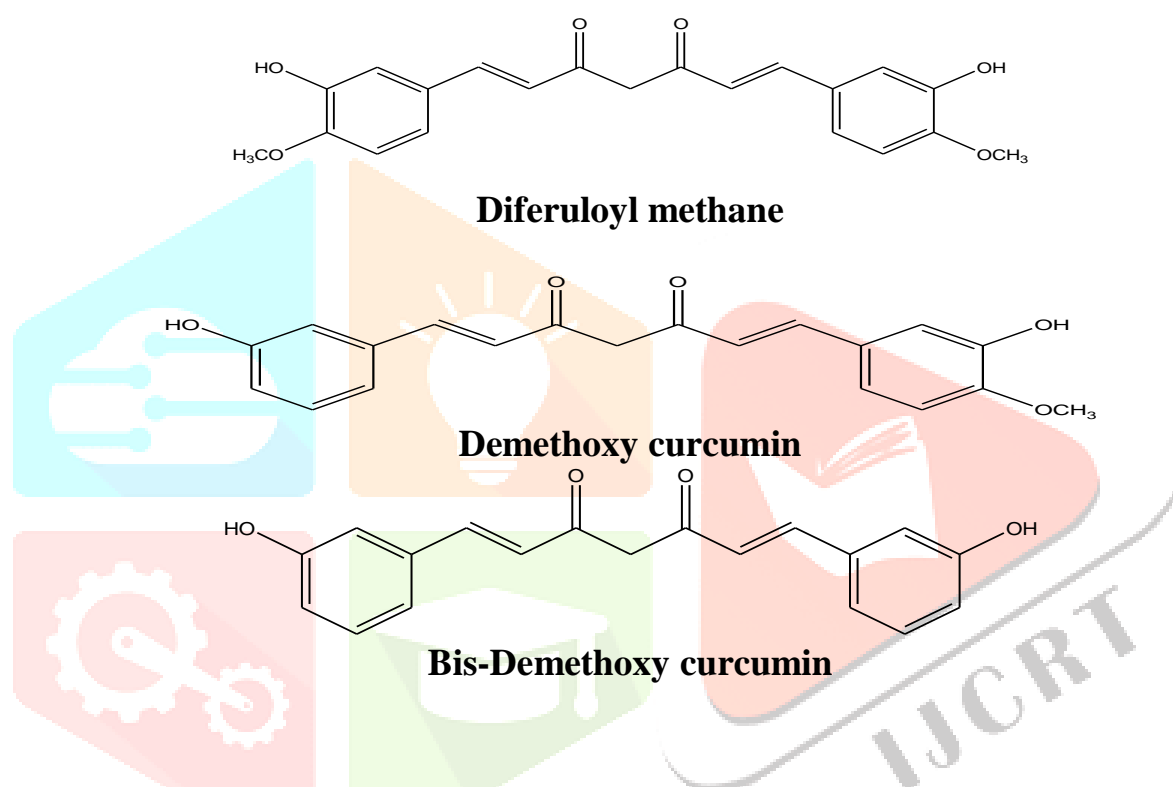
III. Natural products mainly used in traditional medicines for thousands of years, and have shown promise as a source of components for the development of new drugs⁽⁵⁾. *Curcuma longa* L. (Zingiberaceae family) rhizomes, has been widely used for centuries in indigenous medicine for the treatment of a variety of inflammatory conditions and other diseases⁽⁶⁾. In the addition of curcumin, *curcumin longa* contains two other curcuminoids; desmethoxycurcumin and bis-desmethoxycurcumin⁽⁷⁾. it is very freely soluble in organic solvents like DMSO, ethanol, methanol, acetone. Curcumin has very poor solubility in water. Spectrophotometrically, it has a max) in methanol the range is 430 nm while it absorbs at maximally at 415 to 420 nm in acetone⁽⁸⁾. Curcumin, also known as diferuloyl methane, is a symmetric molecule. Curcumin IUPAC name is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, and the chemical formula $C_{21}H_{20}O_6$, curcumin molecular weight is 368.38 g/mole.⁽⁹⁾ Its medicinal properties have been attributed mainly to the curcuminoids and the main component present in the rhizome includes curcumin (diferuloylmethane)—(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)⁽¹⁰⁾. curcumin has been used in India to maintain oral hygiene.⁽¹¹⁾ It has traditionally been used for medical purposes for many centuries in countries such as India and China for treatment of jaundice and other liver ailments. Curcumin is one of the most popular medicinal herbs, with a wide range of pharmacological activities such as antioxidant, anti-protozoal, anti-venom activities, anti-microbial, anti-malarial, anti-inflammatory, anti-proliferative, anti-angiogenic, anti-tumor and anti-aging properties.⁽¹¹⁾ It has also been used to treat ulcers, parasitic infections, various skin diseases, anti-immune diseases and curing the symptoms of colds and flus. The pharmacological activity of turmeric has been attributed mainly to curcuminoids consists of curcumin (curcumin) and two related compounds demethoxy curcumin (DMC) and bisdemethoxycurcumin (BDMC). curcumin itself appears as a crystalline compound with a bright orange-yellow colour. Curcuminoids are commonly used as colouring agent as well as food additives. World Health Organization stated the acceptable daily in take of curcuminoids as a food additive in the range of 0-3mg/kg. Curcuminoids and turmeric products have been characterized as safety by the Food and Drug Administration (FDA) in USA. The average in take of turmeric in the India diet was approximately 2-2.5 gram/day for a 60 kg individually.

