

Phytochemistry, Applications and Patents of *Curcuma Longa* (Turmeric): A Comprehensive Review

Harshal Ashok Pawar*, Bhagyashree Sanjay Dhingra

Dr. L. H. Hiranandani College of Pharmacy,
Smt. CHM Campus, Opp. Ulhasnagar Railway Station,
Ulhasnagar-421003, Maharashtra, India. Contact No. +91-8097148638,

***Corresponding Author**

Email: harshal.dlhcop@gmail.com, harshal.pawar@dlhcop.org

ABSTRACT

Curcuma longa, commonly known as turmeric, has been utilized for centuries in traditional medicine for its diverse pharmacological properties. In recent years, extensive scientific research has shed light on its therapeutic potential, leading to its incorporation into pharmaceutical formulations. This review comprehensively examines the pharmaceutical applications of *Curcuma longa*, encompassing its anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective properties. The molecular mechanisms underlying these pharmacological effects are elucidated, along with insights into its bioavailability and safety profile. Moreover, the synergistic interactions of *Curcuma longa* with other drugs and its potential as a novel drug delivery system are explored. This review underscores the significance of *Curcuma longa* in modern pharmacotherapy and provides valuable insights for future research and development endeavors.

Key words: Turmeric, *Curcuma longa* Linn, Herbal medicine, pharmaceutical industry.

INTRODUCTION

Curcuma longa, belonging to the ginger family, is a perennial herbaceous plant native to South Asia. Renowned for its culinary versatility, it boasts a rich history within traditional medicine systems like Ayurveda and Traditional Chinese Medicine (TCM). The pharmacological properties of *Curcuma longa* are primarily attributed to its bioactive components, notably curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Over time, scientific inquiries have unveiled its potential therapeutic applications, leading to its incorporation into pharmaceutical formulations.

In recent years, there has been a notable surge in the global demand for ayurvedic medicinal formulations. Herbal drugs derived from plants are sought after for maintaining good health and treating diseases. Many pharmaceuticals used in allopathic medicine find their origins in medicinal plants. Turmeric, also known as Haridra, has been a staple spice and household remedy for centuries. Beyond its culinary uses, turmeric is extensively employed for medicinal purposes in various traditional Indian systems like Ayurveda, Unani, and Siddha medicines.

Curcuma longa Linn, belonging to the Zingiberaceae family, stands out as the highest yielding variety of turmeric with commercial value. Its origins trace back to South and Southeast Asia. India stands as the world's largest producer of turmeric, meeting 94% of the global demand. While India holds the central position in turmeric production, other Asian countries such as Bangladesh, Pakistan, Sri Lanka, Taiwan, China, Myanmar, and Indonesia

also cultivate this spice. Additionally, turmeric is grown in Caribbean and Latin American countries like Jamaica, Haiti, Costa Rica, Peru, and Brazil.

India primarily exports dried rhizomes of turmeric, which are further processed into various products for diverse end uses. International markets predominantly feature two types of turmeric: 'Madras' and 'Alleppey'. Both varieties are cultivated in India, with Alleppey turmeric being particularly favored in the United States for its higher content of volatile oils and curcumin. Conversely, the Madras type, with lower volatile oil and curcumin content, finds favor among British and Middle Eastern countries.

Curcumin, a key component of turmeric, finds applications in pharmaceuticals, food, cosmetics, and other industries such as dye-sensitized PV technology and textiles. Pharmaceutical applications account for the largest market share of curcumin, driven by the rising demand for curcumin-based supplements. These supplements, available over-the-counter without stringent regulations, hold significant market potential. Curcumin is utilized in the treatment of various conditions, including arthritis, Alzheimer's, gastric ailments, viral infections, and tumors. Major players in the curcumin market include Biomax Life Sciences Ltd., Synthite Industries Ltd., Hindustan Mint and Agro Products Pvt. Ltd., Arjuna Natural Extracts Ltd., and others. Herbal cosmetics and skincare products incorporating curcumin are popular under brands like Himalaya Herbals, Vicco, and Shahnaz Husain. [1-6]

