

## A comprehensive Review on Pharmacological Updates and Bioavailability Issues of Curcumin (Curcuma Longa)

Mohammad Tarique<sup>1\*</sup>, Mehak Chandel<sup>2</sup>, Nishu Singla<sup>3</sup>

<sup>1,2,3</sup>University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Mohali, Punjab, 140413, India

Date Of Submission: 05-05-2021

Date Of Acceptance: 20-05-2021

**ABSTRACTS:** Curcuma longa is a widely used popular Indian medicinal plant that belongs to the family of Zingiberaceae. Curcumin has various important properties of the due to its various constituents present in turmeric and turmeric is a primary source of the curcuminoids, This review is summarized for the various properties of the curcumin primarily due to various activities reported such as the antimicrobial effects, antifungal, anti-thrombotic, anti-inflammatory, Depression and anxiety, antioxidants activity, anticancer activity, Antiviral, hepatoprotective properties, etc. this review paper also contains that the bioavailability issues of the curcumin and also relates the safety and quality parameter of the curcumin and concluded the future prospective of the curcumin are described the future prospective of the drug delivery system and its valuable significance.

**Keywords:** Curcumin, Molecular constituents, Pharmacological properties, Bioavailability, and Future prospective.

### I. INTRODUCTION

Curcumin is a universal herb which is obtained from the Mother Nature, nearly founded two centuries old in scientific history, and still also attracts the researchers from all over World, curcumin has oleoresin oil and other complexes which are used for the procurement of disease in livings. The importance as the potential sources of drugs various elements. Turmeric oil is extracted from the turmeric and used in aromatherapy and in the perfume industry and curcumin is used as traditionally apart from cultural use. The pigment of the turmeric is one of the most important components which have the several properties which is directly used as for treatment purpose and researcher are broadly evaluated and some researcher has found curcumin to be a genuine natural product having impressive effects such as the antiviral, antibacterial, anti-inflammatory and

other are reported and its wide ranges for treatment purpose used.<sup>[1,2]</sup>

Curcumin is an active compound of turmeric which is used as traditionally herbs medicine. Curcumin is obtained from the Curcuma longa of the family of the Zingiberaceae and the chemical structure of curcumin is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione with its chemical formula  $C_{21}H_{20}O_6$ , Curcuma longa has wide ranges of properties which have evaluated the effects as intern if the medical applications being exposed more the 120 species are compiled among the curcumin species. Curcuma longa is the most recognizing cultivated plant, growth in warm climates, in many region of the World, several of benefits pharmacological properties have been reported including the anti-thrombotic, anti-inflammatory, anticancer, antidiabetic, hypocholesterimic, antimicrobial, antioxidants, and hypotensive effects, bactericidal, anti-venom among other. In India features a very long safe and continuous usages of the many herbal drugs with in officially predictable alternatives system of health namely Ayurveda, Yoga, Siddha, Homeopathy and Naturopathy.

### Historical Background

The historical backgrounds of curcumin species begin in Far Eastern medicine and years backs 5,000 (Ayurveda) and 2,000 (Atharveda) years ago respectively and Curcuma longa contains the curcuminoids and curcumin was found to be the most active one, basically first isolated in 1815 by Vogel and Pelletier, and the purification and crystallinity was described by the Daube, 1870. The curcumin is Latin name and it derived from Arabic words such as named saffron while due to its golden color and taste, Curcuma became the Indian Saffron in Europe.<sup>[3]</sup>

The pharmaceutical industry basically focused on the antidiabetic and anti-cancer formulations and the largest segment accounting for over 50% of the global markets in cosmetics

and food industries. Nowadays curcumin is the most important active constituent which is used in skincare preparation due to its remarkable antioxidants, anti-inflammatory, anti-aging effects. In addition, UV radiation exposures and growing environmental pollution expected to boost the demands for skincare products containing curcumin.<sup>[4]</sup>This review is concluded, the pharmacological properties are include which gives medicinal information about the Curcumin (*Curcuma longa*) also be give the future aspects for better procurement through the herbal constituents such as the curcumin.

