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PHARMACOLOGICAL ASPECTS OF CURCUMIN: A REVIEW

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ABSTRACT: Turmeric (*Curcuma longa*) is a widely used popular Indian medicinal plant which belongs to the family of Zingiberaceae. Curcumin, an important constituent of turmeric, is known for various biological activities, primarily due to its antioxidant mechanism. Epidemiological observations are suggestive that turmeric consumption may reduce the risk of some form of cancers and render other protective biological effects in humans like antidiabetic, anti-inflammatory, anti-angiogenic, anti-oxidant, wound healing and anti-cancer effects. This review summarizes the most interesting biological effects of curcumin.

INTRODUCTION: Turmeric is an Indian rhizomatous herbal plant (Curcuma longa) of the ginger family (Zingiberaceae) of well-known medical benefits [1, 2]. **Fig. 1** shows the *Curcuma longa*. The medicinal benefits of turmeric could be attributed to the presence of active principles called curcuminoids. One of the most interesting components of curcuminoid is curcumin, which is a small molecular weight polyphenolic compound and lipophilic in nature, hence insoluble in water and also in ether but soluble in ethanol, dimethylsulfoxide, and other organic solvents [3]. Curcumin is stable at the acidic pH of the stomach [4]. The other constituents present are volatile oils including tumerone, atlantone, and zingiberone and sugars, proteins and resins [2]. The active constituent of turmeric- curcumin is isolated from *Curcuma longa*, and it provides color to turmeric.

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FIG. 1: ***CURCUMA LONGA***

Such bioactive component has been thoroughly investigated [5]. Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione) is also called diferuloylmethane [6]. It is a tautomeric compound existing in enolic form in organic solvents and as a keto form in water **Fig. 2**. It was found that curcuminoids in the herb *C. longa* is synthesized by a collaboration of two types III Polyketide synthases, diketide-CoA synthase (DCS) and curcumin synthase 1 (CURS1, the first identified CURS) (**Fig. 3A**). DCS catalyzes the formation of feruloyldiketide CoA (4) from

feruloyl-CoA (5) and malonyl-CoA. CURS1 catalyzes the formation of curcumin from feruloyl-CoA (5) and the feruloyldiketide-CoA produced by the action of DCS (4). Thus, DCS and CURS1 catalyze the formation of curcumin. Both enzymes accept p-coumaroyl-CoA (6), but at low efficiency, and are also capable of synthesizing bisdemethoxy curcumin (3) from p-coumaroyl-CoA (6) and malonyl-CoA *via* p-coumaroyldiketide-CoA (7) formation. Although, a pair of DCS and CURS produces a mixture of Curcumin oids; *i.e*., Curcumin (1), demethoxyCurcumin (2) and bisdemethoxycurcumin, from feruloyl-CoA (5), p-coumaroyl-CoA (6) and malonyl-CoA *in-vitro*, it yields the mixture of products with a composition different from that of an ethyl acetate extract of the rhizome of turmeric; the rhizome of turmeric contains a relatively larger amount of bisdemethoxycurcumin (3) than the *in-vitro* reaction products by a pair of DCS and CURS. Therefore, it was assumed that the composition of curcuminoids in the mixture might be regulated by the concentrations of p-coumaroyl-CoA and feruloyl-CoA *in-vivo*.

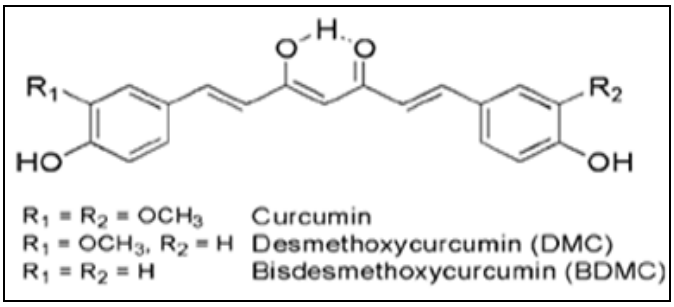

FIG. 2: CHEMICAL STRUCTURES OF CURCUMINOIDS

CURSs catalyzes the formation of curcuminoids (1-3) from cinnamoyl-CoA (10), p-coumaroyl-CoA (6) and feruloyl-CoA (5) when incubated with cinnamoyldiketide-N-acetylcysteine (NAC) (8), an analog of diketide-CoA **Fig. 3** [123].