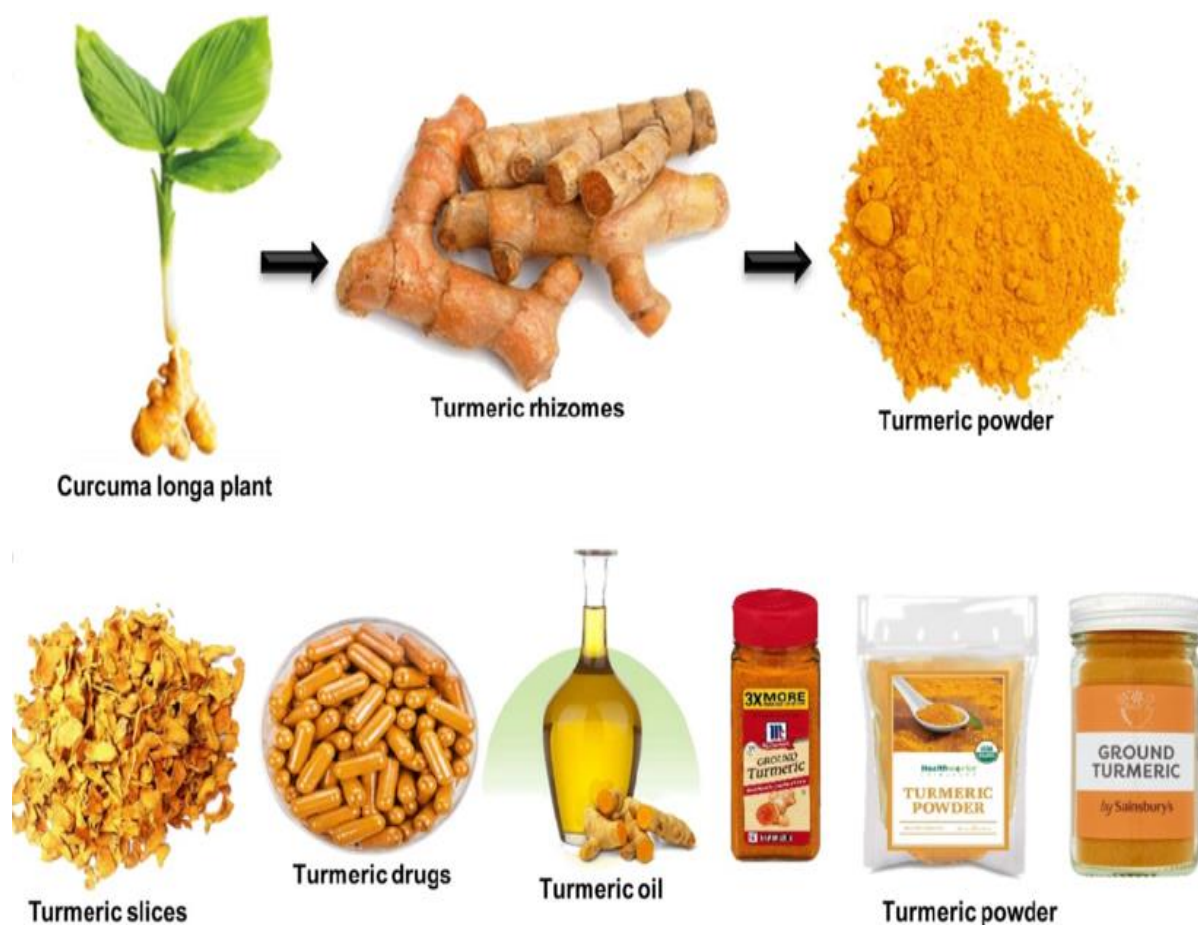


Fig. 1: Turmeric plant and its product

Phytochemistry of Turmeric

Turmeric, renowned for its vibrant yellow hue and diverse pharmacological effects, encompasses a rich chemistry comprising various phytoconstituents. In addition to the previously mentioned compounds, turmeric also contains essential nutrients and bioactive compounds:

a) Nutritional Composition:

- Protein: Turmeric contains approximately 6.3% protein, contributing to its nutritional value.
- Fat: With a fat content of around 5.1%, turmeric provides essential fatty acids.
- Minerals: Turmeric is a source of minerals, comprising approximately 3.5% of its composition.
- Carbohydrates: The carbohydrate content of turmeric is notably high, accounting for approximately 69.4%.
- Moisture: Turmeric contains about 13.1% moisture, affecting its texture and stability.

b) Essential Oil Composition:

- Turmeric's essential oil, obtained through steam distillation of its rhizomes, contains various compounds, including α -phellandrene, sabinene, cineol, borneol, zingiberene, and sesquiterpenes. These volatile compounds contribute to turmeric's characteristic aroma and potential therapeutic effects.

c) Curcuminoid contents:

- Curcumin, also known as diferuloylmethane, is the principal pigment responsible for turmeric's yellow coloration. It constitutes approximately 3-4% of turmeric's composition and is composed mainly of curcumin I (94%), curcumin II (6%), and curcumin III (0.3%). Additionally, demethoxy and bisdemethoxy derivatives of curcumin have been identified.
- Curcumin was first isolated in 1815, and its chemical structure was elucidated by Roughly and Whiting in 1973.

d) Physical and Chemical Properties:

- Curcumin exhibits a melting point range of 176–177°C and forms a reddish-brown salt with alkali. It is soluble in ethanol, alkali, ketone, acetic acid, and chloroform, facilitating its use in various applications. [7-9]

The nutritional value of turmeric is summarized in table-2 [10].