Curcuminoids have achieved the potential therapeutic interest to cure immune related, metabolic diseases and cancer due to a vast number of biological targets and virtually no side effects.⁽¹²⁾

IV. Discovery of curcumin⁽¹³⁾:

Curcumin is a active ingredient of dietary spice of turmeric and it is mainly extracted from rhizomes of curcumin longa from a plant of zingiberaceae family. Fitrst Discovered about two centuries ago ,it is isolated from a ayellow colouring matter and a rhizome of C.longa and it is named as curcumin.

CHEMICAL STRUCTURE OF CURCUMIN:



Structure Details:

Biological activities of curcuminoids:

Curcuminoids are from turmeric and their derivatives has been shown to possess a wide range of biological activities includes the Antioxidaant activity , Anti inflammatory ,Anti cancer activity, Antimicrobial activity,Neuroprotective Cardioprotective and Radio protective etc⁽¹⁴⁾

Antiviral and antifungal activity⁽¹⁵⁾

The anti-influenza activity of curcumin reported that the treatment with 30 mM curcumin are reduced the yield of virus by over 90 percent of the cell culture. Plaque reduction test and HI test are clearly showed that the curcumin interrupts the virus-cell attachment, which leded to inhibition of influenza virus propagation. Time of drug addition experiments demonstrated curcumin had a direct effect on viral particle infectivity that was reflected by the inhibition of hemagglutination; and this effect was observed in H1N1 as well as in H6N1 sub type. curcumin can be a promising potential for using as an antiinfluenza drug. Zhang et al investigated and

compared the action of curcuminoids on the causal pathogens of *Candida albicans* growth by microcalorimetry. The antifungal effect of curcumin was stronger than that of DMC. It was confirmed by the structural activity relationship that the existence of the methoxy group might enhance lipophilicity of the mother nucleus, which made it easier for the molecular to enter into the cell membrane of fungi to inhibit its growth.

Anti-oxidant activity⁽¹⁶⁾:

Oxidative stress plays a major role in the pathogenesis of various diseases including myocardial ischemia, cerebral ischemia–reperfusion injury, hemorrhage and shock, neuronal cell injury, hypoxia and cancer. Curcumin, exhibits strong antioxidant activity, comparable to vitamins C and E. Curcumin itself proven as anti-inflammatory and antioxidant properties has been shown to have several therapeutic advantages. It was shown to be a potent scavenger of a variety of reactive oxygen species including super oxide anion radicals, hydroxyl radicals and nitrogen dioxide radicals. It is also shown to inhibit lipid peroxidation in different animal models. Curcumin protected oxidative cell injury of kidney cells (LLC-PK1) by inhibiting the lipid degradation, lipid peroxidation and cytolysis and also decreased ischemia-induced biochemical changes in heart in the feline model. Vascular endothelial cells treated with curcumin prevented oxidant mediated injury by increased heme oxygenase production. Curcumin was found to protect rat myocardium against isoprenaline (ISO) induced myocardial ischemic damage and the protective effect was attributed to the antioxidant properties by inhibiting free radical generation. It caused a decrease in the degree of degradation of the existing collagen matrix and collagen synthesis, two weeks after the second dose of ISO. These effects were attributed to free radical scavenging properties and inhibition of lysosomal enzyme release by curcumin. Treatment with curcumin showed beneficial effects on renal injury by its ability to inhibit the expression of the apoptosis-related genes Fas and Fas-L. Studies in our laboratory have shown that pretreatment with curcumin resulted in significant restoration of the liver cytokines IL-1alpha, IL-1beta, IL-2, IL-6, and IL-10 to normal levels that were increased by hemorrhage/resuscitation regimen in rats. In fact, IL-1beta levels were lower than sham levels. NF-kappaB and AP-1 were differentially activated at 2 and 24 h post-hemorrhage and were inhibited by curcumin pretreatment. Serum aspartate transaminase estimates indicated decreased liver injury in curcumin-pretreated animals subjected to hemorrhage. These results suggested that protection by curcumin pretreatment against hemorrhage/resuscitation injury might have resulted from the inactivation of transcription factors involved and regulation of cytokines to beneficial levels. Similarly, in chronically hypoxic rabbit hearts Hsp70i trans-located from the particulate to the cytosolic fraction and curcumin