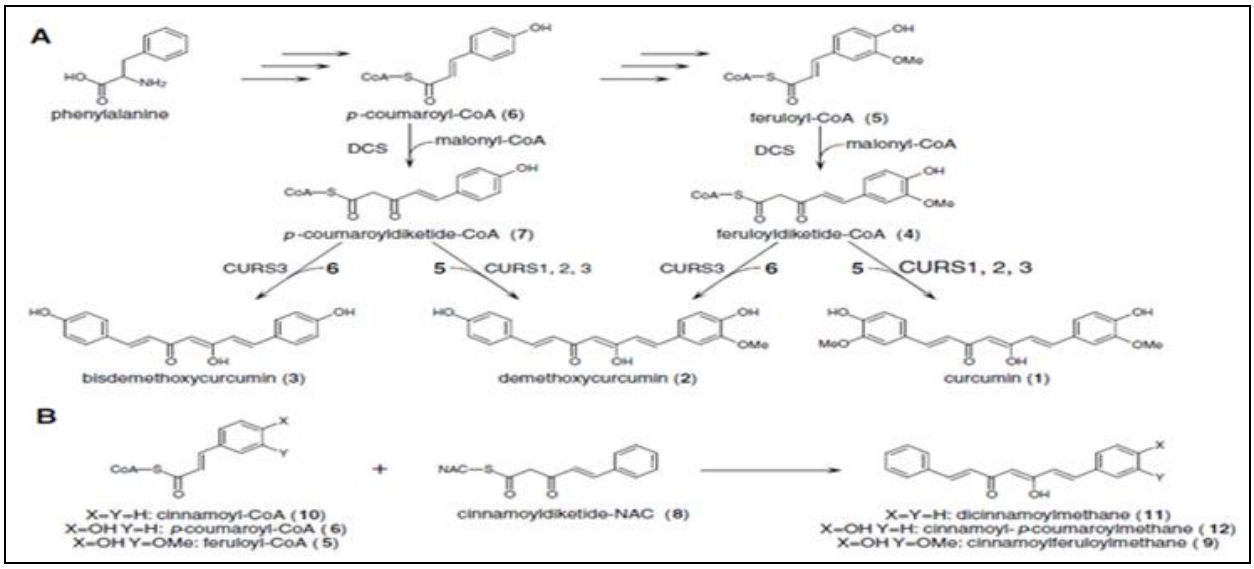

FIG. 3: THE BIOSYNTHESIS PATHWAY OF CURCUMIN OIDS

Turmeric is the boiled, dried, cleaned and polished rhizomes of *Curcuma longa*. After harvesting the whole rhizomes are collected. These rhizomes are transported as whole rhizomes. They are usually like fingers 2 to 8 cm long and 1 to 2 cm wide having bulbs and splits. The dried rhizomes are further processed and reprocessed to obtain the turmeric powder [2]. The use of turmeric dates back nearly 4000 years to the Vedic culture in India, where it was used as a culinary spice and had some religious significance [7]. It has different names in different cultures and countries. In North India, turmeric is commonly called "haldi," and in the south, it is called "manjal," It is known as terre merite in French and simply as "yellow root" in many languages. In Arabic, it is called Kurkum, Uqdah safra. In Sanskrit, turmeric has at least 53 different names [7].

Curcumin has been used in tradition as a medicinal herb due to its various advantages such as antioxidant [8], anti-inflammatory [9] antimutagenic [10], antimicrobial [11] and several therapeutic properties [12]. Curcumin shows poor absorption, rapid metabolism, and rapid elimination. Several agents have been introduced to improve the bioavailability

of curcumin. The most interesting one is piperine, it enhances curcumin bioavailability by blockage of the metabolic pathway of curcumin [13]. Piperine results in an increase of 2000% in the bioavailability of curcumin [14]. Curcumin is available in several forms including capsules, tablets and ointments [15]. Curcuminoids have been approved by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" (GRAS) [16]. It is the purpose of this review to provide a brief overview of the potential health benefits of curcumin.

Medicinal Uses of Curcumin:

Anti-diabetic Activity: Curcumin was reported to possess anti-diabetic activity. The effect of anti-diabetic activity could be attributed to the antioxidant property of curcumin [17]. In their study, researchers demonstrated positive curcumin effect through the improvement of diabetes-induced endothelial dysfunction by decreasing superoxide production and vascular protein kinase C inhibition. Interestingly, recent studies demonstrated the ability of curcumin to have the capacity to directly quench reactive oxygen species (ROS) that can contribute to oxidative damage [18].

This property is known to contribute to the overall protective effects of curcumin. Curcumin can attenuate cell death caused by oxidative stress, indirectly through induction and activation of antioxidant/ cytoprotective enzymes, such as heme oxygenase-1 (HO^{-1}). The protective mechanisms of HO^{-1} in diabetes could present some emerging therapeutic options for HO^{-1} expression in treating diabetic diseases [18].

Curcumin was evaluated for the prevention of type 2 diabetes in pre-diabetic human population [19]. The subjects received curcumin capsules for 9 month period versus placebo capsule group. The curcumin-treated group showed a better overall function of β-cells, with higher HOMA-β and lower C-peptide. The curcumin-treated group showed a lower level of HOMA-IR and higher adiponectin when compared with the placebo group. The results indicated that curcumin intervention might have a positive effect to a prediabetic population [19].

