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## A review on selected pharmacological activities of *Curcuma longa* L.

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### ABSTRACT

Spices have long been a part of human diets and commerce. Since the birth of human civilization, medicinal plants have yielded a wealth of information on treating and preventing illness. Still, the growing understanding of the connection between nutrition and health in the food business has increased its relevance and piqued researchers' interest in deciphering the mechanisms of the action of spices and the plethora of beneficial properties attributed to them. Turmeric is one of the most important spices due to its active biochemical activities. Anti-inflammatory, antioxidant, antibacterial, and hypoglycemic qualities and the ability to promote wound healing and reduce sensitivity to chemotherapy and radiation have been revealed in curcumin. Several human disorders, including fibrosis, lupus nephritis, acne, cancer, diabetes, and irritable bowel syndrome, have been tested in clinics. Consequently, an herb used solely in the kitchen is now used in the clinic. New technologies are being tried in the drug development process to increase the bioavailability of curcumin, such as additives, micelles, nanoparticles, liposomes, and phospholipid complexes. Curcuminoids and other compounds associated with turmeric were examined to learn more about their biological effects and potential applications. Curcumin (diferuloylmethane), a flavonoid, and many volatile oils, including turmerone, atlantone, and zingiberone, are the active ingredients in turmeric. Inhibiting carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor development, curcumin's capacity Turmeric's medical and pharmacological advantages in illness prevention and therapy are the subject of this study. The present study deals with the importance of extensive pharmacological activities of turmeric and its role in the medical industry in creating novel medicines to treat various diseases.

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## Introduction

After an exhaustive review of the literature, *C. longa* is widely recognized as a panacea in herbal medicine, having a wide range of pharmacological effects (Table 1). *Curcuma longa*, often known as turmeric, is an annual herb with a small stem and large oblong leaves with oval, elliptical, or pyriform rhizomes, occasionally branchy and brownish-yellow. In Asia, namely India and China, it is widely cultivated. Turmeric is the component in which the distinctive yellow color of curry powder originates from dried turmeric. Arab globe Curcuma, Indian saffron or Haridra in Sanskrit, Ayurvedic, Chinese yellow ginger Jianghuang, Japanese Kyoo, or Ukon are only a few names.<sup>[1]</sup> For over 4 000 years, turmeric has been utilized in India, dating back to the Vedic culture. It is commonly used in Siddha, Ayurveda, and Unani as home therapy for various ailments. A South-East Asian native, turmeric is utilized in Asian nations such as China, Bangladesh, and Southeast Asia as a food ingredient (spice),

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preservative, and coloring substance. It is grown predominantly in China, Bangladesh, Taiwan, Myanmar, Sri Lanka, Nigeria, Jamaica, the West Indies, Australia, Peru, and the other Caribbean and Latin American nations. India is the world's top turmeric grower and accounts for around 78% of world output. It is also the world's largest turmeric user and exporter.<sup>[2]</sup> This herb is considered lucky and is utilized in religious rituals. It is often used in traditional Hindu medicine to alleviate sprains and edema induced by injury.

Turmeric is called 'Haridra' also known as 'Haldi' includes protein, fat, minerals, carbs, and moisture. Sesquiterpenes, zingiberene,  $\alpha$ -phellandrene, cineol, sabinene, and borneol are all present in the 5–8% essential oil generated by the rhizomes steam distillations.<sup>[3]</sup> Curcumin is turmeric's main curcuminoid. The two others are desmethoxycurcumin and bisdemethoxycurcumin. Turmeric's color comes from curcumin and is now known to have the highest medicinal benefits. 2–5% of turmeric is thought to be curcumin. The most presently accessible curcumin formulation includes diferuloylmethane (77%), desmethoxycurcumin (18%), and curcumin bisdemethoxy (5%). The absorption rate is 425 nm maximum. Turmeric/curcumin turns from yellow to deep red when exposed to acid.<sup>[4]</sup> Standardized therapeutic extracts (STES) or tiny therapeutic compounds (STMS) may be made from the plant. Curcumin is the most widely used spice in Indian cuisine, and the country produces over 90% of all the turmeric used globally. Approximately 70 cultivars or variations of *C. longa* are grown in India, and some of the most significant regional trade varieties of turmeric include Rajapuri, Duggirala, Berhampur, Erode, Nizamad, Koraput, and Kasturi, among others. The tourism industry has two main categories in the international market. The Alleppey Turmeric orange-yellow flesh is most significant in the USA, where users like to be spicy and food-colored. Curcumin Alleppey includes volatile oils (3.05–5.5%) and curcumin (4–7%). In comparison, volatile oils (2%) and curcumin (2%) are present in the Madras variety. The Madras variety turmeric has an intense, luminous, and brighter yellow color favored by the British and Middle East markets and is used as a mustard paste, curry paste, or other pastes in many cuisines. Bengal Type is a favorite for dyes in India. Interestingly, in the US, Turmeric is seen by the food business as a spice, but the FDA has categorized it as a food coloring product. Exports to the majority of the customers are made mainly by India. Approximately 65% of Indian turmeric exports come from the UK, US, Bangladesh, UAE, Japan, Malaysia, and Sri Lanka.<sup>[5]</sup>

Curcuminoids from turmeric and their derivatives have been extensively studied over the past century in many preclinical cell cultures and animal studies to exhibit substantial biological action. A wide range of beneficial effects has been demonstrated, including antioxidant and anti-cancer properties, antimicrobial properties, cardioprotective and neuroprotective properties, and anti-tumor properties. They have also been shown to have anti-inflammatory, anti-acidogenic, and radioprotective properties and anti-angiogenic, anti-diabetic, anti-allergy, and anti-protozoal effects in sexually transmitted infections. According to several clinical investigations, curcuminoids may have therapeutic promise in various chronic conditions, including colon cancer, lung cancer, breast cancer, and inflammatory bowel disorders. According to epidemiological findings, turmeric intake may lower the incidence of several types of cancer and have other beneficial biological effects in humans. Several molecular pathways are emerging from extensive epidemiological, clinical, and animal investigations to explain the diverse physical impacts of curcumin. Curcumin's biological effects have been studied extensively in vitro and in vivo, and the findings presented here synthesize the most important findings. Even though crude leaf extracts have been used for medicinal purposes since antiquity, contemporary medications may be generated after thorough research into the plant's bioactivity, mechanism of action, pharmacotherapeutics, and toxicity following adequate standardization and clinical trials. The creation of modern pharmaceuticals from *C. longa* to manage different illnesses should be stressed. The worldwide situation presently changes toward using nontoxic plant products with traditional therapeutic value. For the benefit of humanity, more investigation is needed into *C. longa* to uncover its hidden regions and practical medicinal uses.

