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CURCUMINOIDS: REVIEW OF THERAPEUTIC POTENTIALS

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ABSTRACT

Curcumin has long been recognized for its medicinal properties and it has received interest from both the medical and scientific world and from culinary enthusiasts, as it is the major source of the polyphenols curcumin. curcumin helps in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, hyperlipidemia and anxiety . It help in the management of exercise-induced inflammation and muscle soreness, thus it enhances recovery and performance in active people. In addition, a relatively low dose of the complex will provide the health benefits for people that do not have diagnosed health conditions. These benefits can be attributed to its antioxidant as well as anti-inflammatory effects as well . Ingesting the curcumin by itself does not lead to the associated with health benefits due to its poor absorption and bioavailability, which appears to be primarily due to poor absorption, rapid metabolism, and rapid elimination. There are several components that will increase bioavailability. The aim of this review was to overview the biological activities of curcuminoids and other biomolecules from turmeric and also discussed the effects and various applications of curcuminoids.

KEYWORDS:

CUR - Curcumin
DCM - Dichloromethane
DMC - Demethoxy curcumin
BDMC - Bisdemethoxycurcumin
BDNF- Brain-derived neurotrophic factor

1. INTRODUCTION

Natural products have been used in traditional medicines from very long time, and have shown promise as a source of components for the development of new drugs.[1,2] Turmeric (Curcuma longa Linn) is from the family of Zingiberaceae and is cultivated in tropical and subtropical regions around the world and it is originated from India, Southeast Asia and Indonesia.[3] Turmeric powder is used extensively as a coloring as well as the flavoring agent in curries. Turmeric is also used in India to maintain oral hygiene.[4] curcumin traditionally been used for many medical purposes in many centuries in countries such as India and China for treatment of jaundice and other liver ailments.[5,6] Turmeric is one of the most popular medicinal herbs, with a wide range of pharmacological activities such as antioxidant,[7] anti-protozoal,[8] anti-venom activities,[9] antimicrobial,[10] anti-malarial,[11] anti-inflammatory,[12] anti-proliferative,[13] anti-angiogenic,[14] anti-tumor,[15] and anti-aging.[16] properties. It has also been used to treat ulcers, parasitic infections, various skin diseases, autoimmune diseases and curing the symptoms of colds and flus.[17] The pharmacological activity of turmeric has been attributed mainly to curcuminoids consisting of curcumin (CUR) and two related compounds demethoxy curcumin (DMC) and bisdemethoxycurcumin (BDMC). CUR itself is crystalline in nature with a very bright orange and yellow color. Curcuminoids are also used as a coloring agent and food additives. . Curcuminoids and turmeric products is characterized as safe by the FDA in the USA market. The average intake of the turmeric in the Indian diet is approximately 2 to 2.5 g for a 60-70 kg individual which corresponds to a daily intake of approximately 60 - 100 mg of CUR. Curcuminoids have achieved the potential therapeutic interest for curing the immune related and metabolic diseases and cancer due to a vast number of biological targets and with virtually no side effects.[17,18]

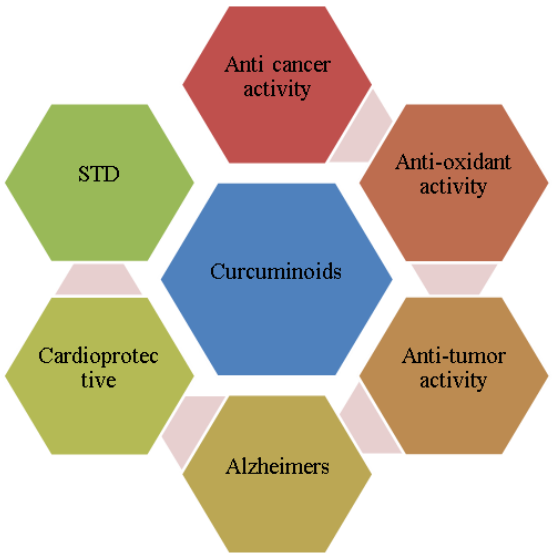

Figure 1: Application of Curcuminoids

2. Extraction of curcuminoids from Turmeric[19,20]

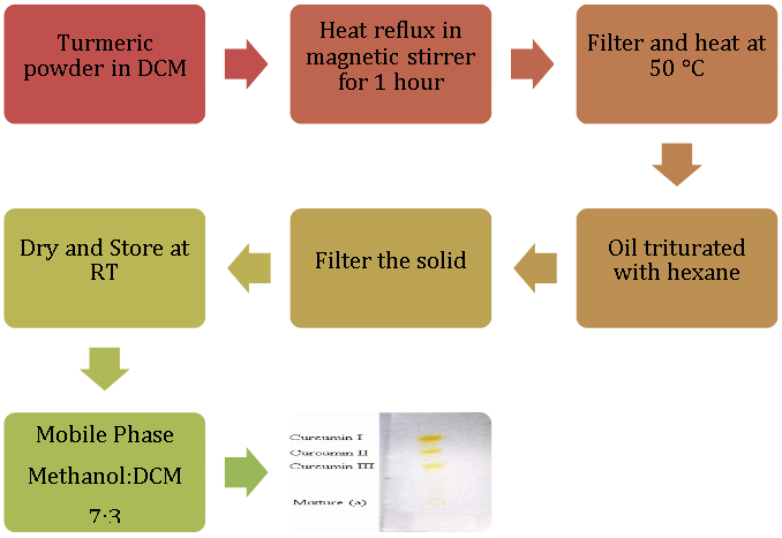

Figure 2: Extraction of Curcuminoids.