### Molecular Constituents of Curcumin

Turmeric contains that rich sources of carbohydrates, and fiber and also contains protein fats but there is no cholesterol in it and also contains vitamin C potassium, calcium, magnesium, in suitable making natural food products.<sup>[5]</sup>Curcumin (diferuloylmethane) is a polyphenol derivative from the rhizome of the plant, yellow color of turmeric exiting of curcumin which consists of more than three main curcuminoids complexes such as the curcumin I, curcumin II, and curcumin III, and also be reported the other constituents in curcuminoids such as the curcumenol, curdione, isocurcumenol, curcumol, stigmosterols, zingiberene, and curcumene.<sup>[3,6-7]</sup>

### Physiochemical Constituents with their Nutritional Values of Curcumin

We all know that rhizomes of the turmeric are the main edible portions of *Curcuma longa* which have their high nutritional value and have particularly rich sources of the proteins, carbohydrate, alkaloids, flavonoids, Vitamine C, Beta carotene, polyphenol, fatty acids, and essential oils. And the rhizomes of the *C. aromatic* used in spices purpose as food flavoring and coloring agent's curcuminoids have a pleasant taste and aromatic odour. The nutritional composition of the dried rhizomes contains lipids (2.5%), carbohydrates (97.5%) and protein (19.44%) and rhizomes have a moisture content of 19% and an ash value is 16.6% and 2.8% acid in insoluble ash, and 3.93% water-soluble ash and extractive values 0.4%(alcohol soluble extractive value and 0.8% water-soluble extractive value),and moisture content 3.14%.<sup>[8,9]</sup>The phytochemical screening of the curcumin is done by the n-hexane, petroleum ether in the ratio of the 60:80,benzene, chloroform, methanol and extract of rhizome *curcuma caesia* that revealed the presence of the alkaloidal,

phenols, Phyto-sterols, terpenoids, tannins , quinones and flavonoids. More than 30 volatile components were identified in the rhizome(28.3), Curcumene (6.8%), 1,8-cineole(5.3%) elements, borneal (4.4%) and other major constituents **Rastogi et, al** reported the components contains that ocimene (15.66%), 1,8-cineol, and borneol (7.4%) as the major constituents.<sup>[10,11]</sup>Quantitative and Qualitative phytochemical analysis on different parts of *C. aromatic* which obtain from the extraction methods and solvent evaporation and various solvents are used for th extraction of the active components or Phytoconstituents such as the saponins, phenol, phytosterols, glycosides, proteins amino acids and volatile oils.<sup>[12]</sup>

### Curcumin Safety and Quality Parameter

Curcumin have various pharmacological activities being reported such as antioxidants, antimicrobial properties and others, the safety and quality have been evaluated the and found to be safe in animals and humans even the dose of up of the 8 g/day accordingly, these substances was declared as GRAS by the Food and Drug Administration (FDA), Curcumin suffers in faster degradation in presence of the sunlight exposure.<sup>[13]</sup>and the curcumin toxicity have been conducted in vitro, in vivo, and in humans, regardless of its well establishments safety, some reported have highlighted deleterious.<sup>[4,14]</sup>

### Pharmacological Properties of the Curcumin

Turmeric has reported the more than a hundred molecular constituents, Each has a variability of biological activities for occurrences, there are at least 30 molecules that are antibiotic activities, 14 molecules are effective in treatments of cancer, 12 molecules shown the anti-tumor effects and 12 are anti-inflammatory, and also be reported more than 20 constituents as anti-oxidants<sup>[15]</sup>*Curcuma longa* have reported several therapeutic effects and pharmacological activities which is described as follows-

### Anti-inflammatory Properties of Curcumin

Inflammation is the most complex biological process that andthis process sis generally mediated by the distribution of tissue homeostatic. Generally this is triggered by the presence of the different biological, chemical or physical agents which is define as the acute or chronic depending on the type of stimuli which leads to cause inflammation. *Curcuma longa* have reported the anti-inflammatory effects due to have volatile oils

in curcuma longa and curcumin and have tendency to the treat the inflammation if we take orally also be much effective in the chronic inflammation.<sup>[17]</sup>

