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A COMPREHENSIVE STUDY ON BIOLOGY, CHEMISTRY AND PHARMACOLOGY OF *CURCUMA LONGA* L.- A REVIEW

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Abstract

Turmeric, or *Curcuma longa*, has been used widely in Indian subcontinental cuisine, cosmetics, preservatives, and ceremonial purposes. Turmeric has long been used to cure a variety of conditions, including allergies, indigestion, coughing, and other illnesses. This review attempts to close the knowledge gap about the wider range of medical applications of *Curcuma longa*, with a special emphasis on the pharmacological characteristics of its main ingredients, curcuminoids and essential oils. Turmeric has shown encouraging therapeutic results in recent trials, most notably in the treatment of rheumatoid arthritis, cancer, diabetes, hyperlipidemia, inflammation, microbiological infections, asthma, snake bites, and Alzheimer's disease. The review objectively evaluates the data pertaining to these assertions, emphasizing aromatic-turmerone and curcumin as main active ingredients. Through a methodical examination of existing literature, this review highlights the possibility of developing turmeric-based novel drugs for modern medicine, thereby contributing to improved health outcomes and quality of life.

Key words: Chemical constituents, *Curcuma longa,* curcuminoids, pharmacological activities, toxicity, turmeric.

Introduction

Many modern medical therapies are inspired by natural medicines, even though the market is predominated by synthetic pharmaceuticals (Frank et al. 2017). When compared to their synthetic counterparts, natural chemicals are frequently less harmful and easier for the body to eliminate (Araújo and Leon 2001). For thousands of years, medicinal plants have been used to cure a wide range of illnesses in traditional medicine. One such plant is *Curcuma longa* L., or turmeric, which is native to Bangladesh and other parts of Southeast Asia. It is regarded as “Haldi” (Gupta et al. 2015) or “Halud” locally, “Ata ile pupa” in Southwest Nigeria (Oyemitan et al. 2017), and “Khamin Chan” in Thailand (Prucksunand et al. 2001). It is also highly valued in traditional medicine and culture. Its importance is highlighted by its ancient usage as “Indian Saffron” (Krup et al. 2013).

Turmeric has long been utilized as a spice, coloring agent, preservative, and cosmetic (Niranjan and Prakash 2008). It is included in a number of religious and marriage rituals (Araújo and Leon 2001). For example, fresh rhizome paste is used to improve complexion (Krup et al. 2013) and turmeric mixed with honey is used

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topically (Prucksunand et al. 2001). Many traditional medical systems, such as chinese medicine (Kuttan et al. 2011), ayurveda, herbal and siddha (Chattopadhyay et al. 2004), rely heavily on turmeric.

There are many traditional medical uses for curcuma longa, including the treatment of various inflammatory diseases, skin concerns, respiratory issues, and digestive disorders. According to Verma et al. (2018), it functions as an antiseptic, antibacterial, and anti-inflammatory agent. Furthermore, studies conducted by Araújo and Leon (2001) have demonstrated its effectiveness in the treatment of muscle spasms, rheumatoid arthritis, tiredness, malaria fever, jaundice, and emotional disorders (Oyemitan et al. 2017). Notable uses of turmeric include the treatment of allergic conjunctivitis in children and eye disorders in Orissa tribal people (Singh et al. 2011, Prucksunand et al. 2001).

Curcuma longa has been the subject of several investigations, but despite this, a thorough assessment is still required to address the specific knowledge gaps in its chemistry, biology, and pharmacology. The possible processes and uses of turmeric's active ingredients, especially curcumin and aromatic-turmerone, in contemporary medicine have not yet been thoroughly investigated in the literature. This study attempts to close this knowledge gap by thoroughly analyzing recent research and provide a thorough evaluation of turmeric's possible therapeutic uses. By discussing these points, the study hopes to draw attention to the importance of Curcuma longa and suggest potential paths for its advancement as a cutting-edge novel medication in modern medicine.

Materials and Methods

Literature Search:

- We conducted a comprehensive literature search using Google Scholar, PubMed, and ResearchGate.
- Keywords employed included "Curcuma longa", "turmeric", and specific pharmacological activities of interest (e.g., "Curcuma longa antivenom activity").
- Inclusion criteria:
    1. Studies published in English within the last 20 years.
    2. Studies investigating the chemistry, biology, or pharmacology of *Curcuma longa* L.
    3. Peer-reviewed articles.
- Exclusion criteria:
    1. Studies published in languages other than English.
    2. Studies solely focused on the cultivation or agricultural aspects of *Curcuma longa* L.
    3. Conference abstracts, book chapters, or non-peer-reviewed articles.
- Selection process:
    1. Titles and abstracts were initially screened to identify relevant studies.
    2. Full-text articles were retrieved and assessed for eligibility based on the inclusion and exclusion criteria.