Chemical analyses have shown that turmeric contains.

Constituent	Percentage
Carbohydrates	69.4%
Moisture	13.1%
Protein	6.3%
Fat	5.1%
Minerals	3.5%
Essential oil	5.8%

3. Chemistry of Curcumin

Curcumin having the molecular formula i.e C21H20O6 is an asymmetric molecule with a molar mass of 368.38 g/mol Structurally, it contains three main functional groups: Two aromatic ring systems containing o-methoxy phenolic groups, and one alpha beta-unsaturated beta-diketone moiety is present in the curcumin. In the aqueous solutions, the curcumin will undergo keto-enol tautomerism with its structure depending on pH: The keto form dominates under acidic and/or neutral conditions, while the enolate form dominates under alkaline conditions. The enol form of curcumin is chemically more labile than in the keto form,

which is accounting for the poor chemical stability of curcumin in high pH solutions.[20]

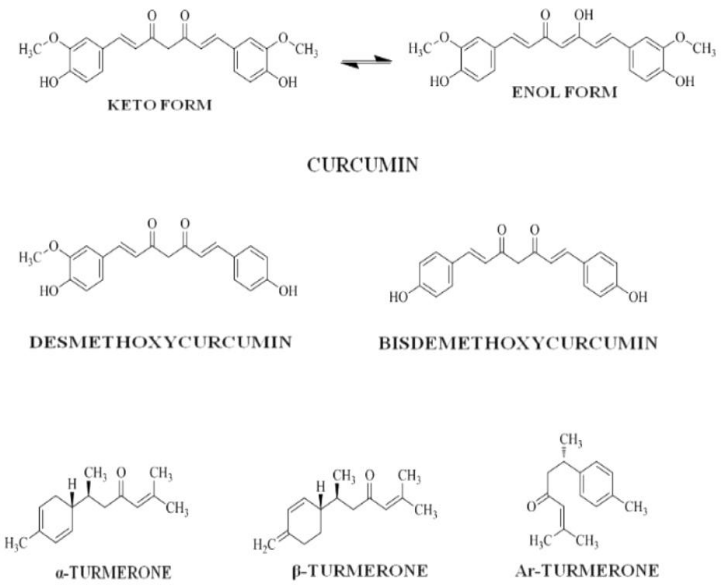

Figure 3: Chemical structure of constituents present in turmeric.

4. Physical, chemical and molecular properties of curcuminoids

The two active components of turmeric are the volatile oil and the curcuminoids and which both are present in oleoresin extracted from the root of turmeric. The essential oils are composed mainly of sesquiterpenes and many of which are specific for the Curcuma genus. The aroma of this spice is principally derived from a- and b-turmerones and aromatic turmerone (Ar-turmerone).[21] The chemical structures of curcuminoids which makes them much less soluble in water at neutral pH and acidic pH, but soluble in methanol, ethanol, DMSO and acetone. The curcuminoids give a very yellow-orange coloration to turmeric powder due to the wide electronic delocalization of electrons inside the molecules that exhibit strong absorption between 420 to 430 nm in an organic solvent. The curcuminoids are a mixture of curcumin, chemically diferuloylmethane[1,7-bis(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione] mixed with its two derivatives, demethoxy curcumin [4-hydroxycinnamoyl-(4- hydroxy-3-methoxy cinnamoyl) methane] and bis-demethoxy curcumin[bis-(4-hydroxycinnamoyl) methane], defining the chemical formulae as C21H20O6, C20H18O5 and C19H16O4 respectively.[17] The chemical structures of important constituents present in turmeric are given in Fig. 1. They share the same structure as with two benzene methoxy rings, and joined by an unsaturated chain. It has three main important functional groups: an aromatic methoxy phenolic group; a,b unsaturated b-diketo linker and keto-enol tautomerism. All these compounds that are existing in the trans-trans keto-enol form. The aromatic groups provides the hydrophobicity and the linker gives flexibility to the structure . The tautomeric structures is also influence the hydrophobicity and polarity of the compound. curcuminoids are poorly soluble in water due to its hydrophobicity . Three acidity constants (pKa) were measured for curcuminoids they are as follows, pKa1 8.38 ± 0.04, pKa2 9.88 ± 0.02 and pKa3 ¼10.51 ± 0.01.[22] Typical curcuminoids composition of popular Indian varieties was found to be in the range of CUR 52 - 63%, DMC 19 - 27% and BDMC 18 - 28%.[17]

Therapeutic View

Biological activities of curcuminoids

Curcuminoids from turmeric and their derivatives have been shown to possess a wide range of biological activities including antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, cardioprotective and radioprotective effects etc.