Table-2: Nutritional Value of Turmeric

Energy	354 Kcal	Folates	39 μ g
Carbohydrates	64.9 g	Niacin	5.140 mg
Protein	7.83 g	Pyridoxine	1.80 mg
Riboflavin	0.233 mg	Vitamin A	0 IU
Dietary Fiber	21 g	Vitamin C	25.9 mg
Iron	41.42 mg	Vitamin E	3.10 mg
Magnesium	193 mg	Vitamin K	13.4 μ g
Calcium	183 mg	Phosphorus	268 mg
Copper	603 μ g	Zinc	4.35 mg
Pyridoxin	1.80 mg	Total fat	9.88g

Source: USDA National Nutrient data base; Cited in www.nutrition-and-you.com

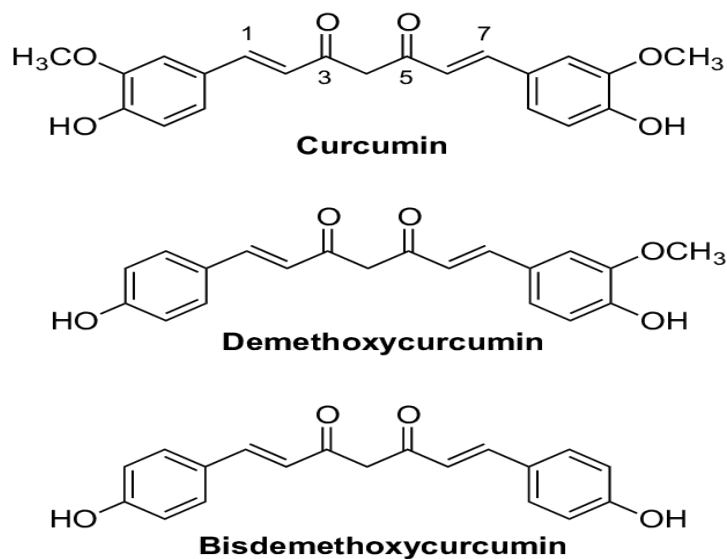


Fig. 2: Chemical structure of Curcumin

Commercial Products of *Curcuma Longa*

The diverse array of products derived from turmeric offers a range of culinary, medicinal, and industrial applications:

- a) **Dried Rhizomes:** Turmeric rhizomes, characterized by their highly branched, yellow to orange appearance, are available in various forms such as fingers, bulbs, and splits. Typically imported in dried form, these rhizomes undergo further processing into powder or oleoresin, catering to the needs of the food, confectionery, and pharmaceutical industries.
- b) **Turmeric Powder:** Turmeric powder, derived from dried rhizomes, serves as a staple ingredient in numerous cuisines. Widely utilized in curry powders and pastes, it lends both color and flavor to dishes in the food industry.
- c) **Curry Powder:** Turmeric holds a crucial position in curry powder formulations, with its content ranging from 10-15% to 30% depending on the blend. This spice blend enhances the flavor and aroma of various culinary creations.
- d) **Oleoresin:** Extracted through solvent extraction methods, turmeric oleoresin is a viscous orange/red liquid comprising curcuminoids, volatile oils, and non-volatile fatty and resinous materials. The curcuminoids and volatile oils are of particular interest, with potential applications in products where turmeric flavor is undesired, such as cheese, ice cream, beverages, and baked goods.
- e) **Essential Oil:** Turmeric essential oil, obtained via distillation or supercritical fluid extraction from powdered rhizomes, contains a multitude of molecules. Its primary constituents include sesquiterpene alcohol, zingeriberene, d- α -phellandrene, cineol, d-sabinene, d-borneol, and valeric acid. Known for its anti-inflammatory, antimicrobial, and antiviral properties, turmeric essential oil finds applications in aromatherapy, skincare, and natural remedies for various ailments.