**Table 1.** Efficacy of turmeric in different pharmacological activities[122–130].

Pharmacological Activity	Disease Model	Turmeric Extracts	Investigated on	Major Finding
Antioxidant, Immunomodulatory Activity	Rat Adjuvant Arthritis	Standard, CurQfen	Serum interleukins IL-17 and IL-1 $\beta$ , blood indices, joint swelling, histological changes in the liver, joints, body weight.	Both turmeric extracts reduced blood parameters, lowered pro-inflammatory cytokines, and boosted antioxidant levels. Both sections decreased edema and restored histological structure in soft periarticular tissues, synovial membrane, and hyaline cartilage. In terms of efficacy, CurQfen was superior to Standard extract.
Antioxidant Activity	Wistar rats	Turmeric root extract	Animals received Doxorubicin (DOX); DOX and turmeric; DOX and vitamin C; DOX and vitamin E; DOX, vitamins C and Turmeric; DOX, vitamin E and turmeric; DOX, vitamin C and vitamin E; DOX, vitamin C, and turmeric.	The formation of free radicals or ROS by DOX increases oxidative stress, which inhibits the activity of endogenous antioxidants, resulting in a reduction in the system's overall antioxidant state. In combination, turmeric root extract vitamins C and E treat all these symptoms individually.
Antioxidant Activity	Zebrafish models	Water extract of Turmeric Leaf (TLE)	Vero cells were treated with H <sub>2</sub> O <sub>2</sub> or TLE, and ROS production and the percentage of cells in the G <sub>1</sub> phase were assessed.	We observed a substantial drop in the percentage of cells in their sub-G <sub>1</sub> phase when TLE was administered at higher doses. A TLE therapy also reduced ROS production and lipid peroxidation in the H <sub>2</sub> O <sub>2</sub> -treated zebrafish model.
Antibacterial Activity	<i>M. gallisepticum</i> and <i>Escherichia coli</i> ( <i>E. coli</i> ) infected chicken	Turmeric nanoparticle	A mixture of extract nanoparticles and bacteria was administered to hens on various days of infection.	Clinical symptoms and gross pathology alterations improved due to increasing body weight and performance in vivo studies.
Immunomodulatory Activity	Healthy albino mice	Nanoparticulate curcumin	After sensitizing the mice with SRBCs from sheep, varied dosages of free and nanoparticulate curcumin were delivered orally to the healthy albino mice.	The immunological response induced by nanoparticulate curcumin was more robust early on. Curcumin nanoparticles encased in poly d, l-lactic-co-glycolic acid might boost the bioavailability of curcumin for better immunity.

(Continued)

**Table 1.** (Continued).

Pharmacological Activity	Disease Model	Turmeric Extracts	Investigated on	Major Finding
Anti-cancerous Activity	Female nude mice	Supercritical Turmeric Oil Extract (SCTOE) NBFR-03	HeLa, SiHa, and ME180 cervical cancer cell lines were in vitro cytotoxic, utilizing the Sulforhodamine B method.	The extract did not affect any cell lines compared to the positive control. In mice pre-treated with NBFR-03, NBFR-03 turmeric oil extract exhibited excellent results.
Immunomodulatory Activity	Immunosuppressed rat model	Nanocurcumin	Nanocurcumin's immunoenhancing and anti-inflammatory effects.	Nanocurcumin might be employed as an immunomodulatory agent in rats that have been given Cyclophosphamide (CP), a drug that has been linked to immunodepression.
Antiviral Activity	Human hepatoma cells Huh7	Curcumin chitosan (CuCs) nanocomposite	Western blot analysis of samples for anti-HCV-4a activity was performed.	Compared to curcumin alone, the CuCs nanocomposite suppressed the entrance and replication of Hepatitis C virus genotype 4a (HCV-4a), showing its potential as an effective treatment agent.
Anti-inflammatory Activity	RAW macrophage cells and carrageenan-stimulated inflammatory rat model	Regular turmeric extract	Pro-inflammatory cytokines, tumor necrosis factor (TNF-), nitric oxide (NO) scavenging, lipoxygenase inhibitory activities, and critical inflammatory mediators including cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS) were inhibited in RAW macrophage cells.	REVERC3 (Bisdemethoxy-Curcumin) demonstrated potential anti-inflammatory efficacy by reducing carrageenan-induced paw edema. Compared to turmeric extract, REVERC3 was more effective in reducing inflammation.

## Pharmacological activities

Whether as powder, extract, or an isolated compound, turmeric has been shown in studies to have a broad range of pharmacological activity with few adverse effects. Curcumin's methoxy group on the phenyl ring, phenolic, and 1, 3-diketone systems play a significant part in its diverse pharmacological effects. There are several curcumins or turmeric-enriched products for various ailments in both domestic and international markets. Unlike other phyto-antioxidants, curcumin is harmless, nontoxic, and a powerful natural component (Table 2). This is what gives curcumin its wide range of biological effects. Turmeric has been utilized as anti-inflammatory medication in Chinese and Indian medicine for a long time. It has a remarkable capacity to heal wounds. Turmeric extract also reduced the generation of aflatoxin by 90%, in addition to its involvement in correcting biliary hyperplasia, fatty alterations, necrosis, and biliary necrosis. Oral administration of curcumin effectively treats diabetes, cancer, gastrointestinal problems, and neurological ailments. Curcumin may also be applied to the skin to alleviate the symptoms of inflammatory skin disorders and allergies by reducing inflammation and irritation. Turmeric has many pharmacological activities; some of the activities are described in the following sections.

**Table 2.** Turmeric extract showing different activities.

Plant Species	Biological Activities	Turmeric Extract
<i>Curcuma longa</i>	Antioxidant Activity	Ethanollic Extract
		Methanollic Extract
		n-butanol extract
		Aqueous Extract
		Fat-Soluble Extract
	Antibacterial Activity	Ethanollic Extract
		Aqueous Extract
		Methanollic Extract
		Ethyl Acetate Extract
		Chloroform Extract
	Antifungal Activity	Methanollic Extract
		Chloroform Extract
		Ethanollic Extract
		Aqueous Extract
		Ethyl Acetate Extract
	Anti-inflammatory	Oil-Free Aqueous Extract
		Ethanollic Extract
Hexane Extract		
Ethyl Acetate Extract		
Supercritical carbon dioxide extract		
Volatile Oil		
Petroleum Ether Extract		
Anti-Cancerous Activity	Ethanollic Extract	
	n-hexane Extract	
Immunomodulatory Activity	Ethanollic Extract	
Antiviral Activity	Methanollic Extract	

### **Antioxidant activity**

Turmeric, its principal constituent, is often considered the most potent antioxidant known. Turmeric and its curcumin component's water and fat-soluble extracts have antioxidant activity equivalent to vitamins C and E. Hepatoprotective effects are primarily attributable to turmeric's capacity to reduce pro-inflammatory cytokines production. Curcumin protects cells in the body from free radical damage by lowering their oxygen content. Demethoxycurcumin and bisdemethoxycurcumin are less effective than pure curcumin for scavenging superoxide anion. It reduces the risk of heart disease, glaucoma, cataracts, high blood pressure, macular degeneration, and high cholesterol. Ryudai gold (RD) turmeric contains a high concentration of phenolic and flavonoids and has intense scavenging action.<sup>[6]</sup> The curcuminoid concentration rises when the extraction temperature is raised right, boosting antioxidant activity. For strong antioxidant properties, 90°C is maintained for 60 minutes. Extreme heat treatment resulted in a decrease in curcuminoids content and antioxidant activity.<sup>[7]</sup> Red blood cells and lipids are protected against hydrogen peroxide-induced peroxidation of turmeric extract. Toxic metabolite binding to DNA is inhibited, and oxidative damage is prevented. Pro-oxidant curcumin is a powerful bioprotectant with a wide variety of therapeutic uses in the presence of transition metal ions (Cu and Fe). ROS, such as superoxide anion, hydroxyl radical, singlet oxygen, peroxyxynitrite, and nitric oxide, are all successfully neutralized by this treatment.<sup>[8]</sup> Turmeric peels are more phenolic than powder form. When combined with ginger peels, it shows a rich phenolic content. As a result, the antioxidant activity of peels is greater than that of the commercial powder version. Its peels contain a large number of well-reserved phytochemicals with antioxidant properties.<sup>[9]</sup> Turmeric of Bangladeshi origin Chittagong's mura ethanolic extract has high polyphenols, flavonoids, and ascorbic acid levels, while chora extract has high yields. Khulna's mura ethanolic extract has DPPH solid radical-scavenging activity, while Khulna's chora has a high FRAP (Ferric reducing antioxidant power) value. Therefore, it is determined that turmeric ethanol extract has a more significant antioxidant effect than the aqueous turmeric extract that protects free radicals against damage.<sup>[10]</sup>