1. Neuroprotective effects and medicinal use in Alzheimer's disease (AD)

Demonstrated that intracerebroventricular (ICV) administration of [Human immunodeficiency virus-1 (HIV-1)] HIV1 gp120V3 loop peptide caused spatial learning and memory dysfunction, diminished LTP and produced significant oxidative brain damage. The administration of CUR significantly ameliorated HIV-1gp120 V3 loop peptide-induced neuronal damage and dysfunctions, and increased the expression of the BDNF. CUR supplementation can be an effective therapy for counteracting the deleterious effects of gp 120 in HIV-1-associated dementia. Antioxidant properties of CUR can be responsible for protection against homocysteine (Hcy) oxidative stress, possibly by increasing the endogenous defenses against oxidative stress. CUR can scavenge superoxide anion (SOA) from hippocampus tissue. Protective effects of CUR against lipid peroxidation lead to decreased malondialdehyde and SOA formation. CUR can prevent neurotoxicity of Hcy in the rat hippocampus. Hyperhomocysteinemia might be one of the pathological

reasons of the neurodegenerative disorders such as sporadic AD or Parkinson's disease, CUR can be an effective prophylactic agent in the prevention of oxidative stress by Hcy. The mechanism of CUR for protecting the hippocampus against the toxicity of Hcy might be to decrease the generation of ROS in the brains of rat. Epilepsy is a chronic neurological disorder. Agarwal et al.[32] studied the effect of acute administration of CUR at various doses orally pentylene tetrazole induced kindling in mice. Two oxidative stress markers are malondialdehyde (MDA) and glutathione were present in brain tissues of rodents. CUR dose dependently suppressed the increasing of kindling in mice. The increases in the levels of MDA and glutathione were reduced by CUR in kindled animals. CUR would be a promising candidate to control developments of seizure and oxidative stress during in period of epilepsy.

Yu et al,[33] investigated the effects of CUR on memory decline of aged mice which focus upon the possible contribution to neuronal NO synthase (nNOS)/nitric oxide (NO) pathway in the memory amelioration effect of CUR.

De Alcantara et al.[39] studied the neuroprotective response of CUR in a model of global ischemia. CUR treatments increased the neuronal viability and attenuated the immuno reactivity for COX-2 and TNF-a in the hippocampus.

Ahmed et al.[45] evaluated the AChE enzyme inhibitory and memory enhancing activities of curcuminoids by in vitro and ex vivo models of AchE inhibitory activity with Morris water maze test on memory which is performed with rats.

The pathogenesis of neurodegenerative diseases like Alzheimer or Parkinson is multifactorial with a complex combination of genetic components and environmental factors. Inflammation, glutamatergic toxicity, dysfunction of mitochondrial activity and ubiquitin/proteasome system are toxic reactions, including the activation of apoptosis pathways, the elevation of iron and nitric oxide and the alteration of the homeostasis of antioxidants/oxidation are involved in the pathogenesis process of neurodegenerative diseases.[26] Dohare et al.[27] showed the neuroprotection mechanisms against experimental cerebral ischemia by curcuma oil isolated from the rhizomes of C. longa. Curcumin oil decrease the rise in the intracellular concentration of Ca2þ-a common component in the signaling pathways. The high levels of Nitric oxide generated by NOS isoforms that are partially responsible for exacerbating the neuronal damage were reduced by the curcuma oil. Curcuma oil prevents post-ischemic brain neutrophil infiltration and Nitric oxide metabolites and reduced the production of ROS. Curcumin oil suppressed the high level of protein Bax, and the mitochondrial translocation and activation of Bcl-2 that is triggered by altering mitochondrial membrane potential. Curcumin oil exerts its major action in the penumbral region of the infarct and it is protected by modulation of apoptosis. The neuroprotective effect is due to the reduction of Nitric oxide induced formation of peroxy-nitrite and apoptosis in the transient MCAo model in animal like rats. Dohare et al.[28] also studied on CUR administered at various dose levels after 4 h of clot implant in the rat embolic stroke model. after 24 hours of rat surgery for neurological dysfunction, locomotor activity and motor coordination test, infarct volume, edema volume, brain tissue nitrate/nitrite, myeloperoxidase, GSH and GSH-Px activity. The flow cytometric estimation in neuronal rich cell population the level of ROS, NO and peroxynitrite generation were studied at 24 h, which contributed to serve neuronal cytotoxicity and were selectively inhibited by CUR treatment. Ischemia which is induced by increase in the level of brain infarct volume and edema volume were significantly decreased by CUR treatment. The neurobehavioral activity assessment and locomotor activity and motor coordination these further strengthen and above biochemical data there by indicating neuroprotective effect of CUR administered at 4 h after ischemia in rat focal embolic stroke model. Sahoo et al.[29] investigated the CUR effect on oxidative stress parameters such as antioxidant defense enzymes and oxidized (GSSG) and reduced glutathione (GSH) levels in testis of L-thyroxine (T4)-induced TNF-a in a concentration dependent manner and their relative potency was also DMC > BDMC > CUR. Curcuminoids can also be used as potential therapeutic implications for various neurodegenerative diseases.[30] Tang et al.[31]

2. Antitumor-activity

Curcuminoids are the main constituents of turmeric and have a wide range of pharmacological activities. The effect of curcuminoids and cyclocurcumin examined on the proliferation of MCF-7 human breast tumor cells. DMC is a better inhibitor than CUR and BDMC due to the presence of phenolic hydroxyl groups, methoxyl groups and the diketone moiety in the structure. Cyclocurcumin had no effect on MCF-7 cell proliferation, suggesting that the diketone system of curcuminoids appears to be the part of the molecule involved in the antiproliferative effect of curcuminoids . Somsri et al investigated the effect of pure CUR on Wilms tumor 1 (WT1) gene expression in leukemic K562 cells line was mediated through PKCa signaling upstream of WT1 transcription factor auto-regular function. Pure CUR affects the WT1 binding of protein-promoter and WT1-mRNA decreased and levels of protein in K562 cells which contributed to the pure CUR anti-proliferative effect. It can attenuate WT1 autoregulatory function through inhibition of PKCa signaling in K562 cells, it can also be useful in the upcoming development of therapeutic approaches for leukemic patients. Jiang et al.[34] have identified the antitumor constituents in curcuminoids from C. longa on HeLa cells were measured using an MTT (3e4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide

