Review

Mahendra Rai*, Raksha Pandit, Swapnil Gaikwad, Alka Yadav and Aniket Gade

Potential applications of curcumin and curcumin nanoparticles: from traditional therapeutics to modern nanomedicine

Abstract: Curcumin (diferuloylmethane) is one of the potent, nontoxic, and major bioactive components present in turmeric. The major drawbacks of curcumin are low absorption and poor bioavailability. The present review highlights on the methods for the fabrication of curcumin nanoparticles and their applications in treatment of cancer and wound infections. Curcumin nanoparticles possess remarkable antibacterial, antiviral, and antiprotozoan activity. Hence, curcumin nanoparticle-loaded nano-gel, microemulsion, and nano-cream can be used for drug delivery.

Keywords: antimicrobial activity; curcumin; curcumin nanoparticles.

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1 Introduction

Curcumin, also known as diferuloylmethane, is the most active curcuminoid found in the rhizome of *Curcuma longa*. Basically, curcuminoids are polyphenolic compounds, which are responsible for the yellow coloration of turmeric. Demethoxycurcumin and bis-demethoxycurcumin are two different types of curcuminoids present in turmeric [1]. *Curcuma longa* is a perennial herb commonly known as turmeric belonging to the family Zingiberaceae. The rhizome of *C. longa* is oblong, ovate, pyriform, and short branched. It is distributed in tropical and subtropical regions throughout the world and widely cultivated in Asian countries, mostly in India and China [2, 3].

Curcumin was isolated for the first time in 1815, while its chemical structure was determined in 1973 by Roughley and Whiting (Figure 1). The melting point of curcumin is 176–177°C, and it forms red to brown-colored salts when treated with alkalis [4]. Commercial curcumin possess approximately 77% diferuloylmethane, 17% demethoxycurcumin (Figure 2), and 6% bisdemethoxycurcumin [5] (Figure 3). Curcumin is a natural compound, which is hydrophobic in nature. It consists of two polyphenolic rings, which are substituted by methoxy ether at the ortho position, and tautomerization of curcumin arises in a pH-dependent condition [6]; in neutral and acidic conditions, curcumin possesses a bis-keto form [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione].

Curcumin functions as an antioxidant, anti-inflammatory, and anti-atherosclerotic. It inhibits scarring, cataract, gallstone formation, liver injury, and kidney toxicity, and also promotes wound healing and muscle regeneration [6]. Curcumin exerts medicinal benefits against psoriasis, diabetes, multiple sclerosis, Alzheimer's, HIV, septic shock, cardiovascular disease, lung fibrosis, arthritis, and inflammatory bowel disease [6]. It has been used to cure liver problems, digestive disorders, and in treatment of several skin ailments and in wound healing [7]. Antioxidant property of curcumin can be enhanced by its structural modification or by synthesis of its analogs [3, 5]. Naz and coworkers [8] reported antimicrobial activity of *C. longa* against different strains of bacteria such as *Bacillus subtilis*, *Bacillus macerans*, and *Bacillus licheniformis*.

Curcumin also possesses broad spectrum activity against insect pests, plant pathogens, fungi, and weeds [9]. It has been observed by trials on human and mouse that oral consumption of curcumin demonstrates lesser bioavailability, and it undergoes intestinal metabolism, whereas the absorbed curcumin shows rapid metabolism and excretion in bile [10, 11]. The activity of curcumin can be enhanced using piperine, which acts as an inhibitor

***Corresponding author: Mahendra Rai,** Department of Biotechnology, S.G.B. Amravati University, Amravati 444 602, Maharashtra, India, e-mail: mahendrarai@sgbau.ac.in
Raksha Pandit, Swapnil Gaikwad, Alka Yadav and Aniket Gade: Department of Biotechnology, S.G.B. Amravati University, Amravati 444 602, Maharashtra, India

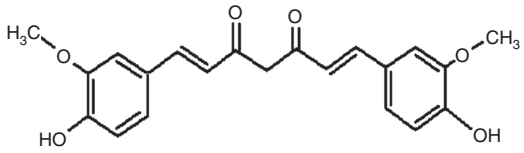

Figure 1: Structure of curcumin.

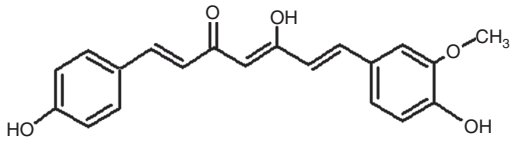

Figure 2: Structure of demethoxycurcumin.

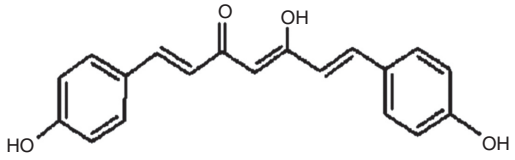

Figure 3: Structure of bisdemethoxycurcumin.

of hepatic and intestinal glucuronidation. By combining curcumin along with piperine, the biological activity of curcumin can be enhanced by about 20 times [3, 12].