Many chronic health issues, including cardiovascular and inflammatory disease, cataracts, and cancer, are linked to free radical damage. Antioxidants protect tissues from free radical-induced tissue damage by inhibiting radical synthesis, scavenging radicals, or hastening their breakdown. Drugs may be harmful because they convert into free radicals or influence FR production. FR may also be caused by pollutants, chemicals, pesticides, etc., in food. According to a new study, synthetic antioxidants may be harmful to human health. Natural substances with antioxidative action have been more sought after in recent years. People who do not access expensive Western medical systems benefit significantly from newer methods that combine traditional health concepts with collaborative research and current technologies. TEL's antioxidant and inhibitory effects (turmeric extract loaded nanoliposomes) have been substantially more significant than those of free turmeric extract. It has helped develop nanocarriers for food function.<sup>[11]</sup> Tumor exhibits the most significant levels of DPPH and FRAP in Turmeric, torch ginger, curry leaf, and lemongrass. Turmeric, torch ginger, and lemon herb utilize acetone (80%) as a solvent in extracting phenolic components.<sup>[12]</sup> In an environmentally acceptable and practical approach, silver nanoparticles may be removed using turmeric oil. These nanoparticles are a potent antioxidant utilized in medicinal products for cancer, dermatitis, AIDS, and excessive cholesterol levels.<sup>[13]</sup> The use of the electron spin-resonance spin-trapping technique against radical superoxide anion ( $O_2^-$ ) *C longa* rhizomes water and methanol extract exhibit antioxidant properties. The activity of ripe turmeric rhizome extracts is greater than that of young rhizome extracts.<sup>[14]</sup> The DPPH test and ferric reduction of power technique and compared to antioxidant BHA were used for black pepper, ginger, turmeric, and cinnamon antioxidants activity. It indicates a higher phenol content for cinnamon methanol extract, resulting in an increased antioxidant potential and a turmeric chloroform extract.<sup>[15]</sup>

Turmeric is suitable for the preparation of nanofibers (NF). Several research areas, including pharmaceuticals, active biological species, food industry components, and other sites, may benefit from the potent antioxidant activity of turmeric-based TNF (Turmeric Nanofibers).<sup>[16]</sup> The relative value and antioxidant activity of turmeric rhizome meal were analyzed and revealed that more of the total phenolic components were present, improving the efficient functioning of the tumor rhizome meal.<sup>[17]</sup> The illness can be increased by increasing free radicals generated by the pollution of the air. Bo.Ci.Cl.D1 and Bo.Ci.Cl.D2 are isolated codes of endophytic fungal extract, coded based on morphological character showing antioxidant properties. Bo.Ci.Cl.D1 extract has a higher phenol-flavonoid concentration and a more potent antioxidant property than Bo.Ci.Cl.D2 extract.<sup>[18]</sup> Rather than turmeric powder and ginger powder, turmeric ginger powder was rich in the total amount of phenol and flavonoid components. Antioxidant activity was shown to be greater in turmeric ginger powder. TGP (turmeric and ginger powder) was shown to have a greater capacity to quench DPPH radicals than TP (Turmeric Powder) and GP (Ginger Powder) (ginger powder).<sup>[19]</sup> 2, 2-diphenyl-picrylhydrazyl and 2, 2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) analyzed the effects of curcumin-rich antioxidant fillets, which were discovered to be ineffective when they were treated with the low-fat content of fish and low-curcuminoids turmeric extract.<sup>[20]</sup>

Anti-oxidant Activity of Gold nanoparticles (TuAuNps) derived from turmeric had a strong anti-oxidant, anti-inflammatory, and antibacterial effect on oral pathogens compared to their standard of comparison. The addition of phytochemicals enhances TuAuNps' biological activity. As a result, this newer turmeric nano-formulation has advantages over conventional synthetic drugs in treating oral mucositis, with fewer side effects.<sup>[21]</sup> The water solubility of nano-encapsulated curcumin (NEC) in sodium caseinate (SC) and Maillard conjugate (MC) was over 90%. NEC had a threefold increase in in-vitro bioavailability over curcumin. Indian Basmati rice was used to incorporate the curcumin and spray-dried NEC. It was found that NEC Basmati rice could be used to develop fortified products because of its high visual appeal and anti-oxidant activity.<sup>[22]</sup>

Several studies on antioxidant capabilities have been conducted and evaluated. Consequently, it was shown that curcumin is an effective scavenger of a wide range of reactive oxygen species, including superoxide anion free radicals, hydroxyl radicals, singlet oxygen, and free radicals with nitrogen centers. The phenolic and methoxy groups greatly enhance curcumin's free radical scavenging properties.

## Antimicrobial activity

Anti-microbial Activity- An ethanolic extract of turmeric (*Curcuma longa*) was tested for microbial susceptibility and found to be active against the bacteria tested, inhibiting all organisms with the highest inhibition zone recorded against *Shigella flexneri* and the least inhibition recorded against *Staphylococcus epidermis*. Turmeric's antimicrobial activity can be explained by a wide range of phytochemicals, such as tannins, alkaloids, phenols, steroids, flavonoids, phlorotannin, cardiac glycosides, terpenoids, triterpenes, saponin, and so on.<sup>[23]</sup> There was significant antioxidant activity in the carbon dots derived from turmeric (S-CD) and carbon dots functionalized with sulfur (S-CD). The sulfur-functionalized CD produced more reactive oxygen than the non-functionalized CD, confirming the S-superior CD's antibacterial activity. Compared to Gram-negative bacteria, the CD had a stronger antimicrobial effect on Gram-positive bacteria (*L. monocytogenes*) (*E. coli*). Curcumin-derived CD has shown improved functionality through sulfur functionalization and has a high potential for use in food packaging and biomedical applications. Because of this, turmeric-based multifunctional CD materials can be used in biomedical and food packaging applications without fear of toxicity.<sup>[24]</sup>

*Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, and *Candida albicans* tested N-hexane, water, chloroform, and ethanol turmeric extract. The growth of *Escherichia coli* and *Salmonella typhi* was inhibited by water turmeric extract. The development of *Escherichia coli* and *Staphylococcus aureus* was decreased by water extract and additional growth of microbes controlled by methanol extracts.<sup>[25]</sup> Turmeric aqueous extracts demonstrated improved *Staphylococcus aureus* inhibitory action. Ethanolic extracts of turmeric, anti-stolonifer and *Mucor* sp. anti-pyroid activity was observed. The sections may function as an antibiotic preservative.<sup>[26]</sup> The incubation temperature did not influence light-activated hydrogel coatings' antibacterial effectiveness. It was shown to be a valuable source for antimicrobial coating when curcumin-loaded hydrogels and UV-A light are combined to prevent *Listeria innocuous* sausage cross-contamination. Using an edible antimicrobial microbial coating in food can reduce the risk of foodborne illness and lengthen the product's shelf life.<sup>[27]</sup> Three curcuminoids, including curcumin, bisdemethoxycurcumin (BDC), and demethoxycurcumin (DMC), have been shown to exhibit antibacterial and antifungal action against bacteria such as *Bacillus subtilis*, *Staphylococcus aureus*, as well as antifungals against *Aspergillus Niger* and the *Candida albicans*. The antibacterial medicine Kanamycin and Fluconazole have been used in various bacterium and fungi as conventional medicine.<sup>[28,29]</sup>

Turmeric, ginger, and garlic are examples of essential spices that contain various bioactive chemicals that have a variety of therapeutic benefits, such as providing protection against a variety of microorganisms and aiding in the prevention of food microbiological deterioration. Turmeric, Ginger, and Garlic have the most potent antimicrobial properties.<sup>[30]</sup> Turmeric oil contains turmerone and zingiberene used in antimicrobial research by sesquiterpenes and monoterpenes that are more volatile. While there were fewer antimicrobial effects on *Bacillus subtilis*, *Cryptococcus neoformans*, *Staphylococcus aureus*, and *Candida albicans*, no antimicrobial impact was seen on *Escherichia coli* and *Pseudomonas aeruginosa*.<sup>[31]</sup> The most activity in commercial ginger paste was examined against *Escherichia coli* at 4°C and 8°C and fresh garlic paste at 8°C. In contrast, the antimicrobial impact was not demonstrated by carrot and turmeric oil.<sup>[32]</sup>