The diverse products derived from turmeric underscore its versatility and widespread use across various industries, from culinary endeavors to pharmaceutical formulations and

beyond. Each product harnesses the unique properties of turmeric, contributing to its enduring popularity and utility in diverse contexts. [11-13]

Pharmaceutical and Medicinal Applications of Turmeric

Curcuminoids refer to three main chemical substances, namely curcumin, demethoxycurcumin,

and bis-demethoxycurcumin. These are used as natural coloring agents in some food products and have been reported to exhibit several biological activities in animal and human clinical studies. Some of the important therapeutic properties exhibited by turmeric due to presence of curcumin are summarized below:

- a) **Antioxidant:** Curcumin possesses free radical scavenging property and therefore act as a strong antioxidant. *Curcuma longa* possesses significant antioxidant properties, which play a crucial role in combating oxidative stress-induced damage. Curcumin scavenges free radicals and upregulates endogenous antioxidant enzymes, thereby enhancing cellular antioxidant defenses. Moreover, it chelates transition metal ions, preventing them from catalyzing oxidative reactions. The antioxidant capacity of *Curcuma longa* has been implicated in various pathological conditions, including cardiovascular diseases, neurodegenerative disorders, and cancer [14].
- b) **Anti-inflammatory:** *Curcuma longa* exhibits potent anti-inflammatory effects, attributed primarily to its ability to modulate various molecular pathways involved in inflammation. Curcumin, the principal bioactive constituent, inhibits the activity of pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), thereby attenuating the production of inflammatory mediators like prostaglandins and leukotrienes. Furthermore, curcumin suppresses the activation of transcription factors such as nuclear factor-kappa B (NF- κ B), which regulate the expression of pro-inflammatory genes. Several preclinical and clinical studies have demonstrated the efficacy of *Curcuma longa* in mitigating inflammatory conditions such as arthritis, inflammatory bowel disease (IBD), and dermatitis. Curcumin lowers the histamine level and stimulates the production of natural cortisone from adrenal glands. Thus it has a major role in reducing inflammation [15].
- c) **Hepatoprotective:** Turmeric is beneficial for its influence on the liver. In spring more consumption of herbs and foods can strengthen the liver. Turmeric shares similar liver protectant compounds that milk thistle and artichoke leaves contain. It protects the liver from a number of toxic compounds such as carbon tetrachloride, galactosamine, acetaminophen and *Aspergillus aflatoxin*. It can be useful to treat liver conditions such as hepatitis, cirrhosis, and jaundice. Studies have shown that turmeric can modulate the activity of liver enzymes involved in detoxification and metabolism, such as cytochrome P450 enzymes and glutathione S-transferases. By enhancing the liver's detoxification capacity, turmeric aids in the elimination of harmful toxins and promotes overall liver function. Liver fibrosis, characterized by the excessive accumulation of extracellular matrix proteins, is a common consequence of chronic liver injury. Curcumin has been found to inhibit hepatic stellate cell activation, a key process involved in liver fibrosis, thereby preventing the progression of fibrotic liver diseases. Turmeric has been shown to protect against various chemical-induced hepatotoxicity in animal studies. For example, curcumin supplementation has been found to attenuate liver damage caused by toxins such as carbon tetrachloride (CCl₄), acetaminophen, and alcohol. These hepatoprotective effects are attributed to curcumin's ability to mitigate oxidative stress, inflammation, and apoptosis in liver cells. Emerging evidence suggests that turmeric may possess chemopreventive properties against liver cancer (hepatocellular carcinoma). Curcumin

has been shown to inhibit the proliferation of liver cancer cells, induce apoptosis, and suppress tumor growth in animal models. These findings highlight turmeric's potential role in reducing the risk of liver cancer development. [16-20].