Many clinical trials have demonstrated that the biological action of drugs like curcumin can be achieved by enhancing the activity of the drug [13–16]. The bioavailability means the rate at which the drug molecule is being circulated and absorbed on the site of action (www.merckmanuals.com). Curcumin possesses better pharmacodynamics but poor pharmacokinetics [17]. Theracurcumin is a form of curcumin, which is highly soluble and dispersible in water. It is formulated by using nanoparticulation and surface processing techniques. Human trials have shown that theracurcumin has the ability to cure liver problems and heart failure [18]. Silver nanocomposite films of curcumin are very effective for antibacterial application. Sodium carboxylmethyl cellulose silver nanocomposite films (SCMC) were prepared for antibacterial applications [19]. Experiments performed on the cancer cell line have shown the inhibitory effect of curcumin nanoparticles on the metastasis stage of cancer. It was revealed that the nanoparticles are effective against malignant brain tumors [20].

β-Diketone moiety in curcumin is the major reason for the instability and weak pharmacokinetic of curcumin. Modifications are performed in the structure of curcumin, and its analogs were synthesized without β-diketone moiety. Because of such structural modifications, the stability and pharmacokinetics of curcumin can be increased. These analogs without β-diketone moiety are called monocarbonyl analogs of curcumin (MACs). MACs have shown to have anticancer and anti-inflammatory activities [21]. Recently, it was demonstrated that curcumin can be delivered through inhalation. The pressurized metered dose inhaler could be used as one of the new vehicles for the delivery of curcumin [22].

The study from the last three decades showed that curcumin exhibits low intrinsic activity, poor absorption, reduced bioavailability, rapid metabolism and elimination. Nanotechnology-based drug delivery will probably be a suitable method for increasing the biological action of curcumin, which increases its absorption. Curcumin nanoparticles, liposomes, and phospholipid may work as novel approaches to increase the bioavailability of curcumin [11]. Curcumin nanoparticles are those, which are nanosized and consist of 100% pure curcumin [23]. Size distribution and charge on nanoparticles can affect the retention property. The smaller the size of the particles is, the more is the retention property of the particle. Zeta potential influences the stability of the particles [24, 25].

2 Methods of synthesis of curcumin nanoparticles

Various methods are being developed for the synthesis as well as to enhance the activity of curcumin nanoparticles (Figure 4).

2.1 Coacervation technique

In this method of synthesis of curcumin nanoparticles, a polymer is dissolved in organic solvent (e.g., dichloromethane, ethyl acetate, or acetonitrile), and the hydrophobic drug-like curcumin is suspended directly in the polymeric solution, and it is allowed to stir and mix properly. The nanoparticles are collected by centrifugation [26]. It is an inexpensive method, and hazardous solvents are not used. The main drawback of the coacervation technique is that it requires a large amount of solvent [27]. Chirio et al. formulated curcumin-loaded nanoparticles by using this technique [26].

2.2 Nanoprecipitation method

Nanoprecipitation method is also known as solvent displacement method. In this method, the desired polymer is suspended in solvent, and curcumin is then added in polymeric solution. After that, this polymeric solution is

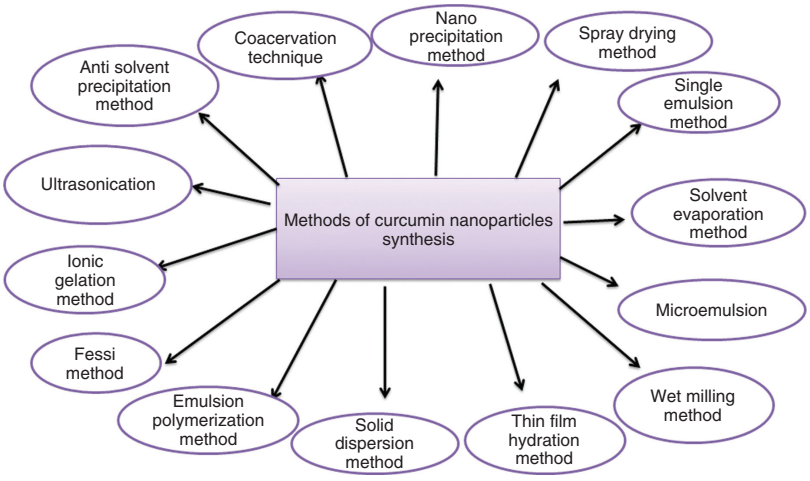

Figure 4: Methods of synthesis of curcumin nanoparticles.

added in water under continuous stirring in water, which results in precipitation [28].