The excellent antibiotic properties against *Staphylococcus aureus*, *Aspergillus Niger*, and *Candida albicans*, were demonstrated by turmeric essential oil. Roma turmeric has the most significant component of turmerone, which serves as a vital source of antibacterial action. To heal infections of the eyes, this offers an opportunity to produce a lens with turmeric rhizome oil.<sup>[33]</sup> Antimicrobial drugs delivered at the right time were used to inhibit bacteria development. Therefore, the conclusion was that the Turmeric oil biopolymer film works as a paper force coating that enhances paper packaging performance by extending the shelf life of food.<sup>[34]</sup> Lignocellulosic crop leftover's natural cellulose fibers and turmeric stem have comparable antibacterial characteristics. The antibacterial and anti-insecticide properties in turmeric oil and extracted exudate leaves and stems have. The



antibacterial effect is practical and helpful in various applications against gram positives and negatives bacteria.<sup>[35]</sup> The preparation of ethanol and marine extracts and antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans* and *Aspergillus flavus* were performed with *Curcuma longa* (Turmeric), *Curcuma amada* (Mango ginger), and *Curcuma aromatic* (Van turmeric). In both *Curcuma longa* and *Curcuma aromatic* ethanol extract, antibacterial and antifungal activities are identified. In contrast, four types of microbe inhibition were not seen in water extract Curcuma.<sup>[36]</sup> Turmeric rhizome ethanolic minerals have been determined using phytochemical screening for alkaloids, flavonoids, saponins, tannins, triterpenoids/steroids, etc. This extract showed superior effects on *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. An antibacterial agent is therefore considered adequate.<sup>[37]</sup>

PVP extract turmeric strong scattering alginate beads demonstrated higher antibacterial activity without solid dispersion with *Staphylococcus aureus* and *Escherichia coli* than with alginate beads containing turmeric extract. The reliable dispersal of alginate turmeric extract PVPs (1:2) is greater than the solid dispersion of the turmeric extract beads.<sup>[38]</sup> Above-temperature heat treatment, the antibacterial activity of turmeric extract is reduced to around 80°C. The heat-treated ethanol extract of turmeric was stable during the heat treatment, and antibacterial activity was demonstrated against the bacterial strain.<sup>[28]</sup> Turmeric's main photo components of curcuminoids include curcumin, demethoxycurcumin, and bisdemethoxycurcumin prevented *Clostridioides difficile* growth. Curcuminoids have not altered human gut bacteria. *Clostridioides difficile* toxin production was more effectively suppressed than fidaxomicin by curcumin.<sup>[39]</sup> The variety of ladies shows that the maximum concentration of total curcuminoids was found in essential oil, methanol mineral extract, total polyphenol, and radical scavenging capability. Turmeric extracts prevented *Staphylococcus aureus* bacteria from growing. The Dame and Bonga 51/71 necessary oil include 75% ar-turmerone, turmerone, and curlone.<sup>[40]</sup> The growth of *Porphyromonas gingival*, *Prevotella intermedia*, *Tannerella forsythia* was reduced by curcumin, and the formation of the *Aggregatibacter actinomycetemcomitans* strain by curcumin at low dosage was repressed. Curcumin is an excellent antibacterial drug to prevent periodontal microorganisms from suffering from several periodontal conditions.<sup>[41]</sup> The most extraordinary inhibitor zone in *Escherichia coli*, *Pseudomonas fluorescens*, and *Staphylococcus aureus* was ethanolic turmeric extract with PAS. PAS turmeric preparations have demonstrated excellent antibacterial action against positive and negative grams.<sup>[42]</sup>

Turmeric extract did not exhibit antibacterial action with the resistance of *Escherichia coli*. Turmeric coupled with other antibiotics gives more potent antibacterial properties. A positive sulfamethoxazole control inhibitory zone was identified, whereas no negative control area was seen.<sup>[43]</sup> Better turmeric incorporation of antibacterial action has been reported in chitosan films employed against *Salmonella* and *Staphylococcus aureus* bacteria. These films can be utilized for foodstuffs because they provide more excellent antibacterial properties and film rigidity.<sup>[44]</sup> The inhibitory activity against 13 bacteria such as *Vibrio cholerae*, *Aeromonas hydrophila*, *Staphylococcus aureus*, *Bacillus subtilis*, *Edwardsiella tarda*, turmeric ethanol extracts, and hexane extracts, as well as curcuminoids, showed an inhibitory effect against eight bacteria such as *Aeromonas hydrophila* and *Staphylococcus aureus*, *Bacillus subtilis*. Therefore, the conclusion was that the ethanol extract of turmeric had a more significant inhibitory effect than curcuminoids and hexane extract of turmeric against specific pathogens of shrimp and chicken.<sup>[45]</sup> Both the turmeric extract and nanoparticles prevented the development of *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, and *Bacillus subtilis*. The MIC against *Staphylococcus aureus* and *Salmonella typhi* is formed using nanoparticles to play a significant role.<sup>[46]</sup> Nanoptic excerpt from turmeric, zedoary, and garlic indicated that *Mycoplasma gallisepticum* (*M. gallisepticus*) exerts antibacterial actions causing chicken chronic respiratory conditions. Three nanoparticles are extracted in combination, which, in preventing chicken CRD, have better antimicrobial action.<sup>[47]</sup> Silver nano-composite movies and the addition of curcumin exhibited more significant antibacterial activity on *E. coli*. It improves the activity to generate more efficiency for wound dressing using curcumin-nanocomposite coated material.<sup>[48]</sup>

Tetrahydrocurcuminoid is a turmeric extract containing curcuminoids that undergo the hydrogenation process. The effects against *Staphylococcus aureus* and *Fusobacterium nucleatum* were more significant than curcuminoids with Tetrahydrocurcuminoid.<sup>[49]</sup>

Turmeric ethanol extract was shown to have higher antibacterial properties against *Escherichia coli*, *Proteus Vulgaris*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Maximum antibacterial effects against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* have been found in ethanol extract. Sensitive was *Pseudomonas aeruginosa*, and ethanol extract resistance was *Proteus Vulgaris*.<sup>[50]</sup> Increasing the lipophilicity of curcumin enhances its bioactivity. Diethyl curcumin was produced by modifying curcumin with a  $K_2CO_3$  base catalyst. The effective antibacterial action of curcumin and diethyl curcumin has been demonstrated with the *Escherichia coli* gram-negative bacteria. In contrast, the *Staphylococcus aureus* gram-positive bacteria development has not been inhibited.<sup>[51]</sup> The di-O-acetylcurcumin conversion was considerably more efficient than acetylation with Ni/SiO<sub>2</sub> catalyst by curcumin acetylation with pyridine. Di-O-acetylcurcumin for *E. coli* and mono-O-acetylcurcumin for *Bacillus subtilis* showed the highest antibacterial efficacy.<sup>[52]</sup> Ethanol extract turmeric dried rhizomes are tested against antibacterial strains and have been shown to have increased antibacterial activity. In medications, this may be utilized to enhance the health conditions of numerous medicines to treat various diseases.<sup>[53]</sup> Ethanolic turmeric extract exhibits antibacterial effects of microorganisms isolated from hot and cold extraction techniques against *Staphylococcus aureus*. The hard extracted turmeric was given a greater hot MIC turmeric extract concentration on *Staphylococcus aureus* pure culture.<sup>[54]</sup>