Turmeric have greater potency to procurement of the inflammatory action with its specific lipoxigenase and COX-2 inhibiting properties Rheumatic complains are related to the inflammatory changes in then joints and must be cured by the etiological factor and pathological changes of inflammation. Curcuminoids have properties that inhibit the LOX, COX, phospholipases, leukotrienes, prostaglandin, thromboxane, nitric oxide elastase, Hylauronidase, collagenase, monocytes chemottract protein-1, interferone inducible protein, TNF and interleukin-12. In case study of animals models, such as the mice are taken application of curcumin at doses are taken between 50-200 mg/kg has inhibited oedema curcumin can reduces more than 50% oddema when applied with a dose of 48mg/kg body weigts.<sup>[18,19]</sup>

### Depression and Anxiety

Depression and anxiety is the major problem during the running world, these are described by the monoamine deficiency theory has been the primary causative model for the rising of antidepressants. Commonly depression is chronic disorder that seriously affects the quality of life and inreceses the risk of the mortality. In traditional chinease medicine (TMC), Curcumin has the only been broadly, realistic alleviate pain, psychological stress as well as hypochondriasis and mania, there are also effective component of the depression and other mental disease 17 the patient who suffering from the diabetes almost twice suffer from the anxiety, depression and stress.<sup>[2]</sup> During this time curcumin is the universal component which is used to treat the anxiety and depression which evidence are evaluated by the various clinical trials, in these studies, curcumin was given orally at doses ranging from 500-1000mg daily uptake, may be the combination or alone with standard antidepressants agents such as fluoxetine, venlafaxine, escitaloprfam, when curcmineadministred reduced the anxiety not depression, which might be the consequences of the shortest administration time (30days vs 5-8 week other studies.) in other two supplementary trials, together with the symptoms scale, blood stress parameter and other clinical biomarkers were measured.<sup>[22,23]</sup>

### Antioxidants Activities

There are the two primary mechanism are explained the majority of curcuminoids, such as the antioxidants and other anti-inflammatory properties. Generally curcumin is act on the free radicles is carried out by the numerousdissimilar mechanism.<sup>[24]</sup>it can forage the altered forms of the free radicals which also known as the reactive oxygen species (ROS) and nitrogen species resultin have tendency to modified the activity of the glutathione (GSH), superoxide dismutase and catalase enzymes ere the active in the neutralizing the free radicles and have tendency to inhibit the ROS generating the enzymes i.elipooxygenase/ cyclo-oxygenase and xanthin hydrogenase, while curcumin is lipophilic compounds which makes the it an efficient hunters of the radicles, therefore like vitamin E curcumin is also considered as the chain clavage antioxidants.<sup>[25]</sup>

### Effects on the Reproductive System

Numerous effects of the curcumin reported in reproductive system both in human and animals which must be compiled the libido, infertility, abnormal spermatogenesis, abnormal prostatic function, miscarriage, preeclampsia, and changes in serum testosterone, and also premature membrane rapture in both males and females. Earlier studies specified that the lead to cause the peritubular fibrosis, resulting have tendency to interrupt the sperm count or number while regulation of the luteinizing hormone, minor testosterone synthesis, distraction of preantral follicles and increased atresia in ovaries and reduced number of primordial follicles I females pups in rodents.<sup>[24,26]</sup>

### Anticancer Activity of Curcumin

Cancer is the one of the most affected disorder in running world while curcumin have also be reported the anticancer agent's curcumin which also effected the squamous cell carcinoma<sup>[23]</sup> Solitary, the major causes of the cancer is the loss of balance between cells proliferative and cell death, when the apoptotic signals are absence, resulting skip the cell death while the uncontrolled the proliferation of cell, leading two types of the cancer are reported signals are generated through major pathways: intrinsic and extrinsic pathways. The intrinsic pathways worked while stimulating the mitochondrial membrane to inhibit expression of antiapoptotic protein such as Bcl-2 and Bcl- XI. Curcumin and its related constituents have ability to treat cancer and which also worked on the different signal. There ae some in vitro studies are

showed ability of curcuminoids to induce apoptosis in dissimilar cell lines by the hindering intracellular transcription factor. These factor included NF-Kb, activator protein 1 AP-1, Cyclooxygenase two (COX-2), Nitric oxide synthase, matrix metalloproteinase-9 (MMP-9) and STAT-3.<sup>[28]</sup>