2.3 Spray drying method

In this method of synthesis, curcumin and a polymer are dissolved in the same solvent or mixture of solvents. After that, the solvent is allowed to evaporate by hot air flow [29]. Spray drying resulted in the formation of drugs in the amorphous state, which may get partially crystallized during processing [30]. Curcumin nano-crystals can be formulated by spray drying method [31].

2.4 Single emulsion method

The single emulsion method is the conventional method of curcumin nanoparticle synthesis. In this method of synthesis, curcumin nanoparticles are prepared by dispersing in solvent followed by high-speed homogenization or ultrasonication. Further solvent is evaporated by continuous magnetic stirring at room temperature or under reduced pressure. The solidified nanoparticles are ultrasonicated and collected, followed by washing with distilled water to remove additives and lyophilized to get the nanoparticles [32]. Curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles can also be prepared [33].

2.5 Solvent evaporation method

The solvent evaporation method includes two major steps: (i) preparation of a solution consisting of polymer and drug-like curcumin (ii) and evaporation of dispersing solvent used for dissolving curcumin. It results in the formation of solid mass [28]. The emulsion formed is then converted into a nanoparticle suspension by evaporation of the solvent [33]. The advantage of this method is that low temperature is required for the evaporation of the solvent, and thermal deposition can be prevented. The disadvantages are (i) the reagents used in the method are quite expensive, (ii) selection of the proper solvent is somehow difficult, and evaporation of the organic solvent is a time-consuming process [34]. PLGA-loaded curcumin nanoparticles were synthesized by this technique [35].

2.6 Microemulsion

Microemulsion is considered as an ideal method for nanoparticle fabrication. The surfactants, which are used in this method, are hydrophobic in nature for water and hydrophilic in nature for oil. Microemulsion is formed when a small amount of surfactant is stirred and curcumin is added in it along with oil and water. It results in the formation of a turbid solution, which generally appears like small droplets. The curcumin nanoparticles are synthesized by this method in order to increase the biological activity of curcumin [36, 37]. Various types of surfactants are used to increase the surface stabilization of curcumin nanoparticles. The method is easy and can be effectively used for drug delivery with less energy expenditure. Microemulsion technique is affected by certain parameters like temperature and pH variation [38–40].

2.7 Wet milling method

Wet-milling is the method of synthesis used for curcumin nanoparticles. The hydrophobic drug-like curcumin is suspended in appropriate dispersing solvent curcumin. The obtained solution is further agitated under ultrasonication method. Distilled water is also required for the synthesis of curcumin nanoparticles. The obtained solution is then allowed to be centrifuged, and the nanoparticles are obtained by this method. The synthesis of curcumin nanoparticles by this technique is reported by researchers [41].

2.8 Thin film hydration method

In this method, curcumin and the surfactants used are allowed to mix in organic solvent under sonication condition. The solvent is allowed to evaporate under certain pressure, and after that, distilled water is added in sonication condition, and the obtained nanosuspension is then centrifuged to obtain curcumin nanoparticles. Moorthi et al. demonstrated curcumin nanoparticles synthesis by this method of synthesis, and they used piperine along with curcumin [42].

2.9 Solid dispersion method

In this method. matrix and hydrophobic drugs like curcumin are mixed. Matrix can be in the amorphous or in crystalline form. This method can be used to dissolve the insoluble hydrophobic drug [34].

2.10 Emulsion polymerization method

This is a fast and readily scalable method used for curcumin nanoparticle synthesis [43]. The organic and continuous phase are two types of emulsion techniques, which can be used for the synthesis of curcumin nanoparticles [44, 45]. A surfactant is dissolved in pure water by ultrasonication, then curcumin is dissolved in organic solvent and finally, the solution is added to the surfactant. Moorthi and coworkers have reported the synthesis of curcumin nanoparticles by using this method, and piperine was used along with curcumin to increase the biological activity of the synthesized curcumin nanoparticles [42].

2.11 Fessi method

In this method of synthesis, curcumin is dissolved in a suitable solvent under sonication condition. The solution thus obtained is further added in pure water along with a certain surfactant with constant stirring. The curcumin nanoparticles can be spontaneously synthesized by this method. Moorthi and coworkers have used this method for the fabrication of curcumin nanoparticles [42].

2.12 Ionic gelation method

This is an easy and simple method of nanoparticle synthesis. A hydrophobic drug such as curcumin is dissolved in the proper solvent, which showed complete solubility of curcumin in it, and then this solvent is added into a polymeric solution under constant stirring condition. This method depends on the crosslinking of the polymer along with the drug such as curcumin. Chabib and coworkers reported the synthesis of curcumin nanoparticles and used chitosan as a polymer. This polymer improved the solubility and stability of the curcumin nanoparticles [46].

2.13 Ultrasonication

This method is generally employed for the drugs, which are less water soluble. For synthesis purposes using this technique, curcumin is first dissolved in organic solvent, and the resulting solution is then added into the polyelectrolye solution under ultrasonication condition for several intervals of time, and after that, the curcumin nanoparticles can be synthesized by this method. Zhang et al. have synthesized the curcumin nanoparticles by using this technique of ultrasonication [47].