Wound Healing Activity: Wound healing includes the repair of tissues in a complex process that involves inflammation, granulation, and remodeling of the tissue [20]. Enhancement of wound healing was reported by curcumin in animals. The mechanisms of action of the wound healing effect of curcumin include: immunohistochemical localization of transforming growth factor-β1 showed an increase in curcumin-treated wounds as compared with untreated wounds [22] and modulating collagen and decreasing reactive oxygen species [21]. Also, curcumin showed earlier re-epithelialization, improved neovascularization, increased migration of various cells including dermal myofibroblasts, fibroblasts, and macrophages into the wound bed, and higher collagen content [22, 23].

Anti-arthritis Activity: Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by hyperplasia of the synovial fibroblasts. Curcumin is known to possess potent anti-inflammatory and anti-arthritic properties [24]. Curcumin treatment was carried out on patients with active rheumatoid arthritis and compared with diclofenac sodium reference group. Interestingly, the curcumin group showed the highest percentage of improvement in overall rheumatoid arthritis scores and these scores were significantly better than the patients in the diclofenac sodium group. More importantly, the curcumin group was found to be safe and did not relate to any adverse events compared to diclofenac sodium group [25].

It is believed that curcumin antioxidant anti-proliferative, anti-inflammatory and immune-suppressive activities shared in the improvement of symptoms to patients suffering from rheumatoid arthritis [26]. One of the important consequences of RA could be decreased apoptosis. Exposure of the synovial fibroblasts to curcumin resulted in growth inhibition and the induction of apoptosis, as measured by MTT assay, fluorescent microscopy, and Annexin-V-based assay. These results show that curcumin might help against hyperplasia of the synovial fibroblasts in RA [27].

Anti-Alzheimer Activity: Alzheimer disease (AD) is by far the most common cause of dementia globally. This neurodegenerative disorder of the brain is chronic and progressive, characterized clinically by the deterioration in the key symptoms of behavioral and cognitive abilities. Researchers reported the advantages of curcuminoids as anti-Alzheimer agents [28].

Curcumin action was demonstrated through the inhibition of the accumulation of amyloid β-peptide (Aβ) and the formation of β-amyloid fibrils (fAβ) from Aβ, as well as the destabilization of preformed fAβ in the central nervous system. Consequently, curcumin would be an attractive therapeutic target for the treatment of Alzheimer's disease [29].

Anti-Parkinson Activity: Oxidative stress has been implicated in the degeneration of dopaminergic neurons in the substantia nigra (SN) of Parkinson's disease (PD) patients. An important biochemical feature of presymptomatic PD is a significant depletion of the thiol antioxidant glutathione (GSH) in these neurons resulting in oxidative stress, mitochondrial dysfunction, and ultimately cell death. Curcumin restores depletion of GSH levels, protects against protein oxidation, and preserves mitochondrial complex I activity which normally is impaired due to GSH loss. Thus, it helps in the treatment of PD [30]. Overexpression and abnormal accumulation of aggregated α-synuclein (αS) have been linked to Parkinson's disease (PD) and other synucleinopathies. αS can misfold and adopt a variety of morphologies, but recent studies implicate oligomeric forms as the most cytotoxic species. Curcumin can alleviate αS-induced toxicity, reduce intracellular reactive oxygen species ROS levels and protect cells against apoptosis. Thus, curcumin could be used as anti-Parkinson [31].

Anti-inflammatory Activity: Curcumin possesses significant anti-inflammatory activity in acute as well as in chronic models of inflammation. It is as potent as phenylbutazone in the carrageenan edema test but only half as potent in chronic tests [32]. Curcumin has been demonstrated to be safe in six human trials and has demonstrated anti-inflammatory activity. It may exert its anti-inflammatory activity by inhibition of several different molecules that play a role in inflammation [33]. Curcumin has been shown to regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation [24].

Anti-Venom Activity: Curcumin was listed as a herbal plant metabolite that can be effective against snake venom PLA2 [34]. Researchers studied the structural relationship between medicinally important herbal compounds such as acalyphin, chlorogenic acid, stigmasterol, curcumin and tectoridin and PLA2 from Russell's viper. The molecular modeling studies revealed favorable interactions with the amino acid residues at the active site of venom PLA2 that could result in the inhibition [35].

Anti-angiogenesis Activity: Curcumin was tested for its ability to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor (bFGF), as well as its ability to inhibit proliferation of an immortalized endothelial cell line. Curcumin was tested for its ability to inhibit phorbol ester-stimulated vascular endothelial growth factor (VEGF) mRNA production [36]. Curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner. Curcumin demonstrated significant inhibition of bFGF-mediated corneal neo-vascularization in the mouse. Curcumin did not affect phorbol ester-stimulated VEGF production. These results indicate that curcumin has direct anti-angiogenic activity *in-vitro* and *in-vivo* [37].