assay based on the composition and activity relationship. Curcuminoids were significantly correlated with antitumor activity via loading a plot and variable importance in projection in orthogonal partial least squares and a correlation coefficient in canonical correlation analysis. The role of CUR in decreasing the lipolytic action was examined upon various stimulations in 3T3-L1 adipocytes. Treatment with CUR attenuated TNF-a-mediated lipolysis by decreasing the phosphorylation of extracellular signal related kinase 1/2(ERK1/2) and reversing the downregulation of perilipin protein in TNF-a-stimulated adipocytes. The antilipolytic effect could be a cellular basis for CUR decreasing plasma free fatty acid levels and improving insulin sensitivity.[35] CUR is a potent tight binding inhibitor of human carbonyl reductase 1 (CBR1) will occupied binding sites of CBR1 receptor as a cofactor that decreases daunorubicinol formation. CUR will give the potential to enhance the therapeutic effect of daunorubicin by preventing heart tissue damage through the inhibition of CBR1 mediated reduction of daunorubicin to daunorubicinol. The inhibition of CBR1 can increase the potency of daunorubicin in cancer tissue and simultaneously decrease its cardiotoxicity.[36] Metabolic profile of Rhizoma paridis saponins when combined with the turmeric intervention in H22 hepatocarcinoma mice tumor growth was validated by histopathological examination. It is mediated by the tumor environment and significantly inhibits tumor growth rate through suppressing levels of amino acids, lipid compounds and carbohydrates in the tumor tissues. Rhizoma paridis saponins combined with turmeric could be a good anticancer agent that targets cancer metabolism by starving tumors, reducing feasibility of cancer cells.[37]

3. Antioxidant activity

Curcuminoids possess very powerful antioxidant activity as demonstrated in many chemicals in vitro tests and in several in vivo trails.The antioxidant activities and capacities of curcuminoids have been studied by Jayaprakasha et al.[38] with in vitro model system such as phospho molybdenum and linoleic acid peroxidation method. These compounds could be used in food to enhance the shelf life due to their good antioxidant capacity of curcumin. The antioxidant mechanism of CUR was explained by using density functional theory with five different mechanisms which will be considered such as single electron transfer (SET), free radical adduct formation (RAF), H atom transfer from neutral curcumin (HAT), to the H atom transfer from deprotonated curcumin (HAT-D) and sequential proton loss electron transfer (SPLET). The reaction between curcumin and DPPH in fact takes place only by the SPLET mechanism, whereas the reaction with eOCH3 and other alkoxy radicals are governed by the HAT mechanism. The contribution of the HAT mechanism to the overall reaction with curcumin and eOCH3 are found to be higher than 95%, regardless of the any solvents polarity and of the reacting curcuma isomer. The antioxidant activity of curcumin has been confirmed experimentally mainly due to the presence of phenolic groups in CUR.[39] Kalpravidh et al7 evaluated hematological profile, oxidative stress and antioxidant parameters in twenty one b-thalassemia/Hb E patients are treated with curcuminoids (2 capsules or tablets of 250 mg) for 12 months. Higher levels of malondialdehyde, superoxide dismutase, glutathione peroxidase in red blood cell, abd serum non-transferrin bound iron (NTBI) and lower level of glutathione in RBC showed the increased oxidative stress in b-thalassemia/Hb E patients. All these parameters are returned close to baseline levels after 3 months of treatment. The Curcuminoids can be used to ameliorate oxidative damage in patients with b-thalassemia/Hb E disease. Naik et al.[40] investigated the protective effects of CUR on experimentally induced the inflammation, and hepatotoxicity and cardiotoxicity using the biochemical parameters such as serum marker enzymes and antioxidants in target tissues of different animal models. CUR treatment inhibited carrageenan and albumin induced edema, cotton pellet granuloma formation. The increased weight to the liver and heart in CCl4 induced in liver injury and isoproterenol induced cardiac necrosis these were reduced by CUR treatment. CUR also inhibits the iron catalyzed lipid peroxidation in liver homogenates, and scavenged nitric oxide spontaneously generated from nitroprusside and inhibited heat induced by hemolysis of rat erythrocytes. Antiinflammatory, hepatoprotective and cardioprotective effects of CUR can be related with its antioxidant activity by both the in vitro and in vivo results. Curcumin can be a useful in the adjuvant in drug therapy along with conventional drugs in oxidative stress induced diseases. Metabolomics can be used as an attractive approach for completely elucidating and studies on the in vivo antioxidant effects or oral administration of a C. longa extract. The experiment was carried out by 12 healthy rats with particularly attention to urinary markers of oxidative stress over a 33 days period and changes in the 24 h urine samples are metabolism were evaluated by 1 H NMR and HPLC-MS. The evaluation effects of the Curcumin extract on the urine composition in healthy rats by a metabolism approach which lead to evidence for an in vivo antioxidant effect caused by a significant reduction in the level of urinary biomarkers of oxidative stress, such as allantoin, m-tyrosine, 8-hydroxy-20 - deoxyguanosine and 3- nitrotyrosine. Metabolomics based study strongly supported by the in vivo antioxidant effect of the oral administration of C. longa extract to healthy rats.[41]