2.14 Antisolvent precipitation method

Antisolvent precipitation is the method of synthesis of a poorly water-soluble drug. In this method of synthesis, curcumin is dissolved in organic solvent followed by the addition of this solution to the deionized water under constant stirring. Hence, the curcumin nanoparticles can be synthesized by this method. Kakarn and coworkers used this method for synthesis of curcumin nanoparticles. The advantage of this method of synthesis is that it is a suitable technique for the synthesis of the poorly soluble curcumin nanoparticles [48]. From the above-described methods of curcumin nanoparticle synthesis, ionic gelation and the antisolvent precipitation method of synthesis are effective and better. Both methods have some or other lacunae, but they are suitable for drugs like curcumin. As curcumin is poorly soluble in nature, these methods of synthesis provide improvement in both the solubility and stability

of curcumin nanoparticles. The ionic gelation method depends on the crosslinking of the polymer along with drugs. In the antisolvent precipitation, synthesis depends on the stirring speed, time, and also on temperature. The microemulsion technique is suitable when the curcumin nanoparticles are used for drug delivery purposes. Investigation of the novel method for curcumin nanoparticle synthesis is the need for further research in the field of formulations of curcumin nanoparticles.

3 Different applications of curcumin and curcumin nanoparticles

3.1 Curcumin as a traditional therapeutic agent

In Indian and Chinese medicine, since centuries, curcumin has been used as a wound healing agent and in curing many diseases. Curcumin has been recognized as one of the most active therapeutic agent of turmeric [49], due to its anti-inflammatory, antioxidant, anticancerous, and antimicrobial effect [50]. Aggarwal and Harikumar [51] reported curcumin as a potential agent in the therapy of Alzheimer's disease, rheumatoid arthritis, metabolic syndrome, neurodegenerative and cardiovascular diseases, etc. (Figure 5).

3.2 Anti-inflammatory property of curcumin

The presence of keto form and double bonds in the structure of curcumin are mainly responsible for its anti-inflammatory action [52]. Curcumin has been known to control various enzymes, proteins, protein kinase, cytokines and transcription factors, which are related to the process of inflammation [53]. From previous work of researchers, it was found that curcumin is an anti-inflammatory agent whose activity can be compared with that of steroidal and nonsteroidal drugs indomethacin and phenylbutazone [54]. Studies of curcumin have focused mainly on the cyclooxygenase (COX) enzyme, which is used for the conversion of arachidonic acid to prostaglandin and decreases the synthesis of prostaglandin [54, 55]. Menon and Sudheer [54] reported that there are two isoforms of the cyclooxygenase enzyme, COX-1 and COX-2. COX-1 enzyme is a constitutive enzyme, which is present in many types of tissues in the body, whereas COX-2 is constitutively expressed in the brain and the spinal cord and can also be induced by the different types of enzymes formed during pregnancy, lactation, and ovulation. Curcumin is used to inhibit the synthesis of inflammatory molecules such as tumor necrosis factor-α (TNF-α), which is mainly responsible for the production of inflammatory products [12]. Curcumin also inhibits the formation of inflammatory interleukin molecules such as interleukin (IL)-1, -2, -6, -8, and -12 and chemokine. The monocyte chemoattractant protein (MCP) and migration inhibitory protein can be inhibited by the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes. The anti-inflammatory action of curcumin is shown in Figure 6. Araujo and Leon [4] reported two models of inflammation, acute and chronic. In acute inflammation, the effect of anti-inflammatory molecules has been well studied, whereas in the chronic model, the proliferative phases are mostly studied. Inflammatory bowel disease (IBD) is a state in which the intestine is inflamed. Ulcerative colitis and Crohn disease are two major types of IBD. Ulcerative colitis affect the colon, whereas Crohn disease generally affects any part of the gastrointestinal tract from the mouth to the anus [56]. From a clinical study, it was found that curcumin is effective against ulcerative colitis [57]. IBD mostly affects 15- to 30-year-old people by acting on the small and large intestine. From the clinical trials, it was found that curcumin can probably be used to treat inflammatory diseases [12, 50, 58, 59]. Curcumin also exhibits antirheumatic and antiarthritic effects. It helps in the regulation of COX2, tumor necrosis factor (TNF), and other inflammatory cytokines [5]. From the animal studies, it was found that curcumin helps in reducing the plaques, which are deposited in the brain of an Alzheimer patient. From preliminary studies on humans, it was concluded that curcumin can be used as one of the promising candidates that can help treat a