Anti-oxidant Activity: Curcumin demonstrated the antioxidant activity by evaluation curcumin using various *in-vitro* antioxidant assays such as 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH) scavenging, 2, 2′-and-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging activity, N, N-dimethyl- p- phenylenediamine dihydro-chloride (DMPD) radical scavenging activity, total antioxidant activity determination by ferric thiocyanate, total reducing ability determination by the Fe^{3+}– Fe^{2+} transformation method, superoxide anion radical scavenging by the riboflavin/ methionine/ illuminate system, hydrogen peroxide scavenging and ferrous ions (Fe^{2+}) chelating activities [38].

Protective against Cardio Toxicity and Liver Toxicity: Researchers investigate the protective effects of curcumin on experimentally induced hepatotoxicity, and cardiotoxicity using various animal models with biochemical parameters like serum marker enzymes and antioxidants in target tissues. The increased relative weight of liver and heart in CCl_4 induced liver injury and isoproterenol-induced cardiac necroses were also

reduced by curcumin treatment. Elevated serum marker enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) increased lipid peroxidation, decreased glutathione (GSH), glutathione peroxidase (GPx) and superoxide dismutase (SOD) in edematous, granulomatous, liver and heart tissues during liver injury and cardiac necrosis, respectively. The study demonstrated the *in-vitro* and *in-vivo* protective effect of curcumin on experimentally induced hepatotoxicity and cardio-toxicity in rats [39].

Anti-bacterial Activity: The antibacterial study of curcumin shows the ability to inhibit the growth of a variety of periodontopathic bacteria and *Porphyromonas gingivitis* Arg- and Lys-specific proteinase (RGP and KGP, respectively) activities [63]. Also, curcumin suppressed *P. gingivitis* homotypic and *Streptococcus gordonii* biofilm formations in a dose-dependent manner [64]. Bacterial growth was suppressed almost completely at very low concentrations of curcumin. A concentration of 20 µg/mL of curcumin inhibited these *P. gingivitis* biofilm formations by more than 80%. On the other hand, 100 µg/mL of curcumin did not suppress the growth of *Aggregatibacter actinomycetemcomitans* [63]. Furthermore, at relatively high concentrations, curcumin targets bacterial membranes (*Escherichia coli*).

Additionally, many features of a bacterial apoptosis-like response were observed after treatment with curcumin at the MIC, including membrane depolarization, Ca^{2+} influx, PS exposure, and DNA fragmentation. A bacterial apoptosis-like response, induced by curcumin, by causing reactive oxygen species generation and DNA damage [65]. The study on *E. coli* and *B. subtilis* demonstrated that curcumin by the inhibitory effect against FtsZ polymerization could suppress the FtsZ assembly leading to disruption of prokaryotic cell division [66].

On another hand, Curcumin - Polymyxin B used clinically for topical therapy to treat or prevent traumatic wound infections of the skin. It would not only increase the spectrum of activity to include Gram-positive bacteria but also combat those isolated resistant. The use of the combination may also reduce the emergence of resistant isolates during treatments, due to the multiple antimicrobial targets of dual drug therapy and ease the selective pressure produced by broad-spectrum antibiotics [67].

Additionally, curcumin loaded in zein (zein-CUR) fibers showed good antibacterial activity towards *S. aureus*, and *E. coli* and the inhibition efficiency increased with the increase of curcumin contents. Due to the different cell membrane constituent and structure, the antibacterial activity towards *S. aureus* was better than that towards *E. coli*. The study displayed that the zein-CUR fibers might have potential as a promising material for antimicrobial applications to inhibit bacterial growth and propagation in food packaging [68]. Also, the antibacterial activity of curcumin-chitosan film against *Staphylococcus aureus* and *Rhizoctonia solani* was studied by the zone inhibition method [69]. A better antibacterial activity was certified compared to PCH film, which is an important consideration in food packaging. The natural blend films of curcumin and chitosan could be as a promising antimicrobial packaging for food and agriculture products [70].

Novel fibrous materials from cellulose acetate (CA) and polyvinylpyrrolidone (PVP) contain curcumin. The incorporation of PVP resulted in increased hydrophilicity of the fibers and faster curcumin release. Likewise, curcumin was found in the amorphous state in the curcumin-containing fibers, and these mats exhibited antibacterial activity against *Staphylococcus aureus* (*S. aureus*). The Curc/CA+Curc/PVP mat prepared by dual-spinneret electrospinning killed all the bacteria at the 4 h. Curcumin fibrous materials are potential antibacterial for wound dressing applications [71].