Turmeric raw powder has been shown to improve the inhibitory properties of antifungal agents *Aspergillus* sp. and *Fusarium* sp. as natural powder, which may therefore be utilized as a natural substance.<sup>[55]</sup> Zedoary Turmeric oil inhibits the growth of *Phytophthora capsici* and *Nicotiana benthamiana* in detached leaves. ZTO has 50 volatile chemical molecules. The inhibitory impact on *Phytophthora capsici* mycelium is strongly determined by Curcumol,  $\beta$ -elemen, Curdione, and Curcumenol, thus preventing Phytophthora blight illnesses.<sup>[56]</sup> Curcumin, demethoxycurcumin, and bisdemethoxycurcumin were found in the most significant quantities in BK2 Turmeric. There was no curcuminoid in *Curcuma zedoaria* and *Curcuma amada*. *Curcuma amada* and *Curcuma zedoria* species that suppressed FSSL development were discovered to have other antifungal compounds. Curcuminoids were found in more substantial amounts in Ryudai gold and BK2 strains of turmeric, as well as *Curcuma xanthorrhiza*, which exhibited practical antifungal activities against FSSL.<sup>[57]</sup> Curcumin-silver nanoparticles (C-Ag-NPs) showed superior antifungal activity against fluconazole-resistant *Candida glabrata* and *Candida albicans* compared to Curcumin and AgNO<sub>3</sub> solution, which can be utilized in medication development for candidiasis.<sup>[58]</sup> The combination of Aloe vera leaf and *Curcuma longa* rhizome extracts has a potent antifungal effect against *Candida albicans* growth. It was discovered that the concentration of extracts affects the antifungal activity of plant extracts.<sup>[59]</sup>

Antifungal efficacy against *Candida albicans* was evaluated for tulsi and turmeric extracts. Tulsi and turmeric combination with copper extract was found to be more effective.<sup>[60]</sup> The thermal stability of *C. longa* aqueous extracts against different pathogens was discovered, with higher antifungal properties and heat-stable turmeric species.<sup>[61]</sup> Plant pathogenic fungus *Fusarium oxysporum*, *Pythium debaryanum*, *Phytophthora infestans*, *Fusarium solani*, and *Alternaria alternata* were all resistant to extracts of *Curcuma longa* L. rhizome. Methanol extract has the most antifungal action. Ar-Turmerone was shown to be moderately toxic to *Culex pipiens* larvae, with moderate antifungal effects on *Phytophthora infestans* and mild antifungal effects on *Fusarium solani*.<sup>[62]</sup> Curcumin at high doses suppressed planktonic organisms of *Candida* strains. *Candida albicans* mature biofilms were resistant to curcumin and fluconazole.<sup>[63]</sup> With a 100% MIC value, *Aspergillus Niger*, *Fusarium oxysporum*, and *Candida albicans* showed strong antifungal efficacy with cinnamon and turmeric, increasing plant extract concentrations improved inhibitory degree.<sup>[64]</sup>

In Turmeric essential oil (TEO) and aloe vera gel (AVG), the total amounts of alkaloids, phenolics, flavonoids, terpenoids, saponins, steroids, and cardiac glycosides are discovered. A novel antifungal agent may be generated by combining the effects of antibiotic creams with natural plant elements to

treat dermatological problems.<sup>[65]</sup> The methanolic and chloroform extracts of *Boswellia carteri* and *Curcuma longa* L. Birdwood reduced the development of *Fusarium* species, showing that the methanolic extract of *Curcuma longa* is significantly more efficient than *Boswellia carteri* in inhibiting *Fusarium* species.<sup>[66]</sup> Turmeric alcoholic extract exhibits antifungal properties against *Candida albicans*, which might help treat *Candida* infections and develop antifungal medicines.<sup>[67]</sup> Plant extracts were found to have antifungal action against *Candida albicans*. Because they contain phenolic chemicals as secondary metabolites, turmeric and myrrh extracts have been proven beneficial against fungus.<sup>[68]</sup> *Curcuma longa* and *Zingiber officinale* methanolic extracts had higher antifungal activity against *Alternaria alternata* than ethanolic, ethyl acetate, and aqueous extracts, leading to the conclusion that *Curcuma longa* and *Zingiber officinale* methanol extracts were the best solvents against *Alternaria alternata*, which causes spinach leaf spot in Kenya.<sup>[69]</sup>

*Curcuma longa* rhizome fractions and clinical isolates were tested for antimicrobial activity in various investigations. Experiments with *C. longa* rhizome extracts have shown that they have broad-spectrum antibacterial properties that may be used to treat microbial illnesses. Microbial species and strains influenced curcumin's potency. The phytochemicals they contain are part of the plant's defensive mechanism against insects, fungus, and other pests. In light of the growing frequency of foodborne illnesses and poisonings, it is not unexpected that these compounds also have significant antimicrobial effects. Finding that turmeric extracts are efficient antimicrobial agents against certain multiple drug-resistant bacteria may have substantial implications for preventing or treating diseases caused by such bacteria. Curcumin may offer therapeutic potential in the treatment of cutaneous and chronic wound infections (*Streptococcus pyogenes*, *Staphylococcus aureus*, *Acinetobacter lwoffii*), urinary tract infections (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*), and root canal infections (*Enterococcus faecalis*), according to published research and our observations. Curcumin's more remarkable ability to combat Gram-positive bacteria than Gram-negative bacteria has been seen in our trials, and additional research is needed to confirm this. We've opened a new door for genetic studies rather than closing the book on the investigation into curcumin activity. According to our findings, the Extract of *C. longa* may be used as a topical antifungal agent in the form of mouthwashes and lozenges, and it seems that turmeric has some antifungal qualities. When used in low quantities, it has both static and fungicidal properties. Drugs in underdeveloped nations tend to have fewer side effects and are more affordable because of these factors. However, more clinical investigations are needed to show its effectiveness in oral Candidiasis.

### **Anti-inflammatory activity**

Turmeric inhibits cyclooxygenase and lipoxygenase, two enzymes that produce ROS and COX-I and COX-II, two other enzymes implicated in the inflammatory response. The impact of AgNPs was shown to be greater than that of conventional diclofenac sodium, leading to the conclusion that turmeric oil mediated by silver nanoparticles can be utilized as an anti-inflammatory drug.<sup>[70]</sup> The amount of Curcumin in Turmeric fermented with *Lactobacillus fermentum* was higher than unfermented turmeric. The turmeric that has been fermented by *L. fermentum* aids cell survival. The suppression of the c-Jun N-terminal kinase (JNK) signal pathway caused the anti-inflammatory action of fermented turmeric. Curcumin concentration rises in lactic acid bacteria fermentation without altering cytotoxicity.<sup>[71]</sup> Many active turmeric and ginger powder or extracts help treat inflammatory diseases.<sup>[72]</sup> The anti-inflammatory activity with receptor COX-2 was demonstrated to be more than eugenol in silica investigations with curcumin, demethoxycurcumin, and bisdemethoxycurcumin. In vivo and in vitro studies revealed the higher anti-inflammation activity of zinc oxide combined with turmeric liquid extract than eugenol and may be used as an alternative to wound dressing with eugenol oxide.<sup>[73]</sup> Turmeric and flaxseed together have more potent anti-inflammatory properties, inhibiting IL-6 and modulating IL-10 levels. It results in a decrease in serum IL 6 levels and IL 10 levels.<sup>[74]</sup>