- d) **Anti-platelet aggregation:** Turmeric may be helpful in preventing the blockage of arteries that can gradually cause a heart attack or stroke in one of two ways. Turmeric makes cholesterol levels low and inhibits the oxidation of LDL (bad cholesterol). Oxidized LDL deposits in the walls of blood vessels and contributes to the formation of atherosclerotic plaque. Turmeric may also prevent platelet build up along the walls of an injured blood vessel. Platelets collecting at the site of a damaged blood vessel cause blood clots to form and blockage of the artery as well. Curcumin prevents clumping of platelets, which in turn improves blood circulation and may also help protect against atherosclerosis [21].
- e) **Antimicrobial Effects:** *Curcuma longa* exhibits broad-spectrum antimicrobial activity against bacteria, viruses, fungi, and parasites. Curcumin exerts antimicrobial effects through multiple mechanisms, including disruption of microbial cell membranes, inhibition of microbial enzymes, and modulation of microbial gene expression. Additionally, it potentiates the activity of conventional antibiotics, thereby overcoming antimicrobial resistance. The antimicrobial properties of *Curcuma longa* have therapeutic implications in the management of infectious diseases and wound healing.
- f) **Antimutagenic and Anticancer Activity:** Curcumin has been shown to suppress multiple signaling pathways and inhibit cell proliferation, invasion, metastasis, and angiogenesis. Turmeric also acts as an antimutagenic, as it potentially helps prevent new cancers that are caused by chemotherapy or radiation used to treat existing cancers. It effectively inhibits metastasis of melanoma cells [22, 23]. *Curcuma longa* demonstrates promising anticancer effects against various malignancies, including breast, prostate, colon, and pancreatic cancer. Curcumin inhibits tumor initiation, progression, and metastasis through modulation of multiple signaling pathways involved in cell proliferation, apoptosis, angiogenesis, and inflammation. Moreover, it sensitizes cancer cells to chemotherapy and radiotherapy, thereby enhancing treatment efficacy while reducing adverse effects. Clinical trials evaluating the anticancer efficacy of *Curcuma longa* are underway, highlighting its potential as an adjuvant therapy for cancer patients.
- g) **Neuroprotective Properties:** *Curcuma longa* exerts neuroprotective effects against neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Curcumin attenuates neuroinflammation, oxidative stress, and protein aggregation, which are hallmark features of neurodegeneration. Furthermore, it promotes neurogenesis and synaptic plasticity, thereby enhancing cognitive function and memory. Clinical studies have demonstrated the neuroprotective benefits of *Curcuma longa* supplementation in patients with cognitive impairment and neurodegenerative diseases. Turmeric, particularly its bioactive component curcumin, has garnered considerable attention for its potential neuroprotective properties. Here's an overview of its neuroprotective effects along with relevant references:
 - 1) **Antioxidant Activity:** Curcumin exhibits potent antioxidant properties, scavenging free radicals and reducing oxidative stress in the brain. This antioxidative action helps protect neurons from damage and degeneration [24, 25].
 - 2) **Anti-inflammatory Effects:** Chronic inflammation plays a significant role in neurodegenerative diseases. Curcumin's anti-inflammatory properties can help mitigate neuroinflammation, thereby preserving neuronal function and structure [26, 27].

- 3) **Neurogenesis Promotion:** Curcumin has been shown to stimulate neurogenesis, the process of generating new neurons, particularly in brain regions associated with learning and memory. This neurogenic effect may contribute to cognitive enhancement and neuroprotection [28, 29].
- 4) **Amyloid-Beta Clearance:** One hallmark of Alzheimer's disease is the accumulation of amyloid-beta plaques in the brain. Curcumin has been found to facilitate the clearance of amyloid-beta plaques, potentially slowing the progression of Alzheimer's disease [30, 31].
- 5) **Protection against Neurotoxicity:** Curcumin can protect neurons from various neurotoxic agents, including heavy metals, toxins, and oxidative stressors. Its neuroprotective effects help maintain neuronal viability and function [32, 33].
- 6) **Regulation of Neurotrophic Factors:** Curcumin modulates the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which play crucial roles in neuronal survival, growth, and synaptic plasticity [34, 35].

Curcumin, the primary active compound in turmeric, demonstrates potential HIV inhibition in laboratory experiments, though clinical trials are necessary to ascertain its efficacy in treating humans with the condition [36, 37]. Incorporating turmeric into the diet may alleviate pain associated with arthritis, bursitis, and tendonitis [38]. Furthermore, turmeric consumption enhances the production of enzymes responsible for fat and sugar digestion while also preventing the formation of cholesterol gallstones, thereby aiding individuals with indigestion; however, its efficacy falls short compared to antacids [39, 40]. Additionally, curcumin holds promise as a treatment for uveitis, potentially matching the effectiveness of corticosteroids in managing this type of eye inflammation [41].

Curcumin is poorly absorbed as a standard ingredient. Its bioavailability is limited due to poor solubility, low rate of absorption from the gut, short half-life with rapid metabolism and rapid systemic elimination. Drug delivery systems such as nanoparticles, liposomes, microemulsions, and polymeric implantable devices are emerging as one of the viable alternatives that have been shown to deliver therapeutic concentrations of various potent chemopreventives such as curcumin into the systemic circulation.

Biopiracy & Patents of Turmeric

The Turmeric Patent Battle unfolded as a contentious clash over the rightful ownership of traditional knowledge. In October 1996, the Indian Council for Scientific and Industrial Research (CSIR) initiated a re-examination claim with the US Patent and Trademark Office (USPTO) against patent application no. 5401540. The patent, which aimed to patent the healing properties of turmeric powder, was challenged on grounds of lacking novelty, as turmeric had long been utilized in India for wound healing and other medicinal purposes. CSIR's legal challenge, supported by evidence of turmeric's traditional use in India, aimed to establish turmeric powder as 'prior art,' contending it was not a new discovery by the US patentee. Despite turmeric's entrenched role in Indian households, finding published literature as concrete evidence proved challenging. However, extensive research uncovered 32 references in Sanskrit, Urdu, Hindi, and a 1953 paper by the Indian Medical Association, bolstering the claim. The patent's inventors argued for the distinctiveness of powdered turmeric compared to paste, citing differences in bioavailability and absorbability. They also highlighted the practice of consuming turmeric with honey, known for its healing properties. Nevertheless, in 1997, USPTO rejected all six claims, declaring the patent invalid due to

