Critical Review on Curcumin as a Therapeutic Agent: From Traditional Herbal Medicine to an Ideal Therapeutic Agent

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ABSTRACT: Traditionally, many natural medicinal plants have been used to treat a variety of diseases since ancient times and are considered a potential source of phytochemicals for the development of new drugs. One of these is curcumin, which is an easily accessible, inexpensive, and nontoxic bioactive compound. Curcumin is a very important, naturally occurring, and highly lipophilic and phenolic substance derived from the rhizomes of plant *Curcuma longa*, a member of the *Zingiberaceae* (ginger) family, which is mostly used as a curry spice, flavoring agent, insect repellent, coloring agent in food, traditional drug, and ingredient in cosmetics. Modern scientific research has demonstrated that it has wide range of pharmacological activities and medicinal properties against various types of diseases, disorders, and syndromes. Because it has been known for many years to have excellent therapeutic potential against various diseases, much research has been devoted to this natural product. This review briefly summarizes the scope, therapeutic potential and clinical applications of curcumin.

KEY WORDS: turmeric, *Curcuma longa*, pharmacological activity

I. INTRODUCTION

Humans have been consuming herbs and plants for the treatment of several diseases since ancient times.[1-5] Plants have been used throughout human history for various purposes,[6-8] and evidence for the use of herbal medicine continues to increase. The role of natural products in human health care cannot be undervalued. It has been estimated that 80% of individuals living in developing countries (notably Pakistan, India, and Bangladesh) depend primarily on natural products to meet their health-care needs.[9,10] Now all over the world, researchers devote considerable attention to traditional and indigenous medicines because of their excellent therapeutic value without known or reported side effects. One very famous, valuable, and important traditional plant compound is curcumin.[11-13]

Curcumin has long been considered one of the most widely studied natural products because of its excellent pharmacological activities and health benefits.[14] In this article, we discuss in detail the physicochemical properties of curcumin, along with its origin, extraction, and metabolites. Moreover, we also describe the diverse role of curcumin for the treatment of different diseases.

II. CURCUMIN

Curcumin, a hydrophobic polyphenol, is a principal active component extracted from the rhizomes of the turmeric plant, *Curcuma longa* L. The chemical name of curcumin is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Curcumin is also known as diferuloylmethane and is insoluble in water. Cur-

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cumin is aromatic, with a slight evocative fragrance of orange and ginger, but it tastes bitter.[15] Turmeric is an important herbaceous or underground stem of *Curcuma longa* L., and it has been used as a traditional medicine since ancient times. It is usually 60 to 100 cm high with a short stem and tufted leaves, with a maximum of 8 to 10 branches. Its flowers are yellow and 10 to 15 cm long (Fig. 1).[16] They are combined in dense spikes that appear from the end of spring until the summer session.[15] The turmeric rhizome is generally yellowish brown, with a dull orange inside that appears bright yellow when powdered.[17-19] The turmeric crops are harvested within 7 to 9 months depending upon the time of sowing. Turmeric is cultivated in warm and rainy regions of the world, such as Pakistan, China, India, and Indonesia, but India is the major producer.[20] Turmeric contains 69.4% carbohydrates, 13.1% water, 6.3% protein, 5.1% fat, and 3.5% minerals.[21,22] Fractions of turmeric are known as curcuminoids. Commercial curcumin is a mixture of curcuminoids, containing approximately 77% curcumin (curcumin I), 18% demethoxycurcumin (curcumin II) and 5% bisdemethoxycurcumin (curcumin III), and cyclocurcumin.[23] The other constituents of raw turmeric include various volatile oils, including tumerone, zingiberone, atlantone, sugars, proteins, and resins.

Many methods had been used to extract the curcumin from turmeric, such as maceration, microwave treatment, digestion, infusion, and Soxhlet extraction methods. By comparing all the reported methods, Soxhlet extraction is much better than the others. A large amount of curcumin can be extracted using less solvent, which saves time, money, and energy.[24]

A. Traditional Uses of Curcumin

Curcumin has also a very long history as a traditional cosmetic. Even now, women living in Pakistan, India, and Bangladesh use it to make a beauty spot on the forehead during wedding ceremonies. People living in the mountains of north India also use it to protect the skin against the rays of the sun.[24-27]

FIG. 1: *Curcuma longa* L. Plant. Reproduced with permission.[16]

B. Therapeutic Potential and Clinical Applications of Curcumin

Turmeric has long been consumed by the people of Indian and other subcontinent regions with no known side effects, not only in food but also in the treatment of a wide variety of diseases.[28,29] The active constituent of turmeric is curcumin (diferuloylmethane). Curcumin has recently acquired attention by chemists due to its wide range of potential therapeutic applications for a variety of diseases.[30] In the following subsections, we describe the potentially significant role of curcumin as a potential therapeutic agent.