#### Effects on Breast Cancer

Curcumin has established the inhibitory effects on multiples types of cancers such as breast cancer has been recognized as the supreme communal type of cancer in developing as well as developed countries,<sup>[29]</sup> While taking about the mutation in BRCA1 and BRCA2 are the genes which is the major constituents of the breast cancer.<sup>[30]</sup> There are the 55-65% chances to mutate the BRCA1 where the BRCA2 have 45%. Doxorubicin is major drug used to treat the cancer which is undertakes in the treatment of the chemotherapeutic agents against the breast cancer.<sup>[31,32]</sup> It belongs to the anthracycline antibiotic. When combination pattern are follows such as curcumin and dimethyl sulfoxide inhibited the development of intestinal adenomas and reduced the frequency of mutation in BRCA genes resulting this combination lead to a extreme reduction in inflammation and apoptosis.<sup>[33]</sup>

#### Anti-viral Activity of Curcumin

The antiviral activity of curcumin have been demonstrated and have tendency to fight against the different viruses such as papillomavirus, influenza virus, Hepatitis B virus (HBV), Hepatitis C, adenovirus coxsackie virus, Human norovirus (HuNoV) virus, Respiratory syncytial virus (RSV) and Herpes simplex (HSV-1). The function of the curcumin graphene oxide showed the together antiviral effects against respiratory syncytial virus infection (RSV), these are the most important pathogens of lower respiratory tract infection in infants, which have been occupied the severe lungs disease, Developing the graphene oxide (GO) with developing betacyclodextrin composite which is display excellent antiviral activity and curcumin loading efficiently, showed that the composite could have been prevents the RSV from the infecting the host cells by the directly virus and inhibiting the viral attachment, which give result as prophylactic and give therapeutic effects towards virus,<sup>34</sup> while if talking about the anti-viral properties of the curcumin was dose dependent manner and also be shown the suppressive inflammation through many different mechanism beyond the scope of review and have supporting its

mechanism of action as a potential antiviral agents.<sup>[35,36]</sup>

#### Effects on Hepatoprotective

Turmeric contain curcuminoids which is the active constituents, which have demonstrated the hepatoprotective and Reno-protective individualities of similar to silymarin mainly due to the its hepatoprotective properties, as well as its facility to decrease the formation of the proinflammatory cytokines. While the animal studies are revealed that turmeric give hepatoprotective effects, there are the variety of hepatotoxins insults, together with the galactosamine, Acetaminophen (paracetamol) carbon tetra chloride and aspergillus aflatoxin, Due to the studies on rats, injuries are observed that the acute and subacute liver injury after the given of curcumin, liver injury are reduced in test animals as compared in controls animals (rats) and the extract of the turmeric is very effective resulting inhibit the production of the fungal aflatoxin by 90% its potential due to ducklings infected with aspergillus parasiticus and treating the cholelithiasis it possible due to the Sod. curcuminat a salt of curcumin which exerts cholesteric effects by increasing biliary of salts cholesterol and bilirubin, as well as increasing bile solubility.<sup>[5,18]</sup>