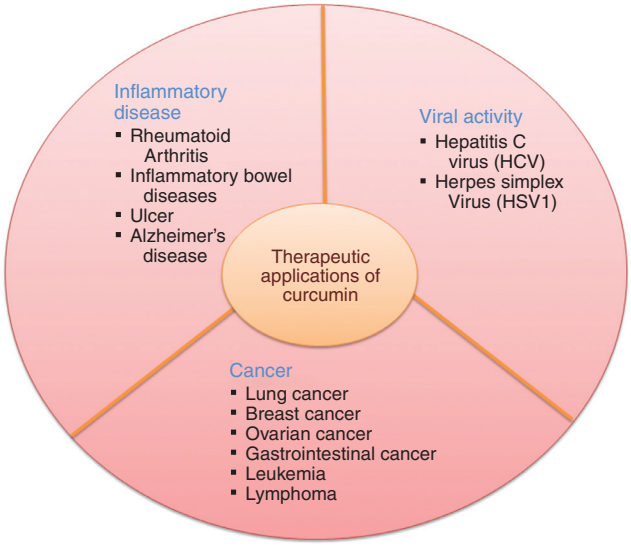

Figure 5: Therapeutic application of curcumin.

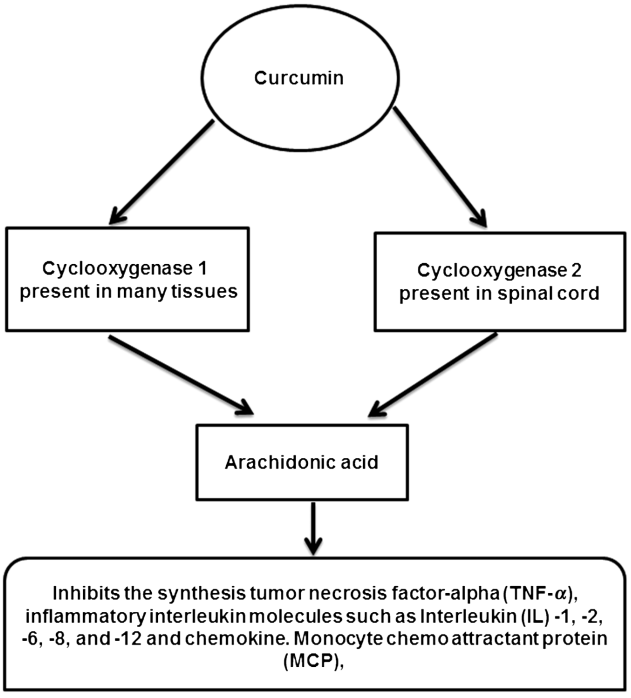

Figure 6: Anti-inflammatory action of curcumin.

disease like Alzheimer's. It is safe to use curcumin in the patient affected with Alzheimer's disease [60]. Kumar and coworkers [61] demonstrated that Alzheimer's disease is the inflammation of the brain, which is mainly characterized by an increase in cytokines and activated microglia.

3.3 Antioxidant property of curcumin

Researchers have studied the antioxidant property of curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin [62]. Curcumin exhibits a higher superoxide-scavenging activity compared to demethoxycurcumin and bisdemethoxycurcumin [52]. Research revealed that curcumin prevents the oxidation of hemoglobin at a concentration of 0.08 mM. The lower level of oxidation induced by nitrate can be inhibited by diacetyl curcumin [53]. Curcumin is an effective candidate for scavenging of the reactive oxygen and nitrogen species. Reactive oxygen species are responsible for causing numerous pathogenic diseases due to which antioxidants are getting impetus as one of the therapeutics that are useful in the treatment of many diseases. Antioxidants like curcumin are effective against Parkinson's disease and various autoimmune diseases. The major drawback of antioxidants is that they display low absorption and low bioavailability. Researchers are trying to develop antioxidant-loaded nanoparticluate carriers like solid lipid nanoparticles or liposomes. Some of the successful instances of encapsulating drugs and other active ingredients are vitamin E, coenzyme Q 10, vitamin A, curcumin, lucopene, silymarin, and superoxide dismutase [63].

According to the free radical theory of aging, it is postulated that aging is because of free radical reaction. The life span of an organism can be enhanced by the administration of an exogenous antioxidant. The effect of exogenous antioxidants like vitamins, lipoic acid, coenzyme Q, melatonin, resveratrol, and curcumin, was studied on the lifespan of various model organisms [64]. Curcumin acts as an antioxidant as well as a pro-oxidant in the presence of copper, which is an attractive phenomenon contributing to its medicinal activity [65].

Moreover, curcumin is active against the oxidative damage of DNA, proteins, and is protective against chronic diseases such as cancer, atherosclerosis, neurodegenerative diseases, and aging [66]. It was investigated by researchers that curcumin exhibits free radical scavenging activity against the peroxidation effect of the biomembrane. Indirectly, curcumin acts as an antioxidant agent by enhancing the synthesis of glutathione, which can suppress the activity of inflammatory molecules. Curcumin was found to be effective than vitamin E [54]. Compared with other antioxidants, curcumin is the most unique antioxidant, which possesses various types of functional groups in its structure as it exhibits β-diketo group, carbon-carbon double bonds, and phenyl rings. The antioxidant property of curcumin is mainly due to the presence of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase [3].