The mixture of turmeric and curcumin essential oils has more anti-inflammatory action as their combination of treatments increases DSS-induced colitis protection than curcumin alone. The induction of anti-inflammatory cytokines such IL-10, IL-11, and FOXP3 in the colon is aided by ETO-curcumin.<sup>[75]</sup> Curcuma-modified molecular weight pectin is a protective inhibitor of pro-inflammatory mediators, such as IL-8, TNF- $\alpha$ , and NF- $\kappa$ B, providing 91% protection. MTrPP suppresses and modulates effects via the expression of IL-10, Galectin-3, H<sup>+</sup> K<sup>+</sup>-ATPase, Oxidative, and gastro-protective mediators (IgA, mucin, NOx, prostaglandin E2, and zinc).<sup>[76]</sup> Nigeria Ginger and turmeric rhizome essential oil inhibit the use by hippocampus and prefrontal cortex of acetylcholinesterase (AChE) or adenosine deaminase (ADA) activity inhibitions of cytokines and inflammatory biomarkers, such as the IL-6, IL-10, or TNF-Alpha, in rats treated with Cd. It was therefore found to be anti-inflammatory in Cd-induced neurotoxicity.<sup>[77]</sup> The anti-inflammatory properties of turmeric and cinnamon Extract are due to the decrease of IL-6 and TNF- levels. Turmeric curcuminoids, demethoxycurcumin, bisdemethoxycurcumin, and cinnamon's main component, cinnamic acid, have shown anti-inflammatory activities.<sup>[78]</sup> Nitric oxide (NO), prostaglandin E2E2 (PGE2PGE2), cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS), nuclear factor- $\kappa$ B (NF $\kappa$ B), tumor necrosis factor-alpha (TNF $\alpha$ ), and interleukin-6 (IL-6) are all reduced in *Rhizopus oryzae* fermented *Curcuma longa* (FCL) without cytotoxicity. FCL extracts contain anti-inflammatory characteristics that might be useful in creating functional foods.<sup>[79]</sup>

The oral dose of *C. longa* hot water extract (WEC) protects against liver damage caused by ethanol. WEC component bisacurone reduces hepatic oxidation and inflammation. Oxidative stress and inflammatory cytokines may be used to treat ethanol-induced liver damage.<sup>[80]</sup> There are secondary metabolites (alkaloid, polyphenolic chemicals, and phenolic acid) in ginkgo's and turmeric roots, gums, and leaves that make them more effective anti-inflammatory drugs than typical ones like aspirin and diclofenac sodium.<sup>[81]</sup> Curcumin (CUR), the active component of turmeric, has several drawbacks, including being poorly soluble in water, limited absorption, and fast elimination of metabolites. As nanoparticle formulations and NLC formulations enhance their stability, CUR has a more excellent anti-inflammatory action.<sup>[82]</sup> The use of nanotechnology to incorporate curcumin into the body enhances the patient's bioavailability and absorption. Curcumin derivatives and analogs help treat arthritis by strengthening the backbone.<sup>[83]</sup> In vitro, bisabolene-type sesquiterpenoids from *C. longa* suppress the production of inflammatory cytokines via stimulating the virus and controlling the activity of the NF- $\kappa$ B/MAPK and RIG-1/STAT-1/2 signaling pathways.<sup>[84]</sup>

Curcumin has potential therapeutic benefits in several inflammatory illnesses. It suppresses inflammatory mediators, oxidation processes, and oxidative stress. According to our analysis, it has no severe impact on animals and people. Curcumin can inhibit oxidative stress, which is a primary cause of inflammation. As a potent anti-inflammatory agent, curcumin inhibits the generation of pro-inflammatory mediators' age by regulating signaling pathways such as NF- $\kappa$ B, MAPK, AP-1, JAK/STAT, and others. When used in the treatment of IBD, arthritis, psoriasis, depression, and atherosclerosis, curcumin may lower the inflammatory response, effectively relieve symptoms, and play a role in treating these and other disorders. Since then, structural modification and curcumin, preparation studies, and medication combination treatment have all helped increase its pharmacokinetics and anti-inflammatory properties. Dietary supplements or adjuvant medicine have a considerable therapeutic impact on curcumin use, currently the most viable method.

### **Anti-cancerous activity**

Curcumin, the primary polyphenol component in turmeric, has many biological actions. It works as an anti-cancer drug by modulating molecular targets that aid cell signaling processes. Transformation, proliferation, and apoptosis are all suppressed by it. With the use of Curcuminoids' analogs and

derivatives, the anti-cancer properties of curcumin may be significantly improved.<sup>[85]</sup> Bisdemethoxycurcumin, demethoxycurcumin, and curcumin are the three active curcuminoids generated from turmeric, and they reduce the development and potentiality of human lung cancer A549, colon cancer HT29, and glioma cell lines T98G. Single curcuminoids reduce the viability and growth of lung cancer cell lines. In A549 lung cancer cells, combining the crude extract with cisplatin reduces cancer cell viability more efficiently than using either component alone. As a result, whole turmeric extract was more effective on lung cancer cells than isolated components.<sup>[86]</sup> A novel bioactive fraction (NCCL) was chemically isolated from *Curcuma longa* hexane soluble fraction (HM) to isolate a novel marker molecule. The NCCL fraction with remaining components induces more significant cell death than the isolated molecule in cell lines. NCCL was proven to have better anti-cancer properties in MCF-7, DU-145, MDA-MB-231, and PC-3 cells and can be employed as an active therapeutic medication.<sup>[87]</sup> Also present in turmeric is a non-curcuminoid group of compounds known as the “turmerones,” bisacurone (also known as elemene, germacrene, cyclocurcumin, calebin A, furanodiene, and curdione). Encapsulating non-curcuminoid substances improves anti-cancer activities, allowing them to overcome their limitations and demonstrate their full advantages.<sup>[88]</sup> The anti-cancer activity of *C. longa* extracts (CRE) rich in curcuminoids was tested against three marker curcuminoids using the green microwave-assisted extraction (MAE) technology. On A549, MCF-7, HeLa, and HT-29 cells, CRE exhibited higher anti-cancer effects. As a result, it was determined that CRE had more beneficial qualities than pure curcuminoids. Using accessible, low-cost, and environmentally friendly procedures, it may be employed in food, nutraceutical, and industrial applications.<sup>[89]</sup>

Turmeric rhizome is a well-known herbal medication used in traditional Chinese medicine to treat cancer in a polyherbal method. Curcuminoids curcumin (CUR), demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC), when combined in a 1:1:1 ratio, have higher synergistic anti-cancer effects and protein expression down-regulation. Turmeric has a holistic anti-cancer activity and integration impact, and turmeric's three curcuminoids have a more significant synergistic effect on PC3 cells.<sup>[90]</sup> The non-covalent and covalent interactions of curcumin's diketone moiety and its two phenolic reactive functional groups allow it to interact with a wide range of biologically active substances. Dimethyl curcumin, which lacks phenolic OH, has anti-tumor properties. Hispolon, half Curcumin, showed gripping cellular action. Curcumin can be structurally altered to provide the desired anti-cancer effects.<sup>[91]</sup> Curcuminoids and anti-cancer activity are recovered more effectively using ethyl acetate extraction than with the traditional Indian method. Turmeric powders have varying levels of efficacy in preventing and curing human illnesses such as cancer, depending on the extraction technique used.<sup>[92]</sup> Androgen deprivation therapy treats advanced prostate cancer and hormone-resistant prostate cancer (HRPC). Maspin is induced by androgen ablation mediated by a cancer patient. Compared to DU145 cells with lower maspin expression, PC-3 cells with higher maspin expression are more responsive to curcumin therapy. Curcumin sensitivity of PC-3 cells was decreased by RNA interference-mediated maspin silencing, as demonstrated by reduced apoptotic cell death. Maspin enhances the susceptibility of HRPC cells to curcumin therapy.<sup>[93]</sup> Turmeric rhizome extract (Turmesac<sup>®</sup>) can induce cell apoptosis two times faster than camptothecin-treated cells. In G0/G1 and S phases, HeLa cells treated with Turmesac<sup>®</sup> exhibited cell cycle arrest. Turmesac<sup>®</sup> is a potent anti-cancer drug that may be used in chemotherapies.<sup>[94]</sup>