#### Anti-Microbial Effects

Over the fifty years of wide-ranging researcher have been launched for succeeding the new era of microbial properties compounds which are collected from the so many sources, bacterial infections are the between the important of the infectious disease. In spite of progress in advances of the antibacterial agents due to the resistance advance of the multidrug therapy, and the study on the aqueous extract of the *C. epidermis* ATCC 12228, *Staphylococcus klebsiellas pneumonia* ATCC10031, and *E. coli* ATCC 25922. While the working against if methanol extracts of turmeric are used, resulting the MIC values of 16g/ml and 128g/ml against *Bacillus subtilis* and *S.aureus* respectively. The study if hexane and ethanol extracts and curcuminoids (from ethyl acetate extract of curcuminoids) isolated from the *C.longa* with 86.5% curcumin value against 24 pathogens. turmeric oil is one of the most by products of the curcumin which is against working from the *B.subtilis*, *B. cereus*, *S.aureus*, *E.coli*, and others. Curcumin show the inhibitory effects of *S.aureus* and strains with have MIC value 125-250g/ml.<sup>[19,37]</sup>

### Hypolipidemic Effects of the of Curcumin

In systems of medicine mainly Ayurveda, turmeric have been helpful in the controlling of the hypercholesteremic and metabolic disorders, Curcumin is one of the most important components of the turmeric. Curcumin have reported the several properties also be included the antidiabetic effects. Curcumin also protects the oxidation of the cholesterol (LDL) and have trend to promote the HDL (good Cholesterol) hence succeeding healthy total cholesterol.<sup>[37]</sup> In case curcumin have tendency regulating the hepatic lipid metabolism via AMPK activation and elevation of PPAR alpha expression.<sup>39</sup> Curcumin also act on the gathering of lipid in intracellularly adipocytes difference it also decreased the pathways of the adipogenesis in 3T3-L1 through the signaling pathways.<sup>5,39</sup> In 3T3-L1 adipocytes curcumin induces brown fat like phenotype through the activation of the AMPK signaling pathway, while brown fat increase due to mitochondrial biogenesis and brown fat specific genes. Bisdemethoxy curcumin suppressed adipogenesis in 3T3-L1, resulting in preventing the obesity by the arrest of cell cycles at the G<sub>0</sub>/G<sub>1</sub> phase, and downregulating of cyclin A and B, have increment of the protein alpha.<sup>[40]</sup> When plasma lipid like cholesterol may be removed from the body by increasing the body by the production of bile, resulting in this are done by the lipid metabolism and beta-oxidation may be required to fulfill the hypolipidemic effects and reduced the lipid induced oxidation may be required to fully explain the effects of curcumin on hypolipidemic effects.<sup>[41]</sup> Curcumin oil could attenuate arterial injury-induced accelerated atherosclerosis, inflammation and macrophage foam cell formation.<sup>[42]</sup>

### Anti-tumor and anti-angiogenesis Effects of Curcumin

Curcumin have reported the several properties along with their anti-cancer it has indirect anti-oxidant activities by the transition metal chelation including expression of anti-oxidative activities by the activating the oxidative enzymes and suppressing ROS generating enzymes expression such as the COX-2, Lipoxigenase (LPO) and inducible NO synthase (iNOS)<sup>[34]</sup>

Curcumin have cytoprotective effects against chemotherapy prompted cytotoxicity, which appears to be mediated through the Nrf2 (Nuclear factor erythroid-derived 2-related factor 2) activated. Nrf2 moves to the nucleus to stimulate the expression of the more than 200 antioxidant

and protective genes through the due to antioxidant response and protectives in the target genes. Curcumin have tendency to inhibit the regulation of the interleukins, TNF-alpha, COX-1, and COX-2,<sup>[39,43]</sup>

### Anti-ulcerative Properties of Curcumin

The effects on curcumin on the ulcer and its activity are evaluated by the experiment on four albino rats that revealed the significant reduction of ulcer index, gastric acid volume, pepsin free total acidity along with the increase the production of the gastric mucus, when the ethanolic extracts of rhizomes of *C. longa* resulting in anti-ulcer index, pepsin activity free and total acidity and volume of gastric juice in group show significant differences in comparison to other group and there was increase in gastric mucus secretion.<sup>[8,39]</sup>