reversed this subcellular redistribution through protein kinase pathways. It is suggested that dietary supplementation with curcumin may be beneficial in neurodegenerative diseases such as Alzheimer's disease. In a focal cerebral ischemia model of rats, curcumin offered significant neuroprotection through inhibition of lipid peroxidation, increase in endogenous antioxidant defense enzymes and reduction in peroxynitrite formation. In conclusion, curcumin exhibits a variety of beneficial effects and appears to have a significant potential in the treatment of multiple diseases that are a result of oxidative stress. These protective effects of curcumin are attributed mainly to its antioxidant properties and should be further exploited to develop novel drugs.

Anticancer activity⁽¹⁷⁾:

curcuminoids, with slight modified version of Pabon's method for an inhibitor more potent than curcumin. Among these, three products are exhibited a remarkably high inhibitory activity against Fos-Jun-DNA complex formation. The product BJC005 is nearly 90 times more effective than curcumin. A series of novel curcumin analogs were synthesized by Adams et al for anticancer and anti-angiogenesis activities. These analogs are symmetrical a,b-unsaturated and saturated ketones. The analogs were more efficacious than curcumin and the commonly used chemotherapeutic drug, cisplatin against a variety of tumor cell lines and also these compounds can be exerted impressive blockade of endothelial cell proliferation. Several compounds were more effective in the anti-angiogenesis assays run at Emory and as potent as the anti-angiogenic drug TNP-470. Some of the analogs effectively reduced the size of human breast tumors grown in female athymic nude mice and showed little toxicity. These analogs can potentially be an effective chemotherapeutic agent. A series of 15 novel cyclic analogs of curcumin were synthesized by condensation of 2-acetylcycloalkanones with a variety of aromatic aldehydes resulted in the formation of 2-arylidene-6-(3- arylacryoyl)-cycloalkanone derivatives under microwave conditions and analyzed for in vitro cytostatic activity. These analogs showed significant anticancer activity against representative murine and human cancer cell lines during in vitro bioassays.⁽¹⁷⁾ Sixty one curcumin-related compounds were synthesized by Wei et al and evaluated for their anticancer activity towards cultured prostate cancer PC-3 cells, pancreas cancer Panc-1 cells and colon cancer HT-29 cells by MTT assay. Structure activity relationship has shown the response of potent anticancer activity viz tetrahydropyran- 4-one or tetrahydrothiopyran-4-one as a core structure, methoxy groups in the aromatic ring and nitrogen heterocycles the distal rings as the promising lead structures. Some of the studied curcumin - compounds were 34e117 fold more active than curcumin for inhibiting the growth of cultured human prostate, pancreas ad colon cancer cells. The studied active compounds were potent