obviousness and acknowledging turmeric's historical use in wound healing. Following a year-long legal battle, USPTO withdrew the patent on August 13th, yielding to India's persistent efforts supported by scientific publications, home remedy books, and Ayurvedic texts. The victory marked a significant milestone, showcasing a developing country's successful challenge against biopiracy. In 1998, with the issuance of a re-examination certificate, the case concluded, safeguarding India's traditional knowledge in the Turmeric Patent dispute—an essential step in combatting biopiracy. [42-51]

Turmeric and its active component curcumin have attracted significant interest in the field of patents, with numerous inventions aimed at harnessing their therapeutic potential. Below is a summary of some patents related to turmeric and its products:

- 1) US Patent No. 3340250 A: Filed in the United States, this patent focuses on extracting values from turmeric. The assignee or applicant is Griffith Laboratories.
- 2) US Patent No. 7763289 B2: This patent, also filed in the United States, pertains to topical turmeric skin care products. The applicant is JoAl's Products, LLC.
- 3) WO Patent No. 2011082290 A3: This international patent involves formulations derived from natural products, including turmeric, and aspirin. The applicant is Organomed Corporation.
- 4) WO Patent No. 2010023128 A1: Another international patent, this one relates to turmeric curcumin compositions with low residual solvent. The applicant is Chr. Hansen A/S.
- 5) WO Patent No. 2013004740 A1: This patent highlights the anticonvulsant activity of turmeric oil and bisabolene sesquiterpenoids. The applicant is Katholieke Universiteit Leuven.
- 6) US Patent No. 4163803 A: Filed in the United States, this patent involves a turmeric coloring process and composition for foods and beverages. The applicant is Goldscher Kenneth J.
- 7) US Patent No. 8895087 B2: This patent focuses on a composition to enhance the bioavailability of curcumin. The applicant is Arjuna Natural Extracts, Ltd.
- 8) EP Patent No. 1837030A1: Filed in Europe, this patent pertains to phospholipid complexes of curcumin with improved bioavailability. The applicant is INDENA S.p.A.
- 9) Indian Patent No. 971/MUM/2004: This patent involves a process for the recovery of pure curcumins from turmeric rhizomes. The applicant is Godavari Sugar Mills Ltd.
- 10) Indian Patent No. 2574/MUM/2015: This patent relates to compositions containing nano size phospholipid-curcumin complexes and the process for their preparation. The applicants are Harshal Ashok Pawar and Bhagyashree Bhangale.

CONCLUSION

The pharmaceutical applications of *Curcuma longa* continue to garner interest in the scientific community, with ongoing research focusing on elucidating its mechanisms of action, optimizing formulations, and exploring synergistic interactions with conventional drugs. Moreover, the development of novel drug delivery systems utilizing *Curcuma longa* holds promise for enhancing therapeutic outcomes and overcoming bioavailability limitations. Future clinical trials are warranted to establish its efficacy in diverse therapeutic indications and validate its potential as a mainstream pharmaceutical agent.

In conclusion, *Curcuma longa* emerges as a versatile botanical remedy with immense pharmaceutical potential, encompassing anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective properties. Its integration into modern pharmacotherapy represents a paradigm shift towards evidence-based utilization of traditional medicine.

However, further research is essential to unlock its full therapeutic repertoire and harness its benefits for improving human health.