Also, surface charge, as well as the small size of curcumin nanoparticles, plays a key role in enhancing cell-antimicrobial interaction and anti-microbial efficacy. The fabricated curcumin nanoparticles showed the best antimicrobial activity against *Listeria monocytogenes*. A size reduction to nano-scale is a recently developed strategy used to improve drug/food delivery and matching the public demand for effective and safe antimicrobial formulations for control of foodborne pathogen [72]. *In-vivo* study of antibacterial effect of curcumin on *H. pylori* compared to OAM (Omeprazole, Amoxicillin, and Metronidazole)

treatment revealed poor activity for the eradication of *H. pylori* (5.9% *vs.* 78.9% for OAM treatment). The reduction in inflammatory cytokine production was not reported from pylori-infected patients treated with curcumin [73]. The *in-vivo* study of 1-week nonantibiotic therapy comprised of curcumin, pantoprazole, N-acetylcysteine, and lactoferrin against *H. pylori* infection was not effective for the eradication of *H. pylori*. However, the decrease in immunological criteria of gastric inflammation and dyspeptic symptoms was reported after 2 months of treatment schedule [74].

Nevertheless, the curcumin administration to the rats with *H. pylori*-induced gastric inflammation revealed a significant reduction in macromolecular leakage and NF activation [75]. In an *in-vivo* study of *H. pylori*-infected C57BL/6 mice administered with curcumin exhibited immense therapeutic potential and pronounced eradication effect against *H. pylori* infection associated with restoration of gastric damage [76].

Anti-Fungal Activity: Substances and extracts isolated from different natural resources especially plants have always been a rich arsenal for controlling the fungal infections and spoilage. Due to extensive traditional use of curcumin in food products, various researches have been done to study curcumin with the aspect of controlling fungal related spoilage and fungal pathogens [77].

The study of addition the curcumin powder in plant tissue culture showed that curcumin at the 0.8 and 1.0 g/L had appreciable inhibitory activity against fungal contaminations [78]. The possible mechanism underlying the mentioned antifungal effect was found to be the downregulation of desaturase (ERG3) leading to a significant reduction in ergosterol of fungal cell. Reduction in production of ergosterol results in accumulations of biosynthetic precursors of ergosterol which leads to cell death *via* generation of ROS [118]. Reduction in proteinase secretion and alteration of membrane-associated properties of ATPase activity are other possible critical factors for antifungal activity of curcumin [79]. Finding new anti-candida substances seems to be crucial due to the development of resistant strain against existing antifungal drug [56]. The study of curcumin, against 14 strains of Candida, showed that curcumin is a potent fungicide compound against Candida species with MIC values ranging from 250 to 2000 μg/mL [79].

In another study, anti-candida activity of curcumin was demonstrated against 38 different strains of Candida including some fluconazole resistant strains and clinical isolates of *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. guilliermondii*, and *C. krusei*. The MIC_{90} values for sensitive and resistant strains were 250-650 and 250-500 μg/mL, respectively. Intracellular acidification *via* inhibition of H^+-extrusion was identified as a possible mechanism for cell death of *Candida species* [80]. The development of hyphae was proved to be inhibited by curcumin through targeting the global suppressor thymidine uptake 1 (TUP1). Curcumin exhibited potent antifungal effect *via* mechanisms associated with disruption of the plasma membrane in *Candida albicans* [81].

Curcumin also showed an inhibitory effect on *Cryptococcus neoformans* and *C. dubliniensis* with MIC value of 32 mg/L [79]. One of the major complications during therapies against chronic asthma is oropharyngeal candidiasis. Curcumin as a potential candidate for the treatment of candidiasis with anti-inflammatory activity was studied in a murine model of asthma. The oral administrator of curcumin is more effective than dexamethasone in reducing fungal burden in BALB/c mice. It also significantly decreased pathological changes in asthma [82]. Adhesion of Candida species isolated from AIDS patients to buccal epithelial cells is also markedly inhibited by curcumin, and it was found to be more effective compared to fluconazole [83].

The investigation of curcumin mediation for photodynamic therapy can reduce the biofilm biomass of *C. albicans*, *C. glabrata*, and *C. tropicalis*. The results demonstrated that the association of four LED influences for light excitation with 40 μM concentration of curcumin at 18 J/cm^2 inhibited up to 85% metabolic activity of the tested *Candida species*. The use of curcumin with light proved to be an effective method for noteworthy improvement in the antifungal activity against a planktonic form of the yeasts [84]. Photodynamic effect considerably decreased *C. albicans* viability in either planktonic or biofilm cultures probably through increasing the uptake of curcumin by cells.