stimulators of apoptosis and can be useful for anticancer activity. The synthesized C5-curcumin-fatty acid conjugates (C5-curcumin-FA) containing decanoic acid or palmitic acid moieties through a two-step synthetic route, 10 analogs in order to determine survey activity relationship (SAR) study using the colorectal adenocarcinoma cell (CCL-229). Decanoic acid moiety at the meta position in C5-curcumin-FA conjugates is important for their anticancer activity effect. C5-curcumin-FA conjugates can affect the replication process of cancer cells, inhibited the relaxing activity of the human DAA topoisomerase-I at minimum inhibitory concentrations. The hypothesis of the results are also strongly supported that the inhibition of both NFκB and DNA topoisomerase I by C5-curcumin-FA conjugates are associated with their anticancer activity. Chemopreventive effects in 1,2-dimethylhydrazine-induced colon cancer in the albino rats model was performed by curcumin and curcumin analogs such as ethyl curcumin and 3,5-bis (substituted cinnamylidene)- N-alkyl-4-peperidone. Chemopreventive treatment with various forms of curcumin extracts caused a reduction in the number of tumor cells ever after 4 weeks. Among these compounds 3,5-bis (substituted cinnamylidene)-N-alkyl-4-peperidone is the most active against the administration of the prophylactic treatment for four weeks before the induction of cancer by 1,2- dimethylhydrazine. Leow et al ⁽¹⁸⁾ synthesized a total of five series consisting of 43 curcumin analogs and screened in HEK293T cells for inhibition of b-catenin transcriptional activity. These analogs were more potent than parent curcumin as effective wnt inhibitors and antiinvasive agents in human osteosarcoma. SAR studies revealed that the wnt inhibitory effects could be markedly enhanced by introducing conformational restriction in the central linker and appropriate ring substituents such as a strong electron donating group at the 40 ring position. Synthesized analogs especially dibenzylideneecyclohexanones and dibenzylideneecyclopentanones templates can be a promising scaffolds for development as chemotherapeutic agents for the treatment and prevention of osteosarcoma. Other studies have identified reduction in radiation induced DNA damage in rat lymphocytes and its anti-mutagenic potential.

Curcumin enhances wound healing^(18&19):

Tissue repair and wound healing are complex processes that involve inflammation, granulation and tissue remodeling. Injury initiates a complex series of events that involves interactions of multiple cell types, various cytokines, growth factors, their mediators and the extra-cellular matrix proteins (ECM). Local application of turmeric is a household remedy in India for several conditions such as skin diseases, insect bites and chicken pox. Based on the ancient use of turmeric in wound healing, our earlier studies evaluated the effect of curcumin on enhancement

of wound healing. We used full thickness punch wound model to study its effect on wound healing. Curcumin treated wound biopsies showed a large number of infiltrating cells such as macrophage, neutrophils and fibroblasts as compared to untreated wound. The presence of myofibroblast in curcumin treated wound demonstrated faster wound contraction. Migration of various cells represents potential sources of growth factors required for the regulation of biological processes during wound healing. Transforming growth factor (TGF- β 1) is important in wound healing as it stimulates the expression of fibronectin (FN) and collagen by fibroblasts and increases the rate of formation of granulation tissue in vivo. Curcumin treatment resulted in enhanced fibronectin (FN) and collagen expression. Furthermore, the treatment led to an increased formation of granulation tissue including greater cellular content, neo-vascularization and a faster re-epithelialization of wound in both diabetic as well as hydrocortisone impaired wounds by regulating the expression of TGF- β 1, its receptors and nitric oxide synthase during wound healing. Other studies involving systemic administration of curcumin have shown its beneficial effects by the enhancement of muscle regeneration after trauma in vivo by modulating NF- κ B activity. Recent studies have suggested that curcumin inhibited the damage caused by hydrogen peroxide in human keratinocytes and fibroblasts suggesting the antioxidant role in enhanced wound repair. Similarly, Curcumin incorporated collagen matrix treatment showed increased wound reduction, enhanced cell proliferation and efficient free radical scavenging as compared with control and collagen treated rats. Curcumin pretreatment enhanced the synthesis of collagen, hexosamine, DNA, nitrite, and histologic assessment of wound biopsy specimens showed improved collagen deposition and an increase in fibroblast and vascular densities suggesting that curcumin may be able to improve radiation-induced delay in wound repair. It has also been studied for antiulcer activity in acute ulcer model in rat by preventing glutathione depletion, lipid peroxidation and protein oxidation. Denudation of epithelial cells during damage of gastric lumen is reversed by curcumin through re-epithelialization. Furthermore, both oral and intraperitoneal administration of curcumin blocked gastric ulceration in a dose dependent manner. It accelerated the healing process and protected gastric ulcer through attenuation of MMP-9 activity and amelioration of MMP-2 activity. These studies clearly suggested that curcumin treatment resulted in faster closure of wounds, better regulation of granulation tissue formation and induction of growth factors. It suggests that it acts at different levels to enhance wound repair. Further studies are warranted to evaluate turmeric/curcumin as a potential therapeutic agent in clinical setting of wound healing.