REFERENCES

- 1) ASTA. A concise guide to spices, herbs, seeds, and Extractives. American Spice Trade Association. 2002; 48-50.
- 2) Lauro, B.G.J. (edited), F. Jack Francis. Natural food colorants science and technology. New York: Marcel Dekker; 2000.
- 3) Turmeric FAO. Post-production Management Organization. Food and Agriculture Organization of the United Nations (FAO), AGST. Prepared by Anne Plotto. Edited by François Mazaud, Alexandra Röttger. Katja Steffel; 2004.
- 4) Weiss EA. Spice Crops. CAB. International Publishing, Oxon, UK; 2002.
- 5) Aggarwal, B. B., Yuan, W., Li, S., Gupta, S. C., & Kumar, A. (2013). Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. *Molecular nutrition & food research*, 57(9), 1529-1542.
- 6) Prasad, S., & Aggarwal, B. B. (2011). Turmeric, the golden spice: From traditional medicine to modern medicine. *Herbal medicine: Biomolecular and clinical aspects*, 2, 263-288.
- 7) Prashar D, Khokra SL, Purohit R, Sharma S. Curcumin: A Potential Bioactive. *Agent, RJPBCS*; 2(4):2011-44.
- 8) A. J. Ruby, G. Kuttan, K. Dinesh Babu, K. N. Rajasekharan, and R. Kuttan, "Anti-tumour and antioxidant activity of natural curcuminoids," *Cancer Letters*, vol. 94, no. 1, pp. 79–83, 1995.
- 9) Roughley PJ, Whiting DA J. *Chem Soc*. 1973; 20:2379-2388.
- 10) Harjeet Singh et al., *International Journal of Nutrition and Agriculture Research*. 1(1), 2014, 68 – 71.
- 11) Nwaekpe J, Anyaegbunam H, Okoye B, Asumugha G. Promotion of Turmeric for the Food/Pharmaceutical Industry in Nigeria. *AJEA* 2015 Jan; 8(6):335-341.
- 12) Gopalan B, Goto M, Kodama A, Hirose T., Supercritical carbon dioxide extraction of turmeric (*Curcuma longa*). *J. Agric. Food Chem*. 2000; 48:2189-2192.
- 13) Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS journal*, 15(1), 195-218.
- 14) Ramirez Bosca A, Soler A, Gutierrez MA. Antioxidant curcuma extracts decrease the blood lipid peroxide levels of human subjects. *Age* 1995; 18:167-9.
- 15) Ammon HPT, Safayhi H, Mack T, Sabieraj J. Mechanism of antiinflammatory actions of curcumine and boswellic acids. *J Ethnopharmacol* 1993; 38(2-3):105-112.
- 16) Deshpande UR, Gadre SG. Raste AS. Protective effect of turmeric (*Curcuma longa* L.) extract on carbon tetrachloride-induced liver damage in rats. *Indian J Exp Biol* 1998; 36(6):573-577.
- 17) Park EJ, Jeon CH, Ko G, Kim J, Sohn DH. Protective Effect of Curcumin in Rat Liver Injury Induced by Carbon Tetrachloride. *Journal of Pharmacy and Pharmacology* 2000; 52(4):437-440.
- 18) Kiso Y, Suzuki Y, Watanabe N, Oshima Y, Hikino H. Antihepatotoxic principles of *Curcuma longa* rhizomes. *Planta Med*. 1983; 49:185–87.
- 19) Donatus IA, Sardjoko, Vermeulen NP. Cytotoxic and cytoprotective activities of curcumin. Effects on paracetamol-induced cytotoxicity, lipid peroxidation and glutathione depletion in rat hepatocytes. *Biochem Pharmacol*. 1990; 39:1869–75.