4. Anticancer activity

Yodkeeree et al.[42] examined the comparison of the influence of CUR, DMC and BDMC on the levels of the of urokinase plasminogen activator, metalloproteinases (MMPs), membrane type 1 (MT1- MMP), tissue inhibitor of MMPs and in vitro invasiveness of human fibrosarcoma cells. They have the differential potency for inhibition of cancer cell invasion was BDMC > DMC > CUR. Zymography analysis demonstrated that CUR,

DMC and BDMC are significantly decrease the level of urokinase plasminogen activator, active MMPs from the cells in a very well dose dependent manner, in which BDMC and DMC showed more potency than CUR. Three forms of curcuminoids significantly inhibits collagenase, MMPs. DMC and BDMC which showed higher anti metastasis potency than CUR by the differentially downregulation of ECM degradation enzymes. The mechanism of their chemotherapeutic effect was study by the role in proliferation of HCT116 human colon cancer cells. Both compounds damaged correct spindle formation and induced a p53 and p21CIP1/ WAF1-independent mitotic arrest, which is more stable and long lasting for BDMC. The anticancer effect of natural borneol with DMC has been investigated with HepG2 cell line by MTT assay,with the flow of cytometry and western blotting assay. Natural borneol-DMC showed a significant decrease in cell viability due to pretreatment of natural borneol enhanced the cellular uptake of DMC. Natural borneol-DMC induced the HepG2 cells growth which was inhibited by induction of G2/M arrest and due to accumulation of the G2/M cell population. The combination of natural borneol and DMC will going to induced G2/M phase arrest in HepG2 through ROS overproduction and this can be the potential for the development of chemosensitizer in the treatment of human cancer.

5. Cardioprotective effects

CUR has very high cardioprotective effects against diabetic cardiovascular complications and cardiac hypertrophy and myocardial infarction. the molecular mechanism of the cardioprotective effects of CUR by a rat model of coronary artery ligation was explored by Hong et al.[43] assessed. 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 CUR some amelioration in cardiac function, infarct size and serum biochemical markers were noted. Cardioprotective effects CUR are associated with cytokine receptor and cytokine interaction, ECM-receptor interaction, focal adhesions and colorectal cancer. very complex disease i.e idiopathic pulmonary arterial hypertension which mainly affects pulmonary arterial circulation. it will undergoes a remodeling along with the subsequent reduction of flow in the small pulmonary arteries in the body. Because of this damage there will be increased vascular resistance gradually develops and over time it carries out in heart failure. CUR is a potent anti-inflammatory agent , which is useful for inflammatory diseases. Long investigations of anti-inflammatory effect of CUR has been showed a role for inactivation of NF-jB mediated inflammation.[44]

6. Sexually transmitted infections

STD and unplanned pregnancies present a great risk to the reproductive health of many women. vaginal controlled Female products directed toward disease prevention and contraception are needed urgently. Patel et al.[45] developed a poloxamer based thermo sensitive contraceptive vaginal in situ hydrogel of CUR, a plant derived CUR compound. Biodegradable hydrogels impregnated with Poloxamers and HPMC K4M which could lead to the development of a non-hormonal, women friendly, long acting and biocompatible intravaginal contraceptive dosage form. The dosage form which was optimized using a three-factor, and a three-level Box-Behnken Design (BBD). From BBD, it is concluded that the batch containing 19.96% Poloxamer 407, 3.83% Poloxamer 188, 0.91% HPMC K4M was optimized, which could have maximum residence time, good efficacy in terms of contraception and highest user compliance. The dosage form that could be used additionally as a spermicide inside of a condom. CUR showed very beneficial effects which is very similar to Clomiphene citrate in treating polycystic ovary syndrome (PCOS) condition and which will inducing ovulation. CUR restored the lipid hormone profile, antioxidant and glycemic status as the ovarian morphology in Letrozole which induces PCOS animals due to its multiple pharmacological activities which could be useful in managing the PCOS condition and preventing ovarian cell dysfunction, ovulation and thereby improving fertility. CUR can be a promising drug for treating clinical and pathological abnormalities in PCOS condition.[46] Akinyemi et al.[47] investigated the preventive effects of turmeric rhizomes on some biomarkers of male reproductive function in L-NAME-induced hypertensive rats. Dietary supplementation with turmeric rhizome was will be associated with restoration of systolic blood pressure and sperm motility, testosterone level and an improvement of antioxidant status in the epididymides of Vas deferens and testes of L-NAME-induced hypertensive rats. Turmeric rhizomes will be harnessed as a functional foods which will be prevented hypertension-mediated male reproductive dysfunction.

7. Anti-diabetic activity

Kim et al.[48] investigated the potential anti-diabetic mechanism of CUR, curcumin C3 complex and tetra hydrocurcuminoids (THC).They also demonstrated that curcuminoids effectively suppressed dexamethasone-induced phosphoenolpyruvate carboxykinase(PEPCK) and glucose6-phosphatase in H4IIE rats hepatoma and Hep3B human hepatoma cells. In addition curcuminoids increased the phosphorylation of AMP-activated protein kinase(AMPK) and its downstream target acetyl-CoA carboxylase (ACC) inH4IIE and Hep3B cells with 400 times with CUR to 1,00,000 times with THC the potency of metformin. AMPK mediated suppression of hepatic gluconeogenesis can be a potential mechanism medi\ating glucose-lowering effects of curcuminoids and can offer a complementary approach in the management of diabetes.