However, to a lesser extent, photodynamic therapy was found to be phototoxic to the macrophages [85]. The strong antifungal activity of *C. longa* rhizome and its low side effect were the main reasons to investigate its probable synergistic effect with existing fungicides. The synergistic activity of curcumin with five azole and two polyene drugs including voriconazole, itraconazole, ketoconazole, miconazole, fluconazole, amphotericin B and nystatin showed a 10-35-fold reduction in the MIC values of the fungicides against 21 clinical isolates of *C. albicans*. The synergistic activity of curcumin with amphotericin B and fluconazole could be associated with the accumulation of ROS which will be suppressed by adding an antioxidant [46].

Anti-viral Activity: Lack of effective therapeutics for the most of viral diseases, the emergence of antiviral drug resistance and high cost of some antiviral therapies necessitate finding new effective antiviral compounds [57, 58]. Additionally, the existing antiviral therapies are not always well-tolerated or quite effective and satisfactory [46]. Hence, the increasing requirement for antiviral substances will be more highlighted. Plants as a rich source of phytochemicals with different biological activities including antiviral activities are in the interest of scientists [59].

It has been demonstrated that curcumin as a plant derivative has a wide range of antiviral activity against different viruses: papillomavirus virus (HPV), influenza virus, Hepatitis B virus (HBV), Hepatitis C virus (HCV), adenovirus, coxsackie-virus, Human norovirus (HuNoV), Respiratory syncytial virus (RSV) and Herpes simplex 1 (HSV-1) [86, 87, 88, 89, 90]. Curcumin functionalized graphene oxide shown synergistic antiviral effect against respiratory syncytial virus infection [87]. Respiratory syncytial virus (RSV), which is considered as the major viral pathogen of the lower respiratory tract of infants, has been implicated in severe lung disease [86].

Developing a β-cyclodextrin (CD) functionalized graphene oxide (GO) composite, which displayed excellent antiviral activity and curcumin loading efficiently, showed that the composite could prevent RSV from infecting the host cells by the directly inactivating virus and inhibiting the viral attachment, which possessed the prophylactic and therapeutic effects towards virus [86]. The antiviral effect of curcumin was a dose-dependent manner [91]. Curcumin inhibits the activity of inosine-mono phosphate dehydrogenase (IMPDH) enzyme in an either noncompetitive or competitive manner. By inhibition of IMPDH, this led to reducing the level of intracellular guanine nucleotides which required for adequate RNA and DNA synthesis [86, 88, 92]. Curcumin mechanism involves in viral entry or other life cycle stages rather than the replication of viral RNA [91]. Therefore, by inhibition of IMPDH Curcumin have potential anti-proliferative, antiviral and antiparasitic effects [92].

Anti-cancer Activity: Cancer is the second largest single cause of death claiming over six million lives every year worldwide [93]. Scientific studies of plants used in various types of ethnic medicine have led to the discovery of many valuable drugs, including taxol, camptothecin, vincristine and vinblastine [94, 44]. Many studies pointed out anticancer activities of curcumin alone or in combination with conventional chemotherapy drugs in the treatment of cancer and its cancer-related complications [94, 95, 96, 97].

In-vitro and *in-vivo* studies have indicated that curcumin prevents carcinogenesis by affecting two primary processes: Angiogenesis and tumor growth [96, 97 98]. Curcumin has exhibited efficient anticancer and antifungal activities alone or in combination with conventional chemotherapy drugs and antifungal agents [99]. Curcumin analogs S1- S3 is containing sulfone strongly inhibited the growth of human prostate, colon, lung and pancreatic cancer cells [100, 101].

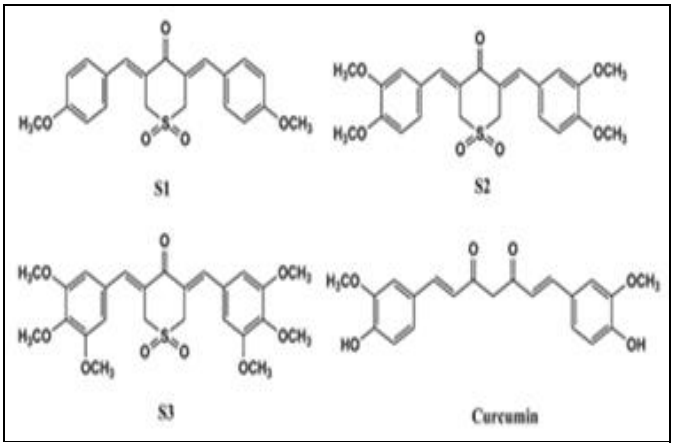

FIG. 4: STRUCTURE OF CURCUMIN ANALOGS CONTAINING SULFONE

Curcumin significantly inhibited the growth of human breast cancer cell by inducing apoptosis in a dose and time-dependent manner, accompanied by a decrease in MCF-7 cell viability [98]. The antitumor action of curcumin is mediated *via* its anti-proliferative effect in multiple cancers, inhibitory action on transcription factors and downstream gene products, modulatory effect on growth factor receptors and cell adhesion molecules involved in angiogenesis, tumor growth and metastasis, while recent works showed the possibility curcumin could exert its antitumor potential by telomerase inhibition [102, 103, 104]. Curcumin oil has bi-functional effects by blocking anti-apoptotic signaling but also blocking anti-oncogenic signaling and interferon-γ production [105, 106]. Moreover, Curcumin showed higher uptake in tumor cells compared to normal cells, suggesting potential diagnostic applications in this field [107].