Image acquisition:

- Images of *Curcuma longa* rhizome and turmeric powder were obtained due to their widespread use as a spice.
- The image of turmeric powder in a marital ceremony was sourced from a personal event of the author's relative with permission.
- An image of Curcuma longa shoots was captured in Rajshahi, Bangladesh.
- Software used: Google Chrome web browser for image searches.

Chemical structure drawing:

- The chemical structures of most of the compounds were drawn using ChemDraw software.

Plant biology

Curcuma longa L. is a perennial herb which is thought to have originated from the Indian subcontinent. Even though it is found in most subtropical and tropical regions of the world, its abundance is seen in Sri Lanka, Pakistan, Bangladesh and India. It can reach a height of 1 m and its rhizomes are about 2 ft (Sawant and Godghate 2013) in length, have a characteristic yellowish orange color, with distinct odor and bitter taste. The herb is evergreen in nature. The rhizomes are underground stems which are thick, fleshy, short-branched, oblong, pyriform and ovate which are ready to harvest in 7-9 months after planting (Prucksunand et al. 2001). The plant grows easily during the rainy season, ranging from May-July and its harvest season is from December to February (Prucksunand et al. 2001). After harvest, the rhizomes are washed, then mild alkaline water is used to boil them for softening and then dried in electric dryers or sun to make the bright distinctive yellow powder called turmeric (Niranjan and Prakash 2008). Turmeric powder has a bitter, peppery flavor and a mild fragrance resembling orange and ginger (Verma et al. 2018). Fat soluble and polyphenolic pigments called Curcuminoids give its characteristic vivid yellow color (Sawant and Godghate 2013). The rhizomes of *Curcuma longa* L. are responsible for its medicinal activity (Singh et al. 2011). The plant is vegetatively breeded through rhizomes and a sterile triploid in nature (Ma and Gang 2006).

The taxonomic classification according to Linnaeus is as follows:

Class: Liliopsida

Subclass: Commelinids

Order: Zingiberales

Family: Zingiberaceae

Genus: *Curcuma*

Species: *Curcuma longa*

C. aromatica is the wild and *C. longa* is the domestic Turmeric species (Chattopadhyay et al. 2004). A pictorial representation of various forms and a use of *Curcuma longa* L. is elucidated in Fig. 1.

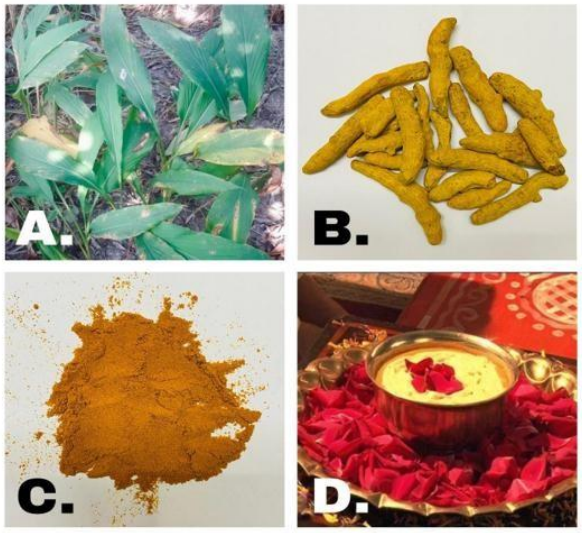


Fig. 1 (A-D): A. Shoots of *Curcuma longa*, B. Dried rhizomes of *Curcuma longa*, C. Powder form of dried rhizomes of *Curcuma longa* (turmeric powder), and D. Use of turmeric in marriage ceremonies.