8. Anti-malarial activity

Curcuminoids-loaded lipid nanoparticles for parenteral admin-istration were successful prepared using trimyristin, tristearin and glyceryl monostearate as a

solid lipid and medium chain triglyceride (MCT) as liquid lipid by a nanoemulsion technique employing high-speed homogenizer and ultrasonic probe. The vivopharm-macro dynamic activity revealed two fold increases in antimalarial activity of curcuminoids entrapped in lipid nanoparticles when compared to free curcuminoids at the tested dosage level. Lipidnanoparticles may increase drug concentrations in the site of action and can help to treat cerebral malaria.[49] Aditya et al 11 explored the potential of liposomes for the intravenous delivery of curcumi-noids, with malaria affected mice as a model. Curcuminoid loaded liposome formulations were prepared by the thin film hydration from phosphatidylcholine. The antimalarial activity of curcuminoids loaded liposomes was evaluated inPlasmodium berghei infected mice. It showed promise and improved antimalarial activity in combination with standard antimalarial drug artemisinin and also prevented recrudescence.

9. Antimicrobial activity

Natural curcuminoids have been modified and gave 46 an-alogs and 8 pairs of 1:1 mixture of curcuminoid analogs and these parent curcuminoids and their analogs were assessed against protozoa of the Trypanosoma and Leishmania species. Among the modified curcuminoid analogs are tested, 8 pure analogs and 5 isomeric mixtures of analogs shows the high antitrypanosomal ac-tivity in submicromolar order of magnitude. Among all of these highly active analogs of curcuminoids , 1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one was the most active compound and more active than the standard veterinary drug diminazene aceturate. Curcuminoids carrying a conjugated enone motif were significantly more active against Trypanosoma brucei brucei B48. It was found to have a high trypanocidal activity against all the Trypanosoma Species and all strains tested. The curcuminoid analogs shows the lower toxicity to HEK cells than to T. brucei brucei bloodstream forms. The curcuminoid constituents such as CUR, DMC and BDMC have been structurally modified to 55 analogs and antimycobacterial activity against Mycobacterium tuberculosis as been evaluated by Changtam et al.[50] Amongs all analogs the highly active curcuminoid is , the isoxazole analogs are the most active group, with mono-O-methylcurcumin isoxazole being the most active compound; it was 1131-fold more active than CUR and was 18 and 2-fold more active than the standard drugs isoniazid and kanamycin respectively. This compound exhibited high activity against the multi drug resistant M. tuberculosis clinical isolates. The structural requirements for a curcuminoid analogs which exhibist antimycobacterial activity are the presence of an isoxazole ring and two unsaturated bonds on the heptyl side chain. The presence of a para-alkoxy group on the aromatic ring which is attached in close to the nitrogen function of the isoxazole ring and a free para-hydroxyl group on another aromatic ring enhances the bioavailability activity of curcuminoids.

10. Anti-inflammatory activity

Seven N-unsubstituted curcuminoid pyrazoles have been syn-thesized from the corresponding-diketones and evaluated thepossibility of curcuminoid pyrazoles regulating the activity of ma-trix metalloproteinases (MMPs) by human intestinal epithelial cells in vitro. Zymographic analysis revealed that three compounds significantly down-regulated MMP-9 activity on inflammation-induced intestinal epithelial cells, making them or original candidates for the treatment of inflammatory bowel diseases.[51] Amet al[52] synthesized a series of CUR analogs and describe the effects of 2,6-bis-4-(hydroxy-3-methoxybenzylidene)-cyclohexanone (BHMC) upon nitric oxide and cytokine synthesis in cellular models of inflammation. BHMC have been showed a significant dose related response inhibitory action upon the synthesis of Nitric oxide due to suppression of both iNOS gene and enzyme expression without any effects upon scavenging of nitrite. BHMC has a very minimal effect upon iNOSactivity with no effect at all upon the secretion of PGE2 but has a strong inhibitory effect upon MCP-1 and IL-10 secretion and gene expression. BHMC should be considered as promising drug which lead for preclinical trials and further pharmacological studies. A variety of novel aromatic and heterocyclic aromatic curcuminoids were synthe-sized, characterized by Khan et al 12 and determined their anti-inflammatory activities by oral administration of female Wistar Rats. Among these, four novel curcuminoids notified as RK-97, RK-103, RK-104 and RK-106 in which the bis-methoxy-phenyl group of CUR was replaced with bis-dimethyl butenolide, ascorbate, bis-naphthyl and bis-furanyl derivatives respectively had potent ac-tivity in the antiarthritic assay with little gastric or systemic toxicity compared with the vehicle-treated controls. Of the curcuminoids the furan RK-106 was the only compound to inhibit production of TNFa and IL-1b in a monocytic cell-line THP-1in vitro. The inactivity of RK-106 on the production of PGE2 may be related to its absence of gastric toxicity. This RK-106 may warrant the development of new low gastro toxic anti-inflammatory agents with selective inhibitory activity of cytokine inflammatory mediators.Six new 3(5)-trifluoromethyl-5(3)-substituted-styryl-1H-pyr azoles have been synthesized and their tautomerism studied in both solution and solid state. Five out of the six compounds presented inhibition percentages of the I NOS isoform higher than 50%;only two of the studied compounds showed an inhibition of about50% with regards to the NOS inhibitory activity.[73] A series of novel CUR bisacetamide have been synthesized for enriching their biological activities such as in vitro antioxidant, anti-inflammatory and cytotoxic activities. All the compounds exhibited potent anti-inflammatory, antioxidant and significant cytotoxic activities.[74] Three series of dimethylamino curcuminoids viz. 4-phenylamino methyl curcumin, arylidene curcumin and pyrazolecurcumin derivatives have been synthesized and studied for their in vitro anti-inflammatory, antioxidant and antibacterial activities.Dimethylamino curcuminoid

derivatives have shown potent anti-inflammatory properties than parent CUR. Molecular docking interactions proved the dimethylamino curcuminoids derivatives have very good cyclooxygenase inhibition.