The free radical scavenging ability, antilipid peroxidation effect, and cytotoxicity of curcumin nanoparticles were evaluated against human hepatoma cell lines HepG2, PLC/PRF/5, and Hep3B. Curcumin nanoparticles were found to inhibit the activity of HepG2 cells effectively. On comparing curcumin nanoparticles and curcumin in water for the antioxidation activity, nanoparticles were found to be much more effective compared to bulk curcumin [67]. Lipid peroxidation is a degeneration process, which mainly affects the tissues, and it results in the free radical formation and saturation of unsaturated fatty acids. From *in vitro* study, it was found that curcumin can be used in the peroxidation effect, due to their free radical scavenging activity [68]. Lipids present on the surface of the skin are generally unsaturated and, hence, are prone to attack by free radicals. When the ultraviolet rays of the sun penetrates on the surface of the skin, the damage caused by free radicals increase rapidly and may degrade the collagen and elastin fibers present on the skin. Curcumin was

found to be effective in this case as it detoxifies free radicals and prevents degradation of the fibers present on the skin. This activity is mainly due to the antioxidant activity of curcumin [61]. On comparison of the antioxidant property of curcumin and curcumin nanoparticles, it was found that the latter showed higher antioxidant property than the former [48] due to the decrease in the size of curcumin and the formation of an amorphous state; with hydrogen bonding, the efficacy of curcumin can be increased [67].

3.4 Anticancer property of curcumin

In 1987, Kuttan and coworkers, for the first time, reported on the anticancerous activity of curcumin on humans. They performed clinical trials on 62 patients with external cancerous lesions. It was found from the study that curcumin is effective and remarkable in the case of itching, lesion size, and pain [69]. Topical curcumin was found to produce symptomatic relief as evidenced by reductions in smell. Curcumin, either alone or in combination with other agents, acts as a potential agent against the different types of cancer such as colorectal cancer, pancreatic cancer, breast cancer, prostate cancer, multiple myeloma, lung cancer, oral cancer, and head and neck squamous cell carcinoma (HNSCC) [56].

The *in vitro* activity of curcumin is tested on animal models like rats. The studies demonstrated that curcumin has the potential to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor growth [61]. Curcumin has been nominated as an anticancerous agent by the National Institute of Cancer [66, 70]. It has been reported that curcumin has been recognized as an agent that can induce apoptosis, suppresses cell cycle progression, and finally prevents cancerous cell growth progression [71].

Curcumin downregulates the expression of genes, which are involved in tumor growth and apoptosis, *c-myc*, *bcl-2*, *Bcl-x L*, etc., and upregulation of apoptotic genes, *p53*, *bax*, and *Bcl-xs* [70]. It also prevents the activity of topoisomerase enzyme, which is required for the replication of DNA. It prevents cell cycle progression by arrest in the G2/M phase in malignant tumors [66]. It was found that curcumin exhibits activity against different types of cancer such as leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma [50].

Recently, it was reported that curcumin inhibits papillary thyroid cancer cells. *In vitro* study proved that by regulation of E-cadherins and metalloproteinase-9 expression pattern, curcumin can inhibit the metastasis of the papillary thyroid cancer cells. This is the first evidence, which proves curcumin's ability to enhance mesenchymal-epithelial transition. Hence, curcumin can be used as an adjuvant in the treatment of thyroid cancer [72] and in the treatment of oral squamous cell carcinoma [73].

1,7-Bis (4-hydroxy-3-ethoxyphenyl)-1,6-heptadien-3,5-dione EAC (12) and 5-bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone PAC (13) are two new curcumin analogs, which possess anticancerous activity against normal and breast cancer cells. PAC (13) was found to be five times more active than curcumin in inducing apoptosis [74].

3.5 Antimicrobial activity of curcumin

It has been reported that curcumin possesses activity against *Helicobacter pylori*. Matrix metalloproteinase 3(MMP3) and metalloproteinase 9(MMP9) are inflammatory molecules, which are present in *H. pylori*. Curcumin regulates the expression of both the MMP3 and MMP9, making it effective against *H. pylori* [75, 76]. Curcumin showed significant activity against *Streptococcus*, *Staphylococcus*, and *Lactobacillus* [2]. It also exhibits activity against *Salmonella paratyphi* [77], *Azotobacter* [8], *Candida* species, *Aspergillus* species, and other pathogens. Furthermore, curcumin is also known for its action against protozoans such as *Plasmodium falciparum* and *Leishmania major* [66]. The antiviral activity of curcumin is also known against hepatitis C virus (HCV) [66]. Researchers demonstrated that curcumin is used for the treatment hepatitis virus [78], herpes simplex virus type-1 (HSV-1) [79].