The Gemini surfactant-curcumin (Gemini-Cur) nano compound induces apoptosis, inhibiting cancer cell growth. In breast cancer cells, Gemini-Cur efficiently increases the expression of p16INK4a, p14ARF, and Bax while decreasing the expression of Bcl-2. Curcumin distribution is improved by Gemini surfactants, which enhances its anti-cancer properties. A nano substance called Gemini-Cur is a potent anti-cancer agent.<sup>[95]</sup> Turmeric curcumin and black long pepper piperine are active dietary polyphenols with anti-cancer properties in various cancers, including colorectal cancer (CRC). Piperine aids in the therapeutic action of curcumin. Piperine therapy had little effect on HCT116 cell growth in free and emulsion forms. The level of Caspase 3 was improved with CurcuEmulsomes. The combination of CurcuEmulsomes and PiperineEmulsomes raises the number of apoptotic markers. CurcuEmulsomes and Piperine Emulsomes

combined treatment of HCT116 cells improves the anti-cancer effects of the chemicals.<sup>[96]</sup> Curcumin (CUR) availability and anti-cancer bioactivity were increased by using carrier FCT (fungal chitosan) nanoparticles (NPS). CUR/FCT NPS treatment with A-549 and HCT-116 cancer cells leads to decreased cell viability. After 72 hours of 150 M CUR/FCT-NP therapy, most cancerous cells enter the apoptotic phase. CUR loading was proven to be successful with FCT-NPS bio-safe agents.<sup>[97]</sup> Curcumin therapy targets many distinct pathways involved in essential intracellular functions such as cell death, invasion, and genomic regulation. It is thus regarded as the most significant molecular component in preventing and treating cancer.<sup>[98]</sup> Curcumin had a high activity level against human HCT-116 colorectal cancer (CRC) cells, but curcumin-free Turmeric (CFT) had a low activity level. CFT inhibited the development of CRC xenografts. Turmeric includes bioactive chemicals and curcumin with higher anti-cancer efficacy in vivo against human CRC. Turmeric and curcumin have positive benefits in humans at modest dosages, whereas CFT may be administered at more significant levels with favorable action without any loss.<sup>[99]</sup>

Curcumin has demonstrated substantial anti-cancer benefits against various distinct forms of cancer, including prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, and head and neck cancer both in vitro and in vivo. Furthermore, its effectiveness and safety in cancer patients, either alone or with other anti-cancer drugs, has been shown in multiple clinical investigations with human subjects. Curcumin is thought to exert its anti-cancer effect through many methods, interfering with distinct cellular pathways and inducing/inhibiting the production of various kinds of cytokines, enzymes, or growth factors such as MAPK, EGF, NF $\kappa$ B, PKD1, COX-2, STAT3, TNF- $\alpha$ , and I $\kappa$ K $\beta$ . However, the anti-cancer use of curcumin has been restricted mainly owing to its low water solubility, which leads to low cellular absorption and poor oral bioavailability, as well as low chemical stability.

### **Immunomodulatory activity**

Turmeric extract includes phenolic and flavonoid antioxidants, functional monosaccharides, and curcuminoids. On fake human stomach and intestinal juice, TE exhibits superior resistance. In the HT29-19A cell line, TE has prebiotic potential and suppresses LPS-induced IL-8 production.<sup>[100]</sup> When albino mice were given an Aflatoxins-added diet, they gained weight, had lower FER and spleen weight, and had higher blood MDA and IL-6 levels than when given a baseline diet. It does not affect food intake or relative thymus weight. When turmeric is combined with aflatoxins, the pro-inflammatory effects of the aflatoxins are amplified. Turmeric contains antioxidant properties that aid in the enhancement of the immune system.<sup>[101]</sup> Curcumin has reduced CD4+, CD8 + T cell, VAS, C-reactive protein (CRP), B cell, and Th17 cells in OA (osteoarthritis) immune response patients. Treg lymphocytes increased in number, whereas the ratio of Treg/Th17 lymphocytes shifted toward Treg lymphocytes. Curcumin has been shown to have immunomodulatory properties in people with osteoarthritis.<sup>[102]</sup> Curcumin nanoparticles promote a more robust early cell-mediated immune response as well as a primary humoral immune response. Nanocurcumin also increases the formation of white blood cells and the weight of lymphoid organs. Cumin nanoparticles in poly D L-lactic-co-glycolic acid enhance curcumin bioavailability for improved immunity.<sup>[103]</sup> In *Oreochromis niloticus*, dietary turmeric (TUM) supplementation has an immunomodulatory impact via affecting IL-2, IL-4, lymphocyte count, and antibacterial enzymatic activity, resulting in weight increase. Turmeric's curcumin and curcuminoids are bioactive chemicals that are chemo preventative against various illnesses.<sup>[104]</sup>

Curcumin inhibited the production of IL-2, IL-12, IFN- $\gamma$ , and TNF- $\alpha$  by splenic T cells. LAK cells were less susceptible to curcumin's suppressive effect at identical dosages.<sup>[105]</sup> In the last two decades, curcumin has been discovered to be a potent immunomodulatory medication, affecting B cells, T cells, neutrophils, macrophages, natural killer cells, and dendritic cells activation. By activating the transcription factor NF-B, Curcumin inhibits inflammatory cytokines such as chemokines, IL-1, IL-2, TNF, IL-6, IL-8, and IL-12. Curcumin in small doses can also help to increase antibodies.<sup>[106]</sup> Curcumin's ability to impact the immune system might explain why it's thought to help with arthritis, allergies, asthma, Alzheimer's disease, atherosclerosis, diabetes, heart disease, and cancer.<sup>[107]</sup> One of turmeric's most potent active

constituents is curcumin. Curcumin is a polyphenolic phytochemical with a wide range of health-promoting qualities. Curcumin has been found to have anti-allergic properties, including an inhibitory impact on histamine release by mast cells. The results reveal a substantial reduction in allergic reactions in rats given curcumin, indicating that curcumin has a function in reducing allergic responses.<sup>[108]</sup> Curcumin (diferuloylmethane) is an anti-inflammatory, antioxidant, and chemo preventive substance. Curcumin suppresses IL-2 and NO production, PHA-induced T-cell proliferation, and lipopolysaccharide-induced nuclear factor-B (NF-B) production, although it increases NK cell cytotoxicity. Curcumin reduces the cell growth and cytokine production of these immunological markers by decreasing the activation of NF-B target genes.<sup>[109]</sup>

Curcumin treatment improved the running ability of animals suffering from ischemia. According to histological studies, curcumin therapy significantly decreased the skeletal muscle damage and fibrosis associated with ischemia injury. TNF-, IL-1, and IL-6 levels all dropped following curcumin treatment, indicating reduced macrophage infiltration and inflammatory responses on the local level. Curcumin treatment inhibited the NF-B signaling pathway. Curcumin inhibits LPS-induced NF-B activation in macrophages. Curcumin medicine has been shown to lessen the degree of hindlimb damage following ischemia surgery, indicating that it might be used to treat PAD.<sup>[110]</sup> *Aspergillus oryzae* fermented CL (FCL) 's immunomodulating effect was examined on RAW 264.7 cells. TNF- $\gamma$  was substantially increased when FCL extracts were added. Finally, FCL extracts revealed lower LP-BM5 eco mRNA expression, especially in the 20% ethanol extracts group. Sections of FCL might be utilized as a functional material because of their immunomodulatory properties.<sup>[111]</sup> Curcumin inhibits phospholipase, leukotrienes, lipoxygenase, prostaglandins, cyclooxygenase 2, thromboxane, nitric oxide, elastase, collagenase, hyaluronidase, IL-12, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor, and interferon-inducible protein. In six human studies, curcumin is safe as well as anti-inflammatory. It may have anti-inflammatory effects since it inhibits several molecules involved in inflammation.<sup>[112]</sup> Higher primary and secondary antibody titers see polysaccharide fraction increases humoral immune response at the exact dosage. In a splenocyte proliferation experiment, the polysaccharide component of *C. zedoaria* substantially aided splenocyte development. The polysaccharide portion of *C. zedoaria* can be used as an immunomodulator.<sup>[113]</sup>

Curcumin, the primary ingredient of *C. longa*, has influenced several signaling pathways at the molecular level. Despite regulatory constraints for clinical trials and the absence of actual data acquired in preclinical testing, Curcuma species have been researched in a few unsystematic case studies. Researchers have shown that curcumin, the most bioactive metabolite, has a considerable impact on immune response regulation in animal and human trials. However, more comprehensive, well-designed, and well-conducted controlled randomized trials are required for human use. The development of immunomodulatory medicines that are both safe and efficacious requires extensive preclinical pharmacokinetics and toxicity research.