Curcuminoids and their analogs are often a source of biological activities such as drugs or drug templates with limited toxicity and high activity.

Biological activities of various curcuminoid formulations

Activity	Formulations	Effect of curcuminoids treatment	References
Anti-cancer and anti-angiogenesis activity	Symmetrical,b-unsaturated and saturated ketones curcuminoids	The analogs were more efficacious than CUR and the commonly used chemotherapeutic drug, cisplatin against a variety of tumor cell lines.More effective in the anti-angiogenesis assays run at Emoryand as potent as the anti-angiogenic drug TNP-470.	Adams et al [53]
Anticancer activity	Cyclic analogs of CUR with aromatic aldehydes	Significant anticancer activity against representative murine and human cancer cell lines during in vitro bioassays.	Youssef et [54]
Anticancer activity	C5-CUR-FA containing decanoic acid or palmitic acid moieties	Inhibition of both NFkB and DNAtopoisomerase I by C5-CUR-FAconjugates is associated with their anticancer activity.	Sanabria [56]
Anticancer activity	Five series consisting of 43 CURanalogs	These analogs were more potent than parent CUR as effective Wnt Inhibitors and anti-invasive agent in human osteosarcoma	Leow et [57]
Antioxidant and anti cytotoxicity activity	4H-pyrimido [2,1-b] benzothiazole,pyrazole and benzylidene derivatives of CUR	Derivatives of CUR exhibited better antioxidant activity than CUR due to involvement of electron in free radical capturing ability of molecules by phenolic hydroxyl group	Sahu et [58]
Anti-tumor activity	CUR analogs	Analogs inhibit TrxR even in the low micromolar rang.Analogs with furan moiety have excellent inhibitory effect on TrxR.	Qiu et [59]
Anti-tumor activity	Aldehyde-free 2-hydroxycinnamaldehyde (HCA) CUR analog	2-hydroxycurcuminoids havestrong generator of ROS andstrongly inhibited the growth of SW620 colon tumor cells due to thepresence ofb-diketone moiety ofcurcuminoids.	Han et[60]
Anti-tumor activity	(Mariva®) - a patented formulation	The prepared curcuminoidssuppressed systematic oxidativestress in patients and antioxidant effects have shown significant improvement of health related quality of life.	Panahi et[61]
Anti-diabetic activity	Mono-carbonyl analogs of CUR	HSD1 These analogs were highly selective and favoring 11b-HSD1 and showedanti-diabetic effects without any associated toxicity.	Yuan et[62]
Cardiovascular activity	CUR mimics with diverse alkyl sulfonyl and substituted benzene sulfonyl modifications	Synthetic CUR mimics can act as dual antagonist scaffold of L-typeCa2þchannel and endothelin A/B2 Receptor in vascular smooth muscle cells	Park et[63]
Radioprotective effect	CUR analog (bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione	CUR-analog showed a significant decrease in the levels of thiobarbituric acid reactive substances and DNA damage.CUR analogs protected the hepatocytes against-radiation-induced damage by inhibition of peroxidation of membrane lipids and free radicals-induced DNAstand break formation	Srinivasan et[64]
Radioprotective effect	CUR analog (bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione)	decrease in the levels of thiobarbituric acid reactive substances and DNA damage.CUR analogs protected the hepatocytes against-radiation-induced damage by inhibition of peroxidation of membrane lipids and free radicals-induced DNAstand break formation	Srinivasan et[65]
Anti-tuberculosis activity	Monocarbonyl analogs of CUR	The analogs were proved to inhibit efficiency of in vitro growth of Mm and Mtb by disk diffusion	Baldwin et[66]