Curcumin nanoparticles and microemulsion are also known for its antimicrobial activity. Formulated curcumin microemulsion such as curcumin-loaded myristic acid microemulsion is used to inhibit *Staphylococcus epidermidis*, which is mainly responsible for nosocomial infections [80]. It was also demonstrated that curcumin nanoparticles have antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and antifungal activity against *Penicillium notatum* and *Aspergillus niger* [41]. Vimla and coworkers [19] reported that the antimicrobial activity of curcumin can be improved by the formation of curcumin-encapsulated chitosan polyvinyl alcohol silver nano-composite film.

3.6 Biomedical applications of curcumin nanoparticles

Curcumin when administered orally exhibits problems such as low systemic bioavailability and solubility.

Hence, the nanoparticles are synthesized to overcome these obstacles and in order to enhance the efficacy of curcumin. Nano-curcumin shows better biological activity and exhibits better solubility and stability [49, 81]. It was reported that the target drug delivery can be easily achieved by using curcumin nanoparticles rather than using curcumin. The unwanted side effects of several drugs and medicine can be minimized by using nanoparticles. A study revealed that the polymer-based curcumin nanoparticles have applications in cancer-related diseases and are known as "nanocurcumin" [49].

Curcumin nanoparticles have wide applications in the field of medicine. It also depicts activity against various microorganisms. Nanoparticles increase the bioavailability of curcumin powder and can also be used in the treatment of various protozoan and parasitic diseases. It was reported that curcumin has antiprotozoal activity against *Giardia lamblia*. The efficacy can be enhanced by the synthesis of curcumin nanoparticles. From the study, it was revealed that the activity of curcumin against protozoan can be increased by the combination of curcumin nanoparticles along with chitosan and silver nanoparticles [82].

3.7 Curcumin nanoparticles in the treatment of cancer

It was reported that nanotechnology-based synthesis of curcumin or its analogs can be used in the inhibition and the progression of cancerous cells. Curcumin nanoparticles enhanced the chemotherapeutic effect of anticancer drugs when used in combination with it [83]. Curcumin nanoparticles used in the treatment of ovarian cancer may improve the efficacy of curcumin [84]. Curcumin-mediated PLGA nanospheres can be used in the prostate cancer therapy [81, 85].

Curcumin particles also showed activity against various cancer cell lines. A study demonstrated that polymer-based curcumin nanoparticles (nanocurcumin) are effective in the treatment of human cancer [67]. Curcumin-loaded cellulose nanoparticles were synthesized, and its cytotoxicity test and cell culture investigation were performed. It was proved that curcumin showed its apoptotic activity and inhibits cell proliferation of prostrate cell line. It is used as a tool that can be used in the treatment of prostate cancer [86]. The curcumin-loaded chitosan nanoparticles can be used to enhance the bioavailability and solubility of curcumin. *In vitro* study was performed on the T74D cells. On comparing curcumin nanoparticles with curcumin powder, it was found that curcumin nanoparticles have better activity against cancerous cell lines compared to curcumin powder [46]. Silk fibroin-derived curcumin nanoparticles were synthesized by the capillary-microdot technique. Curcumin nanoparticles showed higher efficacy against breast cancer [87]. Serum albumin was used for the synthesis of nanoparticles in order to enhance the activity of curcumin nanoparticles as curcumin has the problem of low solubility. *In vitro* study, clinical trials, and cell culture study revealed that curcumin-formulated nanoparticles have significant efficacy against the breast cancer cell line MDA-MA 231 [88].

The cytotoxicity and preliminary tests of curcumin-loaded solid lipid nanoparticles were performed on the colon cancer cell line, which was found effective [26]. Recently, the activity of curcumin-loaded magnetic nanoparticles was measured by inducing tumor in mice. Animal studies on mice revealed the inhibition of pancreatic tumor growth, and the bioavailability of curcumin was increased by 2.5-fold compared to free curcumin. Hence, it can be concluded that curcumin-loaded nanoparticles are a novel and valuable therapy against pancreatic cancer [89]. Polymer-based nanocurcumin possesses increased systemic bioavailability of curcumin in plasma and tissue. Preclinical study demonstrated that nanocurcumin can inhibit the primary growth and metastasis of pancreatic cancer, hence, proved to be a promising anticancerous therapeutic agent [90]. Curcumin-loaded lipid nanodisks were formulated, which proved to be effective against cancer [91]. The polymer-based curcumin nanoparticles were formed by using polymers such as alginate and chitosan. Cytotoxicity assay and *in vitro* studies proved that these nanoparticles were much more effective against cancer cell growth. Polymer-based curcumin nanoparticles were evaluated against multiple brain tumor cell cultures, including the embryonal tumor-derived lines DAOY, D283Med and the glioblastoma neurosphere lines HSR-GBM1 and JHH-GBM14. The study revealed that nanoparticles can prevent the growth of malignant brain tumor cells [20]. Curcumin microemulsion inhibited the growth of oral squamous cell carcinoma. *In vitro* cytotoxicity study was performed under ultrasonication condition on oral squamous cell lines (OSCC-4 and OSCC-25). It was reported that as the frequency of sonication is increased, its efficacy also increases, and it can be used as one of the novel method in the treatment of cancer [92]. Silica-modified curcumin nanoparticles are used as vehicle for the delivery of curcumin, which can be used against oral cancer. From the cellular uptake and microscopy study, it was noticed that curcumin-modified nanoparticles are more potent compared to free curcumin [93]. Curcumin nanoparticles cause inhibition of NF-κB and suppression