1. Antioxidant Activities

Oxidative stress plays a major role in the pathogenesis of various chronic diseases. Curcumin is a powerful and strong phenolic antioxidant agent, much like vitamins C and E and beta-carotene, and it protects vital organs of the body from the damaging effects of free radicals produced during oxidative stress.[16,31] Scientific studies indicate that curcumin is several times more potent than vitamin E as a free radical scavenger.[30,32] Its effectiveness as an antioxidant is mainly contributed by the phenolic hydroxyl group, which scavenges free radical by donating its H (electron) atom to the free radicals.[15,33,34] Curcumin prevents the formation of free radicals in the blood (protect hemoglobin from oxidation) and tissues of living organisms. Hence, it helps to protect the vital organs of the body suffering from various cardiovascular, viral, and other chronic diseases induced by oxidative stress.

2. Anticancer Activities

Experimental studies have provided the evidence that curcumin also has anticarcinogenic activities.[35] Most recently, curcumin has been shown to exhibit anticancer effects against several types of malignancies in humans. The treatment of cancer with different synthetic drugs (also known as chemotherapeutic agents) is one of the important life-extending techniques. However, the nonselective actions of many antitumor and anticancer agents can cause serious side effects and patient distress by damaging normal cells along with the target cancer cells. Many patients who undergo chemotherapy suffer hair and weight loss, nausea, depression, and a range of related physical and mental stresses. Cancer is a hyperproliferative disorder that is usually treated with synthetic chemotherapeutic agents, which have some drawbacks and produce major side effects. To reduce such side effects, scientists continuously struggle to develop agents that are therapeutic role and have fewer side effects. One promising approach is the use of natural and herbal medicine that has been proven to have no side effects. Most recently, curcumin has been shown to exhibit anticancer effects in several types of human cancers.[36-42] A lot of scientific research suggests that consumption of turmeric, curcumin, and its derivatives may reduce the risk of several types of cancers.[14,43-45]

3. Antiulcer Activities

Li et al.[46] studied curcumin–piperine mixtures in self-microemulsifying drug delivery systems (SMEDDS) for the treatment of ulcerative colitis. For *in vivo* studies, mice were used to test its therapeutic effectiveness against ulcerative colitis. Acute ulcerative colitis was induced by the oral administration of 5% dextran sulfate sodium (DSS) ad libitum for seven consecutive days. They measured the severity of clinical symptoms by assessing the body weight loss, stool consistency and stool blood, and finally, they evaluated the therapeutic effects of curcumin–piperine SMEDDS treatment. Their findings demonstrated that curcumin–piperine SMEDDS treatment significantly suppressed DSS-induced colitis in mice by improving their body weight and stool consistency as well as decreasing intestinal bleeding. Ali et al.[16] also developed and characterized mucoadhesive microspheres of curcumin for the potential use of treating gastric adenocarcinoma, gastric and duodenal ulcer associated with *Helicobacter pylori*. The drug released from the optimized formulation showed a controlled-release pattern that offered both local and systemic action for effective treatment of *H. pylori* infection.

4. Cardiovascular-Protective Activities

Curcumin is an inhibitor of p300 histone acetyltransferase activity, and this enzyme is associated with heart failure. It has been reported that native curcumin, at a dosage of 50 mg/kg, prevented deterioration of systolic function in the rat models of heart failure by inhibiting the activity of p300 histone acetyltransferase.[47]

5. Antidiabetic Properties

Curcumin has shown to be effective against various causative factors of diabetes mellitus and its associated complications. Steigerwalt et al.[14] evaluated the improvement of diabetic angiopathy and retinopathy with curcumin. They administered curcumin at the dosage of 2 tablets/day (each tablet containing 500 mg curcumin phospholipid, corresponding to 100 mg curcumin) for at least 4 weeks. These observations indicated the potential value of curcumin in the management of diabetes-associated peripheral microangiopathy and retinopathy. Joshi et al.[48] also increased the effectiveness of curcumin by introducing a self-nanoemulsifying drug delivery system (SNEDDS) for curcumin to enhance its bioavailability and then evaluated its efficacy in experimental diabetic neuropathy and found that it has significant therapeutic potential for the treatment of various diabetes complications.