- 20) Soni KB, Rajan A, Kuttan R. Reversal of aflatoxin induced liver damage by turmeric and curcumin. *Cancer Lett.* 1992; 66:115–21.
- 21) Srivastava R, Puri V, Srimal RC, Dhawan BN. Effect of curcumin on platelet aggregation and vascular prostacyclin synthesis. *Arzneimittelforschung* 1986; 36:715-7.
- 22) Mehta K, Pantazis P, McQueen T, Aggarwal BB. Antiproliferative effect of curcumin (diferuloylmethane) against human breast tumor cell line. *Anticancer Drugs* 1997; 8:470-81.
- 23) Menon LG, Kuttan R, Kuttan G. Anti-metastatic activity of curcumin and catechin. *Cancer Lett* 1999; 141(1-2):159-165.
- 24) J. P. Lim, A. M. Gleeson, and M. A. K. Cheema, "Antioxidant and prooxidant activities of curcumin derivatives depend on their chemical structure," *Free Radical Biology and Medicine*, vol. 53, no. 2, pp. 383–389, 2012.
- 25) A. K. Tiwari et al., "Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/ β -catenin pathway," *ACS Nano*, vol. 11, no. 11, pp. 10405–10418, 2017.
- 26) C. A. Toscano and A. P. R. Guilarte, "Lead neurotoxicity: from exposure to molecular effects," *Brain Research Reviews*, vol. 49, no. 3, pp. 529–554, 2005.
- 27) M. K. Ahuja et al., "Attenuation of neurobehavioral and neurochemical abnormalities in animal model of cognitive deficits of Alzheimer's disease by fermented soybean nanonutraceutical," *Journal of Neurochemistry*, vol. 126, no. 3, pp. 313–331, 2013.
- 28) N. M. Babu and D. S. Nair, "Neuroprotection by Curcumin in Alzheimer's Disease: A Review," in *Alzheimer's Disease*, IntechOpen, 2020.
- 29) H. Kim et al., "Neuroprotective effects of PEP-1-carbonyl reductase 1 against oxidative stress-induced ischemic neuronal cell damage," *Free Radical Biology and Medicine*, vol. 41, no. 1, pp. 116–129, 2006.
- 30) M. B. Hafez et al., "Neuroprotective effect of curcumin-loaded lactoferrin nano particles against rotenone induced neurotoxicity," *Neurochemical Research*, vol. 39, no. 8, pp. 1537–1548, 2014.
- 31) S. Hu et al., "Curcumin induces neuroprotection, improves cognitive function, and attenuates tau hyperphosphorylation and neuropathology in a 3xTg-AD mouse model," *Neurochemistry International*, vol. 79, pp. 66–74, 2014.
- 32) A. B. Kunnumakkara et al., "Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases," *British Journal of Pharmacology*, vol. 174, no. 11, pp. 1325–1348, 2017.
- 33) S. Balaji S et al., "The neuroprotective role of curcumin in myocardial infarction," *Life Sciences*, vol. 233, p. 116750, 2019.
- 34) R. C. Gupta et al., "Cytotoxicity and apoptosis induction by curcumin in human malignant glioma cells," *Brain Research*, vol. 19, no. 2, pp. 300–313, 2003.
- 35) P. Mathew and S. B. Augustine, "Design of Curcumin Analogs and Their Anticancer Potential," in *Anticancer Plants: Properties and Application*, Springer, 2020.
- 36) Mazumder A, Raghavan K, Weinstein J, Kohn KW, Pommier Y. Inhibition of human immunodeficiency virus type-I integrase by curcumin. *Biochem Pharmacol* 1995; 49:1165-70.
- 37) Barthelemy S, Vergnes L, Moynier M, Guyot D, Labidalle S, Bahraoui E. Curcumin and curcumin derivatives inhibit Tat-mediated transactivation of type 1 human immunodeficiency virus long terminal repeat. *Res Virol* 1998; 149(1):43-52.
- 38) Deodhar SD, Sethi R, Srimal RC. Preliminary studies on antirheumatic activity of curcumin (diferuloyl methane). *Indian J Med Res* 1980.

- 39) Thamlikitkul V, Bunyapraphatsara N, Dechatiwongse T, Theerapong S, Chantrakul C, Thanaveerasuwan T, et al . Randomized double-blind study of *Curcuma domestica* Val for dyspepsia. *J Med Assoc Thai* 1989; 72(11):613-620.
- 40) Kositchaiwat C, Kositchaiwat S, Havanondha J. *Curcuma longa* Linn. In the treatment of gastric ulcer comparison to liquid antacid: a controlled clinical trial. *J Med Assoc Thai* 1993; 76(11):601-605.
- 41) Lal B, Kapoor AK, Asthana OP, Agrawal PK, Prasad R, Kumar P. Efficacy of curcumin in the management of chronic anterior uveitis. *Phytotherapy Res* 1999; 13(4):318-322.
- 42) Tyler VE. Herbal medicine: From the past to the future. *Public Health Nutrition*. 2000;3(Suppl. 4a):447–452.
- 43) Schulz V, Hänsel R, Tyler VE. *Rational Phytotherapy. A Physician's Guide to Herbal Medicine*. 4th Edition. Berlin: Springer-Verlag; 2001.
- 44) Tarunika J, Tamilselvi J. Traditional knowledge and patent issues in India. *International Journal of Pure and Applied Mathematics*. 2018;119(17):1249-1264.
- 45) Bruchac M. Indigenous knowledge and traditional knowledge. In: Smith C, editor. *Encyclopedia of global archaeology*. New York: Springer; 2014. p. 3814-3824.
- 46) Vansina J. *Oral tradition as history*. Madison, WI: University of Wisconsin Press; 1985.
- 47) Thakur R, Puri HS, Husain A. *Major medicinal plants of India*. Lucknow: Central Institute of Medicinal and Aromatic Plants; 1989.
- 48) Kumar S. India wins battle with USA over turmeric patent. *The Lancet*. 1997;350(9079):724. DOI: 10.1038/37838.
- 49) Jayaraman K. US patent office withdraws patent on Indian herb. *Nature*. 1997;389(6). DOI: 10.1038/37838.
- 50) Hellerer U, Jarayaman K. Greens persuade Europe to revoke patent on neem tree. *Nature*. 2000; 405:266–267.
- 51) World Intellectual Property Organization. *Documenting Traditional Knowledge – A Toolkit*. Geneva: WIPO; 2017.