Plant chemistry

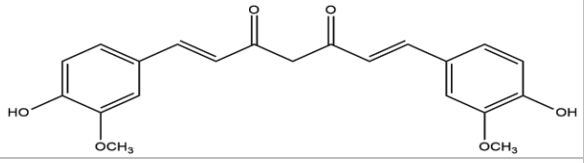
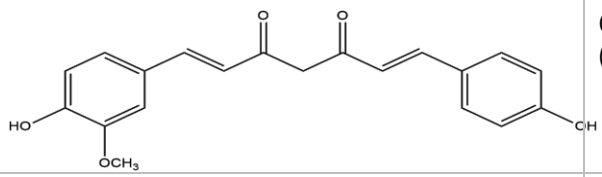
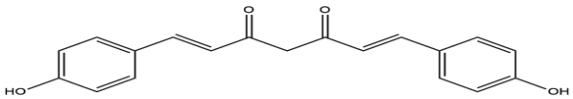
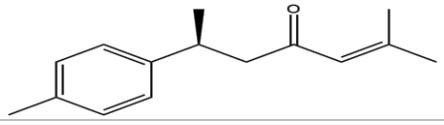
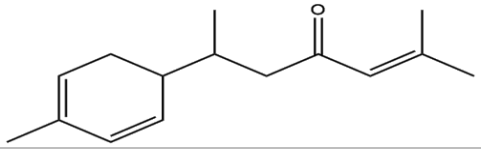
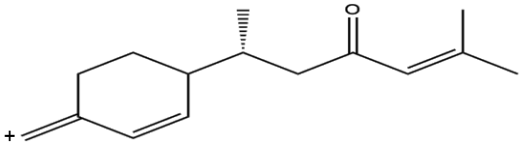
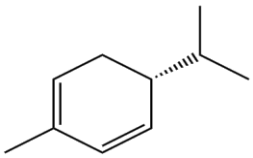
Curcuma longa L. contains a plethora of phytochemicals, consisting of abundant primary and secondary metabolites. A brief summary of the types of chemical compounds present within *Curcuma longa* L. is given in Table 1.

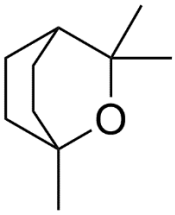
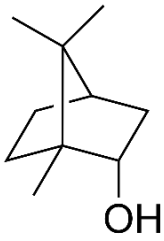
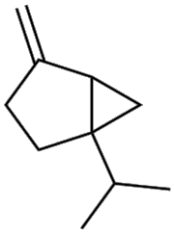
Table 1: Biochemical composition of *Curcuma longa* L.

Phytochemical components	Percentage (%)	References
1. Carbohydrates	69.4	
2. Proteins	6.3	
3. Fats	5.1	Kapoor (1990)
4. Minerals	3.5	
5. Moisture	13.1	
6. Essential oils	5.8	
7. Ash	2.85	
8. Alkaloids	0.76	
9. Flavonoids	0.4	
10. Saponins	0.45	Gills (1992)
11. Tannins	1.08	
12. Phenols	0.08	
13. Glycosides	0.85	

The result in Table 1 shows that among primary metabolites, carbohydrates have the highest percentage at about 69.4% while essential oils have the highest percentage (5.8%) among secondary metabolites. The chemical compounds derived from *Curcuma longa* L. can be classified into 2 major groups (Ma and Gang 2006), Curcuminoids, which belong to a class of compounds namely diarylheptanoids (Araújo and Leon 2001) essential oils, consisting sesquiterpenes. The chemical compounds are elucidated in Table 2.

Table 2: Chemical constituents of *Curcuma longa* L.

Compound name	Structure	References
1. Curcumin		Niranjan et al. (2003)
2. Demethoxycurcumin		Gomes et al. (2002)
3. Bisdemethoxycurcumin		Unnikrishnan et al. (1995)
4. Ar-turmerone		Kapoor (1990)
5. α-turmerone		Kapoor (1990)
6. Curlone		Kapoor (1990)
7. α-phellandrene		Kapoor (1990)

8. Cineole		Kapoor (1990)
9. Borneol		Kapoor (1990)
10. Sabinene		Kapoor (1990)

Curcuminoids

Curcuminoids are available in the rhizome extract of *Curcuma longa* mainly consisting of 3 components namely curcumin, demethoxycurcumin and bisdemethoxycurcumin. Curcumin is the most important one among them, making up around 90% of curcuminoids (Chainani-Wu 2003), which also gives the yellow color and has a broad spectrum of pharmacological activities like antioxidant and anti-inflammatory effects.