### Effects of Curcumin on Coagulation

This is the pleiotropic molecules with an excellent safety profile, this also known as the pleiotropic molecules, and its process remarkable and the beneficial effects such as the anti-thrombotic, antioxidants, anti-inflammatory, curcumin show that the anticoagulation action and prolong the clotting time, as observed in the TT, PT, and APTT assays, the presence of the hydrophobic groups containing the curcumin. Anticoagulation activity of curcumin showed the prolongation of the clotting time in plasma based PT and APTT assays. In this mechanism through the decreasing the thrombin, inhibitory effects of the curcumin is on generation and further the generation of the thrombin give evidence of the anti-coagulation properties of the curcumin, while finding the anticoagulation activity of the curcumin makes decreasing the penultimate and final enzymes in the blood clotting cascade, when consider the anticoagulation effects on curcumin is better than BDMC,<sup>[33,45]</sup> it would suggest that the ortho-methoxy group in curcumin have been different redox properties due to this which regulating the anticoagulation functions of curcumin, orthomethoxy group in the position 3 of the phenyl group in curcumin.<sup>[46]</sup>

### Attempts to Manage the Bioavailability and its Pharmacokinetics

Curcumin is golden molecules which is widely used by the Chinese and Indian medicine.<sup>[47]</sup> The bioavailability is the important factor of the any drug while the curcumin have

been showed the poor absorption, and rapid metabolism. There are many agents have been introduced to improve the bioavailability of curcumin, the most interesting one is the piperine it enhances the curcumin bioavailability by blockage the metabolic pathways of the curcumin, due to it's shown the poor bioavailability in blood stream, many researcher have been reported the after the oral administration of the curcumin, resulting found the less bioavailable molecules it mainly focused on the improve the bioavailability like many others natural polyphenols, curcumin is poorly soluble in water and this is documented in well-mannered and its limitation of the curcumin based formulation is its poor solubility and fast metabolism therefore for the increasing the its solubility and its therapeutic activities and study if the chemical modified curcumin derivatives as well as improve the formulation and delivery system should be studied to achieve its optimization therapeutic effects. There are several techniques (physical parameters) are reported that improve the curcumin solubility such as pH and complexation with metals ions, polymers or serum have been applied for solubility enhancement.<sup>[48]</sup>

Solubility of the curcumin can increased the twelve folds of by the use of heat without heat mediated disintegration of curcumin and its bioavailability of curcumin is limited by the intestinal and hepatic glucourinidation, while the role of additives leads to block the metabolism of curcumin and also have been demonstrated the curcumin to increase its bioavailability. In some case when 25mg of piperine are taken with the 2gm of curcumin, resulting serum level determination was done it one hours which found that increment of availability of molecules in blood stream at level of twenty folds and no toxicity was observed who were participated in the study.<sup>[17,13,43,48]</sup>

### Future Prospectives

Curcumin is the gold coin of the herbal medicine which have the several pharmacological and therapeutic properties and the low bioavailability is the major concern on clinical trials due to the poor absorption, poor water solubility and chemical stability as well as rapid metabolism. <sup>[49]</sup>these problem have overcome by using the carrier molecules and designing the novel drug delivery system such as the phospholipid complexes, liposomes, Nano formulation have tendency to improve the bioavailability while Piperine have been used to decrease the

glucourinadation resulting improved the bioavailability, and effective preparation of the nanoparticles colloidal solid dispersion with enhanced the oral bioavailability.<sup>[51]</sup>

Nano formulation is one of the best way to improve the clinical therapeutic activity which enhance the solubility and specific for the tissue of interest and site-specific delivery of curcumin with its high permeability and great performance. Researcher have focused on combination of curcumin with available drugs have been shown the better outcome.<sup>[52]</sup>

## II. CONCLUSION

The wisdom and scientific knowledge of the curcumin, it's a golden coin in herbal medicine which is also called as the pleiotropy molecules which were used in many countries as the traditional medicine. There are various pharmacological activities are reported such as the anti-microbial, antibacterial, anti-cancerous, anti-thrombotic, hepatoprotective, hypoglycemic and also used in treatment of the fibrinolysis, etc. In this review also focused on the solubility and bioavailability issues and give small description of the future sticks approaches in the drug delivery system.

### Conflicts of Interest:

The author declares that there is no conflicts of interest regarding the publication of this paper.

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