### **Antiviral activity**

Curcumin works as an anti-infective agent against a variety of viruses. These strategies entail either direct interference with viral replication machinery or regulation of viral replication-related cellular NF-B and PI3K/Akt signaling pathways. This study covers existing research, emphasizing curcumin's antiviral properties and potential molecular pathways.<sup>[114]</sup> Curcumin has antiviral, inflammatory, antinociceptive, antipyretic, and antifatigue effects that control COVID-19 symptoms. It contains antioxidant, antiapoptotic, and antifibrotic qualities and inhibitory actions on NF-B, Toll-like receptors, inflammatory cytokines, bradykinin, and chemokines, among other molecular processes. According to scientific research, curcumin may have a function to play in treating COVID-19.<sup>[115]</sup> There is scientific evidence that curcumin, the principal curcuminoid ingredient in turmeric, may reduce inflammation and protect against oxidative stress. It also has antibacterial and antifungal properties and hypoglycemic and wound-

healing properties. As part of a new method of drug development to increase curcumin bioavailability, essential technologies such as nanoparticles, adjuvants, liposomes, and phospholipid complexes are being studied. It has often been used for coughs, sore throats, and respiratory disorders as a home treatment. It could be an excellent immune booster against SARS-CoV-2 therapy during the current pandemic.<sup>[116]</sup> Turmeric spice can inhibit SARS-CoV-2 critical proteins and hence could be used as a therapeutic or protective drug against SARS-CoV-2 by inhibiting essential SARS-CoV-2 virus proteins. The most potent inhibitors of the virus's major protease, spike glycoprotein, and RNA polymerase, respectively, are compounds 4, 23, and 6.<sup>[117]</sup> At the maximal nontoxic concentration, a methanol extract of *Curcuma longa* suppressed the poliovirus (MNTC). The phytochemical investigation found terpenes, saponins, alkaloids, flavonoids, tannins, cardiac glycosides, and phenol as bioactive phytochemicals. *Curcuma longa* has high inhibitory activity and could develop an efficient antiviral against polio and measles viruses.<sup>[118]</sup>

Curcumin treatment has not altered HCV RNA replication or viral assembly/release. HCV cocubation with curcumin effectively blocked the entrance of all main HCV genotypes. The antiviral activity demonstrated other curcumin compounds but not tetrahydrocurcumin, which suggested antiviral action in non-saturated ketone groups. HCV envelope fluidity decreases with curcumin, decreasing viral binding and fusion and cell/cell transmission. Turmeric curcumin inhibits HCV entrance in primary human hepatocytes, regardless of genotype, via altering membrane fluidity, preventing viral binding and fusion.<sup>[119]</sup> Curcuma, a chemical produced from a medicinal plant in the Zingiberaceae family, was studied for its anti-PRRSv properties. Turmeric extraction (curcuminoids) was obtained and found to have no cytotoxicity impact on MARC-145 cells. Curcuminoids were shown to strongly suppress PRRS viral replication at a 1.56 g/mL dosage. This finding is intriguing in using herb extraction to combat PRRS infection, and it should be investigated further in vivo.<sup>[120]</sup> The impact of curcumin chitosan (CuCs) nanocomposite, as a potential anti-HCV-4a drug, was investigated in this study on human hepatoma cells Huh7. CsNPs exhibited no cytotoxic impact on the cell lines that were examined. Nanocomposite CsNPs and CuCs reduced HCV core protein production, viral entry, and replication. Compared to curcumin alone, CuCs nanocomposite reduced HCV-4a entry and replication, indicating that it might be used as a therapeutic agent.<sup>[121]</sup>

Curcumin and its equivalents can inhibit many viruses in various ways. However, in human clinical studies, curcumin's usefulness as an antiviral agent has been hampered by its poor bioavailability and quick metabolism. On the other hand, Curcumin formulation technology has shown promising results in improved solubility of curcumin and its derivatives. Curcumin may be developed into a broad-spectrum antiviral for human clinical use if more research into such formulations and the production of new curcumin-derivatives that exhibit increased antiviral activity with less toxicity is conducted.

## Conclusion

Turmeric has a vital role in Asian culture, and its wide variety in traditional medical systems such as Ayurveda, Siddha, and Unani have long been utilized. Turmeric, a golden spice of the long-plant Rhizome of the *Curcuma longa* plant, has been used in food preparations from ancient times to give color, taste, and flavor. Due to its high phenolic and flavonoid content, which provides excellent antioxidant activity, it is also used as a medicine to treat a variety of diseases. Gynecological problems, gastric problems, hepatic disorders, cough, sore throat, respiratory ailments, infectious diseases, and blood disorders have all been treated with this spice as folk medicine in the past. Polyphenols, alkaloids, diterpenes, sesquiterpenes, triterpenoids, and sterols have been isolated from this spice's chemical constituents. Curcumin, which makes up 2–5% of turmeric, is probably the most researched component. Turmeric has been shown to have antimicrobial,



antimutagenic, anti-cancer, insecticidal, larvicidal, and radioprotector properties in cell studies. Several animal studies have proven the anti-inflammatory, neurodegenerative, cancer, diabetic, depressive, obese, and atherosclerotic effects of this spice.

Drug-resistant pathogens are becoming more common nowadays. Identifying new active chemicals against targets is a matter of urgency to tackle this worrying challenge. Many physiologically active chemicals may be isolated from spice extracts and utilized to create new medications. It means that everyday spices, shared in our kitchens, may help protect us against infection in little ways. The evaluation of phytomedicinal items such as *Curcuma longa* should be encouraged. A wide range of therapeutic qualities, including biological targets and interactions, have been related to curcuminoids, a potential natural chemical with many therapeutic capabilities. Unfortunately, the poor solubility, low absorption, and low bioavailability of curcuminoids, as well as their quick metabolism, restrict their therapeutic potential. It has been a monumental undertaking to increase curcumin's bioavailability, potency, and specificity for the target tissue. Nanoparticles derived from dried turmeric (*Curcuma longa* Linn.) rhizome (TE-NPS) have been shown to have a higher cytotoxic effect on HepG2 human hepatoma cells when compared to curcumin (free curcumin). Using pure curcumin as a comparison, this study is the first to show that nanoparticles made from turmeric rhizome extract are more effective at killing hepatic cancer cells. These nanoparticles could be used as a delivery system for cancer treatment.

However, there are still various difficulties that must be addressed. Medicinal chemistry procedures have not significantly improved curcumin's pharmacological characteristics, and curcumin derivatives are not more potent than curcumin itself. Various drug delivery methods have been tested to improve curcumin's cellular absorption and activity; however, none of these formulations has been examined in clinical studies. Suppose curcuminoids or their derivatives are employed as innovative drugs in the future. In that case, they will need to be changed and combined with fatty acids, micelles, nanoparticles, liposomes, and metal complexes. Before they can be sold on the pharmaceutical market, these curcumin delivery systems must first be tested in people to determine their safety and effectiveness. Additionally, most current curcumin delivery methods cannot target particular tissues. As a result, the curcumin delivery methods still have a long way to go in their ability to target specific tumor regions. Suppose *Curcuma longa* is accessible in its pure form. In that case, new medications may be developed that are more effective and have fewer side effects because of their biological features. Turmeric, which is nontoxic and has a broad range of physical activities, may be used to make a variety of medicines that will help treat different disorders. Even though much research has already been done on this plant, more research is needed for medication development. This plant is a unique source of various chemical compounds responsible for the plant's many functions. It is clear from the results that turmeric has a medicinal value that can be used in both pharmaceutical and pharmacological forms. More research should be done on it as a medicinal plant, especially when herbal medicines are becoming more popular.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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