		and liquid culture assays.	
Anticarcinogenic activity	Bisdemethoxycurcumin analog(BDMC-A)	BDMC-A influence on histological changes, cholesterol, bile acids and phospholipid metabolism in DMH-treated rats through its chemopreventive effect	Devasena et[67]
Antimalarial activity	Curcuminoids-loaded lipid NPs	n vivopharmacodynamic activityrevealed two fold increases inantimalarial activity ofcurcuminoids entrapped in lipidNPs.	Nayak et[68]
Antimalarial activity	Curcuminoid loaded liposome	It showed improvement of antimalarial activity in combination with standard antimalarial drug artemisinin and also prevent recrudescence	Aditya et[67]
Antifungal and antibacterial activity	Curcuminoids with polyethylene glycol	All extracts exhibited a 100%inhibitory effect on the growth of tested fungi and showed low antibacterial activity	Perko et[69]
Anti-cytotoxicity	Aromatic ring glycosylation of CU	Compounds displayed a good selectivity and much less toxic against non-tumorigenic Vero cells	Ferrari et[70]
Anti-cytotoxicity	Fifteen CUR analogs	Cell morphology study revealed that the cytotoxicity of CUR analogsor CUR-anti-androgen conjugates detected from both prostate cancer cell lines might be due to the suppression of pseudopodia formation	Shi et[71]
Anti-cytotoxicity	Triazole-curcuminoids	inhibit NF-kB without showing cytotoxicity	Caprioglio et[72]
Anti-inflammation	Aromatic and heterocyclic aromaticcurcuminoids	prepared curcuminoids had potent activity in the antiarthritic assay with little gastric or systemic toxicity compared with the vehicle-treated controls	Khan et[73]
Anti-inflammation	CUR bisacetamides	All the compounds exhibited potent anti-inflammatory,antioxidant and significant cytotoxic activities.	Sribalan et[74]
Anti-inflammation	Dimethylamino curcuminoids	Dimethylamino curcuminoidderivatives have shown potentanti-inflammatory properties thanparent CUR	Bhanupriya et[75]
Antimicrobial activity	Chemically modified naturalcurcuminoids	1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one was the most active compound and more active than the standard veterinary drug diminazene aceturate	Changtam et[76]
Antimicrobial activity	Structurally modified 55 CUR, DMCand BDMC analogs	The presence of a suitable para-alkoxy group on the aromatic ring which is attached in close proximity to the nitrogen function of the isoxazole ring and a free para-hydroxyl group on another aromatic ring enhances the biological activity	Changtam et[78]
Antimicrobial activity	C5-curcumin-2-hexadecenoic acid	The conjugate was active against eight MRSA strains at MICs due to the presence of 2-hexadecenoic acid (2-HAD) and also increased 4e8 fold its antibacterial activity	Sanabria et[79]
Antibacterial activity,antifungal activity and cytotoxicity	Curcumin derivatives with sulfonamides	One sulfonamide molecule attached to carbonyl group of CUR showed the most potent biological activity against tested bacteria and fungi and also displayed higher cytotoxicity than CUR	Lal et[80]

Safety and Toxicity

Curcuma longa and its constituents have been investigated in many studies for safety through in vitro studies, animal experiments and clinical studies. According to a comprehensive review on this subject, oral administration of standardized powder / turmeric and curcumin extracts showed no significant side effects or toxicity to animals. In addition, cell culture studies of "curcumin has antiproliferative effects in normal cells and may reduced cell viability." However, there were no reports of mutagenicity and genotoxicity. Oral use of turmeric and curcumin in humans appears to be safe even at abnormal doses. Very few cases have been reported with itching, flushing of the tongue, tachycardia, and gastrointestinal symptoms (flatulence, diarrhea, nausea, constipation, etc.). It should be noted that there are some

issues regarding the bioavailability of oral curcumin. However, its intravenous formulation has greater absorption. Therefore, intravenous curcumin should be given at lower doses than oral administration.[81]

It should be noted that curcumin can cause several types of pharmacokinetic changes in cardiovascular, antibiotics, antidepressants, chemotherapeutic agents, anticoagulants, and antihistamines. Therefore, concomitant use with some conventional drugs should be done with caution.[82] According to animal studies, oral intake of turmeric and curcumin during pregnancy should be considered harmless. However, it has been reported that oral administration of curcumin weighing approximately 1000 mg / kg may slightly reduce the weight gain of F2 generation chicks.[81] Regarding the application of drug delivery technology to improve the bioavailability of turmeric, the safety of these latest formulations needs to be discussed. For example, the use of excipients or surfactants as a strategy to improve bioavailability can make the product toxic.[83] In addition, some inorganic metal nanoparticles (such as gold-curcumin nanoparticles) are highly toxic.[84]

However, most of these new products appear to be safe. The formulation of solid lipid nanocurcumin particles showed no side effects in patients with osteosarcoma and healthy people.[85] Another new system for transporting curcuminoids from the nose to the brain, the poly (n isopropylacrylamide) delivery system, showed no toxicity.[86] Curcumin dipeptide nanoparticles are also safe. The dipeptide is synthesized from the amino acids α, β-dihydroxyphenylalanine and methionine. These are safe and can be decomposed in nature.[87] The new curcumin analog is another option recently used in medicine. In vivo studies showed that they were not toxic.[88] In addition, curcumin-loaded human serum albumin nanoparticles showed no toxicity during intravenous administration in the tumor xenograft HCT116 model.[89] In some cases, modernized formulations of curcumin appear to be safer than traditional ones. The results of a new intravenous curcumin study showed that rabbits in the curcumin nanosuspension group had a lower risk of local irritation and phlebitis and less red blood cell hemolysis than rabbits in the curcumin solution group.[90]

CONCLUSIONS

Curcuminoids are natural compound which have large variety of therapeutic properties, particularly biological targets and interactions, linked to various diseases. The clinical applications of curcuminoids are restricted due to its poor solubility, low absorption and low bioavailability, and high metabolism rate. these limitations, can be overcome by modifying and attaching with lipids, micelles, nanoparticles, liposomes and metal complexes with curcuminoids and their derivatives. In this review, the properties of curcuminoids alone and in association with other modified form have been shown to have effective on neuroprotective, antitumor, antioxidant, anticancer, antiinflammatory, anti-acidogenic, radioprotective, sexually transmitted infections, anti-esophageal, anti-nephrotoxicity, antimicrobial, antiviral, anti-angiogeneic, anti-proliferative, antiimmunomodulatory, hepatoprotectivity, antimalarial, anticytotoxicity and anti-diabetic properties. Overall, it is clear from the studies described that curcuminoids are highly promiscuous and can be used as a novel drug in future.

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