of NF-κB-regulated proteins involved in invasion (MMP-9), angiogenesis (VEGF) [94].

It was found that stability and solubility of curcumin-loaded dextrin nanogel is much more than free curcumin. Cell culture study has proved that curcumin nanogel demonstrated its activity against the Hela cell line. Hence, curcumin nanogel can be used as nanocarrier in the therapy of cancer [95]. Lipid-based curcumin nanoemulsion was synthesized and on performing cytotoxicity assay on B16F10 and leukemic cell lines. It was demonstrated that curcumin emulsion was effective compared to curcumin [96].

From various *in vitro* and *in vivo* cancer studies, it is clear that curcumin possesses anticancerous properties because of the inhibition of various signaling pathways. Different curcumin-mediated delivery techniques are now being developed for increasing the activity of curcumin. Examples of curcumin-mediated delivery techniques are nanoparticles, liposome micelles, polymer-based nanoparticles and curcumin-encapsulated polymer nanoparticles. Prior research studies have shown that curcumin nanoparticles have improved anticancer effects compared to normal curcumin formulations [97].

GnRH-R is a minute group of neurons, which is located in the septal-preoptic hypothalamic region [98, 99]. In human beings, the *GnRh* gene is present on the chromosome 8p11.2-p21, and it is composed of four exons and three introns [100, 101]. *GnRh* is a novel candidate, which can be used as a molecular target in the treatment of cancer. Curcumin hybrid is one of the agonists, which can be used as one of the promising vehicles for the delivery of anticancerous drug [102].

Recent studies have demonstrated the interaction of curcumin nanoparticles with plasma proteins, which is a new platform and can be used to improve cancer therapy [103].

3.8 Applications of curcumin nanoparticles in other diseases

It was demonstrated that curcumin-loaded solid lipid nanoparticles (SLN) can be used in the formulation of facial cream, which acts as an anti-aging cream. After the clinical trials, it was noted that curcumin-loaded SLN nanoparticles can be used to reduce facial wrinkles and other problems such as melanin content, biological elasticity, and viscoelasticity related to skin problems. The cream was found to be effective against aging problems and, hence, can be used as a safe and efficient method for the treatment of skin infection [104].

Curcumin demonstrates an antimalarial activity [105], and after the synthesis of the curcumin-loaded chitosan nanoparticles, its efficacy is increased. *In vivo* and *in vitro* studies have depicted that these nanoparticles are more potent than the curcumin powder. Hence, the curcumin nanoparticles can be used in antimalarial therapy [106]. Curcumin-loaded hydrogel nanoparticles were fabricated by the solvent emulsion method. These nanoparticles were synthesized in order to enhance its bioavailability and absorption of curcumin. *In vivo* antimalarial study of curcumin nanoparticles showed that curcumin nanoparticles can be used along with the standard therapy. From the cytotoxicity test, it was investigated that oral administration of these nanoparticles may be safe [107]. Curcumin-loaded nanoliposomes were synthesized, and from the resonance experiment, the high affinity for amyloid linkage was evaluated; due to this, it can be used in Alzheimer's disease. Curcumin-loaded PLGA nanoparticles in conjugation with Tet-1 peptide can be used for the treatment of Alzheimer's disease. Tet-1 is a peptide that has affinity with the neurons. By conjugation of curcumin with this type of peptide, it can be used as a novel candidate for the treatment of the dreadful Alzheimer's disease [108].

4 Conclusion

It can be concluded that curcumin is a natural therapeutic agent with many versatile activities such as anti-inflammatory, antioxidant, anticancer, and antimicrobial activities. Studies have revealed that novel delivery strategies including those of nanoparticles, liposomes, and defined phospholipid complexes can be used to enhance the activity of curcumin. The curcumin nanoparticles can be synthesized by various methods and can be used for the treatment of different types of cancer. Curcumin nanoparticles can also be used for the treatment of Alzheimer's disease. Recent studies showed that curcumin-loaded microemulsion, formulated cream, and nanogel can also be used as one of the modern and novel tools for drug delivery. Thus, nanocurcumin can be used as a potential therapeutical agent against broad spectrum microorganisms.

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