In a study, the Gallium-Curcumin complexes showed an uptake in A549 lung cancer cells, at least equivalent to the respective free curcumin, confirming potential applications as cancer-detecting radiotracers. Natural products play a major role in chemotherapy drugs and primarily target proliferating tumor cells [94]. Their use could be of great interest and is considered to be an inexpensive, safe and accessible approach to cancer control and management. However, in spite of the useful biological activities of curcumin but it limited due to its poor bioavailability, water solubility and some possible adverse effects [96, 109].

The development of formulations of curcumin in the form of nanoparticles, liposomes, micelles, or phospholipid complexes to enhance its bio-availability and efficacy is still in its early stages [110]. Various nano-sized curcumin delivery systems, such as nanoparticles, nanospheres, solid lipid nanoparticles, micelles, and liposomes have been shown to overcome these shortcomings and significantly improve the anticancer and antifungal activities of curcumin. Many studies on curcumin and its nanoformulations are still in the preclinical stage at present [110, 111].

PLGA curcumin nanoparticles efficiently inhibit the growth of prostate cancer cells both *in-vitro* and *in-vivo*. This was achieved through lysosomal activity, apoptosis, and inhibition of Androgen receptor and nuclear b-catenin activity. PLGA-CUR NPs significantly modulate the expression of miR-21 and miR-205 genes. Shown significant prostate tumor-specific targeting in a xenograft mouse model [112]. Curcumin exhibits the ability to modulate multiple targets via the regulation of diverse transcription factors, inflammatory cytokines, growth factors, different protein kinases, and various other enzymes. Furthermore, safety and tolerability as evidenced by multiple clinical trials carried out thus far together with cost-effectiveness are some other added yet inevitable advantages offered by this agent [113].

Delay of Cataract Development: Cataract is responsible for more than one-third of blindness worldwide. Twenty-five percent of people over the age of 65 and 50% of people larger than an age of 80 have a serious defeat of vision due to cataracts [114, 115]. Cataract extraction surgery is the majority treatment for cataract. Whereas cataract surgery is considered to be not dangerous and mature, irreversible blindness is a possible risk. There is no recognized drug which can treat or overturn cataract. If cataract onset is late by 10 years, it is expected to decrease the risk for cataract surgery by 50%. Thus, much emphasis is being laid on identifying compounds with high effectiveness and low toxicity that can either avoid the onset or delay cataract progression.

It is supposed that oxidative damage to the eye lens responsible for the development of different kinds of cataracts [116]. The antioxidant characteristics of curcumin are the main anti-cataract mechanism [117]. In cultured human lens epithelial cells (hLECs) *in-vitro*, curcumin inhibits peroxiredoxin 6 (a pleiotropic oxidative stress-response protein). By reversing the activity of increasing the activities of superoxide dismutase (SOD), decreasing ROS, and antioxidant enzymes, the bioactive derivatives of curcumin were reported to inhibit the selenite inducing cataract [118, 119, 120].

Additionally, curcumin was found to have a protective effect against cataract development and progression of diabetic cataract in numerous *in-vitro* and *in-vivo* cataract models [120, 121]. Vitamin C is a potent non-enzymic antioxidant, and the level of vitamin C is high in the human lens, suggesting that vitamin C may have a preventive role in

cataract progression. The decreased levels of vitamin C linked with selenite-induced rat cataracts. So by the administration of curcumin was found to increase vitamin C levels so protect rat eyes [122]. Pre-treatment of curcumin may prevent oxidative damage and delay the development of cataracts [118].

Hepatoprotective Activity: The liver is one of the most important organs of the body, that plays an important role in maintaining various physiological processes and is involved in numerous vital functions, such as metabolism, secretion, and storage [123]. Also participating in the biochemical processes of growing, providing nutrients, supplying energy, and reproducing. In addition, it aids in the metabolism of carbohydrates and fats, in the secretion of bile, and in the storage of Vitamins It plays a central role in detoxifying endogenous (waste metabolites) and/or exogenous (toxic compounds) substances of organisms, as well as for synthesizing useful agents, has been analyzed since the 1970s by many researchers. Curcumin has been discussed by various researchers for their hepatoprotective. New evidence has proven the hepatoprotective activity of curcumin, but its underlying mechanisms remain to be elucidated.