Cardioprotective effects⁽²⁰⁾

Curcumin has extensive cardioprotective effects against diabetic cardiovascular complications, cardiac hypertrophy and myocardial infarction. Honget al-assessed and explored the molecular mechanism of the cardioprotective effects of curcumin by a rat model of coronary artery ligation. The genechip results suggested that gene expression in the border zone of infarcted left ventricle of rats is a dimensional process after myocardial infarction. After treatment with curcumin some amelioration in cardiac function, infarct size and serum biochemical markers were noted. Cardioprotective effects curcumin are associated with cytokine-cytokine receptor interaction, ECM-receptor interaction, focal adhesions and colorectal cancer. The idiopathic pulmonary arterial hypertension is a complex disease that mainly affects pulmonary arterial circulation. This undergoes a remodeling with subsequent reduction of flow in the small pulmonary arteries. Because of this damage an increased vascular resistance gradually develops and over time it carries out in heart failure. Curcumin has been considered a potent anti-inflammatory agent useful for inflammatory diseases. Long investigations of anti-inflammatory effects of curcumin showed a role for inactivation of NF- κ B mediated inflammation.

Radioprotective or radiosensitizing effect⁽²¹⁾:

Curcuminoids are well antioxidant polyphenols with radiomodulatory properties, radioprotecting non-cancerous cells while radiosensitizing tumor cells. Lopez-Jornet et al investigated the possible protective effects of lycopene and CUR on the parotid glands of 40 female Sprague Dawley rats during irradiation of radiotherapy. Morphological and histopathological analyses showed less cell necrosis in the group treated with CUR than other groups. Lycopene and CUR given 24 h before irradiation reduced the structural damage to the salivary glands. Sebastia et al reported the dual action viz radioprotective and radiosensitive of polyphenols presence in CUR. They proposed for the observed radiosensitization is related to the G2-checkpoint abrogation by compromising its effectiveness to arrest the damaged cells in the G2-phase, resulting in a significant increase in the yield of radiation-induced chromatid breaks. These polyphenols exert simultaneously a dual mode of action but the overall radioprotective or radiosensitizing net effect would depend on the cell-cycle status of the cells at the time of irradiation.

Anti-tuberculosis activity⁽²²⁾:

Baldwin et al synthesized a series of monocarbonyl analogs of curcumin and evaluated for their capacity to inhibit growth of the pathogenic mycobacteria such as *M. tuberculosis* (Mtb) and *Mycobacterium marinum* (Mm). Several analogs were proved their inhibition efficiency of *in vitro* growth of Mm and Mtb by disk diffusion and liquid culture assays. Structural activity analysis of the analogs indicated that Michael acceptor properties are critical for inhibitory activity.

Anti carcinogenic activity⁽²³⁾:

The effect of bis 1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5 dione, a bisdemethoxycurcumin analoge (BDMC-A) on 1,2-dimethylhydrazine (DMH) induced colon carcinogenesis in male wistar rats and effects were compared with curcumin as a reference drug. The results suggested that BDMC-A can be influenced on histological changes, chloestrol, bile acids and phospholipids metabolism in DMH-treated rats through its chemopreventive effects. The terminal phenolic groups and the conjugated bonds in the central seven carbon chain may be responsible for the anti carcinogenic action of the BDMC-A

Anti –diabetic activity⁽²⁴⁾:

A series of mono –carbonyl analogs of curcumin were designed and synthesized by removing the reactive β -diketone moiety; which is responsible for the pharmacokinetic limitations of curcumin. Curcumin analoges significantly inhibited the rat 11 β -hydroxy steroid dehydrogenase type -1 activities (11 β -HSD1). The level of these inhibition was 4-20 times more than that of curcumin and these analoges were highly selective and favouring 11 β -HSD1. These analoges showed anti –diabetic effect without any associated toxicity and can potentially used novel therapeutic agents targeting 11 β -HSD1 for the treatnebt of diabetes.

Antitumor activity⁽²⁵⁾:

A series of CUR derivatives were synthesized and evaluated the inhibitory activities on thioredoxin reductase (TrxR) of all analogs by *in vitro* DTNB assay. Most of the analogs inhibited TrxR even in the low micromolar range. Structure-activity relationship analysis revealed that the analogs with furan moiety have an excellent inhibitory effect on TrxR in an irreversible manner, indicated that the furan moiety can serve as a possible pharmacophore during the interaction of CUR analogs with TrxR. [154](#) Aldehyde-free 2-hydroxycinnamaldehyde (HCA)

analog were synthesized based on the CUR, which is called as 2-hydroxycurcuminoids for the effect of antitumor activity against various human tumor cells *in vitro* and *in vivo*. 2-hydroxycurcuminoids have a strong generator of ROS and strongly inhibited the growth of SW 620 colon tumor cells due to the presence of β -diketone moiety of curcuminoids. These analogs can be used as chemotherapeutic agent against human tumors.

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