6. Antimalarial Properties

Malaria has always been a major global health concern because it is the most prevalent parasitic disease and the foremost cause of morbidity and mortality in the world. Many investigations have shown that curcumin exhibits antimalarial activity both *in vitro* and *in vivo*.[49-51]

7. Antimicrobial Activities

Bhawana et al.[52] studied the antibacterial and antifungal properties of curcumin against different strains of bacteria and fungi. They also converted curcumin into nanoparticles and found that they were much more effective than curcumin against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Penicillium notatum*, and *Aspergillus niger*.

8. Wound Healing Properties

Skin is usually injured by wounding or physical strain. Skin damage initiates a series of complicated and well-orchestrated repair processes ending with complete reestablishment of the integrity of damage tissue and restoration of this functional barrier.[53-55] In cases of severe damage, complete cure takes a long time. Therefore, a variety of studies were focused on wound dressings that promote wound healing and to minimize scar formation.[56-59] Studies conducted on curcumin indicate that it may heal wounds and minimize the chance of scar formation more effectively than other synthetic therapeutic agents.[60-62]

C. Curcumin as an Additive for Food Industry

Modern research on food chemistry has revealed diet and health-related problems, and now people are demanding natural ingredients that are considered and expected to be safe and promote health. Curcumin, which is used worldwide as an edible dye, flavoring and coloring agent in different food grade products, such as fruit drinks and other beverages, cheese, margarine, and butter. As a food additive, its E number is E100.[1] In the food industry, curcumin is also used as a stabilizer in jellies, a natural coloring agent, and a substitute for artificial colorants in cheese, pickles, mustards, cereals, soups, ice creams, and yogurts.[63] In addition to its use in foods, it is used as an environmentally friendly and biodegradable dye for cotton, silk, wool, leather, paper, and toys. Studies have also revealed that curcumin combined with aloe vera and chitosan may suppress microbial growth in cotton and wool.[41,64]

D. Degradation of Curcumin

Curcumin is photodegradable (UV/visible radiation), both in the liquid and solid states. It is also self-degradable in the dark and in alkali medium. At acidic pH (1 to 6), the degradation of curcumin is

extremely low compared to what occurs when it is exposed to neutral and alkaline pH. Therefore, it is stable in the stomach and small intestine.[65] The main degradation product is a cyclization of curcumin, which is formed by the loss of two hydrogen atoms from the molecule. During degradation of curcumin, *trans*-6-(40-hydroxy-30- methoxyphenyl)-2,4-dioxo-5-hexenal is found to be a major degradation product, Vanillin, vanillic acid, ferulic aldehyde, ferulic acid, feruloyl methane, and 4-vinylguaiacol are minor degradation products.[66-68]

E. Toxicity of Curcumin

The literature indicates that use of curcumin causes no toxic effects. The US Food and Drug Administration has also declared that curcumin is safe[69,70] and well tolerated, even at the doses of 8 g/day for 3 months and 12 g/day for 3 to 4 month.[40,71-74]

F. Limitations of Curcumin

In spite of diverse pharmacological potential of curcumin, its use has some serious drawbacks, such as poor water solubility, limited physicochemical stability, low oral bioavailability, poor absorption from the gastrointestinal (GI) tract, rapid metabolism, short biological half-life, rapid clearance from the body, and degradation at alkaline pH, which decreases its bioavailability and absorption in the preintestinal region, leading to the reduction in the dose of the drug.[31,32,75,76]

III. CONCLUSION AND FUTURE PERSPECTIVES

Pharmaceutical chemists are diligently working to discover more therapeutic benefits and identify new pharmacological properties from naturally occurring plants. The studies mentioned in the previous sections highlight the significant role of curcumin to treat and even cure different diseases. In addition, the data presented here also indicate that the use of curcumin even at high doses for long periods of time is quite safe and nontoxic. There are also some major barriers (poor water solubility, limited physicochemical stability, low oral bioavailability, rapid metabolism, and short biological half-life) for the use of curcumin as an active and effective therapeutic component. So, more research is required to find ways to overcome these critical issues and limitations by utilizing an efficient drug delivery system. Overall, our review shows that curcumin has great pharmaceutical potential and scope. Studies may also be needed to determine ways to attain full benefits from curcumin using polymeric particulate systems for its efficient delivery to the target site and prolonged therapeutic effects.

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