Phytosome Curcumin had a strong protective effect against paracetamol-induced with acute hepatic damage in mice. The hepatoprotective effect of phytosome curcumin may be explained by increasing levels of antioxidant enzymes and decreasing the lipid peroxidation and liver enzyme on paracetamol-induced damage in mice. Furthermore, an investigation of the protective effect of curcumin on hepatic damage *via* measuring the antioxidant capacity and regulation of different enzymes. Curcumin treatment of bile duct ligated rats led by elevation of antioxidant (thiols, SOD, and catalase) and hepatic enzymes (ALP, AST, and ALT). And curcumin attenuated liver damage through down-regulating of Ras-related C3 botulinum toxin substrate 1, Rac1-GTP, and NADPH oxidase 1 as well as reducing oxidative stress in serum and liver tissue of BDL rats.

Curcumin may serve as effective hepatoprotective agents for mercuric chloride-induced hepato-toxicity. The protective effect is due to their free radical scavenging activities and recovery of antioxidant enzymes and function markers of the liver. In additionally, the protective effects of curcumin against Diethyl nitrosamine induced hepatocarcinogenesis in albino rats is due to modulated the hepatic pathological alteration, liver function enzymes serum levels, induced the hepatic anti-oxidant system and suppressed the proinflammatory cytokines.

Anti-fibrotic Activity: Idiopathic pulmonary fibrosis (IPF) is a progressive disease of unknown etiology that can result in respiratory failure. The resulting fibrotic changes in lung architecture lead to decreased gas exchange and pulmonary compliance. Notably, curcumin effectively reduces profibrotic effects in fibroblasts *in-vitro via* the inhibition of key steps in the signaling pathway of transforming growth factor beta (TGF-b) a multifunctional cytokine belonging to the transforming growth factor.

It was reported that the activation of peroxisome proliferator-activated receptor gamma (PPAR-g) by curcumin blocked platelet-derived growth factor (PDGF) signaling pathway in hepatic satellites cells. However, the relationship of PPAR- g and PDGF signaling pathway is unclear in TGF-b induced differentiation of lung fibroblasts to myofibroblasts. Curcumin inhibits TGF-β2 driven differentiation of mouse lung fibroblasts to myofibroblasts. Curcumin and PPAR-γ could potentially be used for effective treatment of IPF.

Anti-atherosclerosis and Anti-hypertension Activity: Atherosclerosis and hypertension can potentially progress into dangerous cardiovascular diseases such as myocardial infarction and stroke. Statins are widely used to lower cholesterol levels while antihypertensive agents such as captopril are widely prescribed to treat high blood pressure. Curcumin, a phenolic compound isolated from *Curcuma domestica*, has been proven effective for a broad spectrum of diseases, including hypertension and hypercholesterolemia. Therefore, curcumin is quite promising as an alternative therapeutic compound. By studying the effects of Curcumin on hyperlipidemia and hepatic steatosis in high-fructose-fed Wistar rats, the results showed the ability of curcumin in treatment high-fructose induced fatty liver, lipid derangements and obesity

through modulation of lipid metabolism in the liver as evidenced by decreased expression of lipogenic enzymes and transcription factors. Therefore, it is suggested that the use of curcumin may be beneficial as an adjuvant in the prevention and management of diet-induced obesity and its associated complications.

Another study reported that encapsulated of curcumin in a nanoemulsion showed significant cholesterol-lowering activity compared to a standard drug, pravastatin and this encapsulated increased not only the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition but also Angiotensin-converting enzyme inhibitors like effect by producing vasodilation by inhibiting the formation of angiotensin II. These effects are suggested to be the result of improved solubility in the nanoemulsion system.

CONCLUSION: The wisdom and scientific knowledge of curcumin, a highly pleiotropic agent, which were used for its therapeutic effects in many countries as traditional medicine. For that, the pharmacological properties and applications of curcumin are a rapidly growing, progressing, and expanding enterprise, as evidenced by the studies reviewed above and the many more being reported every day.

Of the most obvious therapeutic weight of curcumin, researchers typically pointed at diseases like diabetes, wound healing, arthritis, Alzheimer, Parkinson, inflammatory, venom, angiogenesis, cataract, cancer, atherosclerosis, and hypertension, etc, which is in use since ages owing to its multiple pharmacological activities. Curcumin is enriched with many useful phytoconstituents, which are responsible for its efficacy proven by experimentally and clinically. It has been established beneficial in treating anti-inflammatory, anti-allergic, anti-oxidant, anti-hyperglycaemic, anti-cancer, anti-microbial, anti-atherosclerosis and anti-hypertension properties. Because of curcumin facility to affect a large range of molecular targets and a good safety profile, was established to be a potential candidate for the avoidance or/and treatment of several diseases.

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CONFLICT OF INTEREST: Nil

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