Essential oils

Steam distillation is used to extract essential oils from *Curcuma longa* (Kuttan et al. 2011) and it was seen that major constituents were found as ar-turmerone, α-turmerone, α-phellandrene and curlone. Interestingly, it was seen that the chemical components of essential oil of *Curcuma longa* varies markedly geographically (Oyemitan et al. 2017). Although all studies concluded that ar-turmerone has the highest percentage (60-68%) among chemical constituents (Singh et al. 2011), in Iran and Malaysia, α-turmerone had the highest percentage after ar-turmerone, while it is α-phellandrene on Vietnamese species (Oyemitan et al. 2017). These are sesquiterpenoids, also having a wide range of pharmacological activities. Since they have low weight, they can transport easily across plasma membranes to initiate biological activities. As of present, they're getting popular gradually for their potential use as preservatives and antioxidants (Kuttan et al. 2011). A recent study found that the underground stem (rhizome) of this plant contains around 4% essential oils. The main components identified through a gas chromatography analysis were ar-turmerone (40%), α-turmerone (10%), and curlone (23%) (Guimarães et al. 2020).

Among plant parts, rhizome yields the most identified chemical components, ranging to about 87% and followed by roots (67%), leaves (52%) and shoots (41%). Furthermore, 17% compounds were found only in rhizomes while others like shoots contained no shoot-specific compounds (Verma et al. 2018).

Plant pharmacology

Curcuma longa is a wonder drug, because only very few crude drugs exist with such a vast range of pharmacological activities. Some well renowned therapeutic uses are given below:

Antioxidant activity

The essential oil of *Curcuma longa* has a very potent antioxidant activity. *C. longa* and its active component, curcumin, exhibit significant antioxidant activity comparable to that of vitamins C and E in both water- and fat-soluble extracts. Curcumin aids in the elimination of hydroxyl radicals, singlet oxygen, superoxide radicals, nitrogen dioxide, and nitric oxide (NO) from the body. Furthermore, pretreatment with curcumin has been shown to reduce ischemia-induced mutations in the heart (Dikshit et al. 1995). The concentration of essential oil for 50% scavenging of hydroxyl radicals, superoxides and lipid peroxidation were 200 µg/mL, 135 µg/mL and 400 µg/mL, respectively. Weak DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity was also shown at more than 1000 µg/mL. In addition to that, elevated levels of free radicals scavengers like superoxide dismutase, glutathione peroxidase, catalase were noticed in Swiss albino and Balb/C mice treated with 100 mg/kg body weight while highest activity at 500 mg/kg b.wt. It is assumed that presence of a phenyl ring as well as 13-unsaturated ketone function in ar-turmerone is responsible behind antioxidant activity (Kuttan et al. 2018). Previous studies have demonstrated that Curcuma longa can protect hippocampal cells in male Wistar rats from damage induced by lead and can reduce lipid peroxidation caused by toxic heavy metals. (Al-Basher et al. 2020) found that both resveratrol and curcumin mitigate oxidative stress in tissues by boosting antioxidant responses and scavenging free radicals, often working synergistically to repair this damage.

Besides, curcumin and its derivatives demethoxycurcumin, bisdemethoxycurcumin exhibited hemoglobin protection from oxidation at even 0.08M while diacetylcurcumin didn't show much of an effect in this nitrite induced oxidation. It has also shown lipid peroxidation inhibition in rat liver microsomes, brain homogenates and erythrocyte membranes which is important since lipid peroxidation plays an important role in cancer, inflammation and cardiovascular diseases. Phenolic and methoxy moiety present on the phenyl ring as well as 1,3-diketone system of curcumin might be responsible behind this effect. The diketone system also can bind metals like iron (Araújo and Leon 2001).

Moreover, methanolic, hot water and acetone extracts of rhizomes has also shown antioxidant activity in scavenging DPPH (2,2-diphenyl-1-picrylhydrazyl) and ferrous ion in DPPH (2,2-diphenyl-1-picrylhydrazyl), FTC (ferric thiocyanate) and FRAP (ferric reducing ability of plasma) assays. Curcumin also protects from oxidative stress through blocking superoxide anion production as well as promoting nitric oxide release which can relax the porcine coronary arteries (Niranjan and Prakash 2008).

Interestingly, a study found out that the antioxidant activity of a plant extract is directly proportional to its phenolic components, owing to their ability to donate hydrogen atoms and capture free radicals. This theory is applicable even when the plant extracts are used coherently. For example, in DPPH (2, 2-diphenyl-1-picrylhydrazyl) assay, mixture of kesum (*Polygum minus)* and turmeric and that of ginger (*Zingiber officinale)* and turmeric had significantly higher antioxidant activity than lone turmeric extract, (73.4 ± 2.7% and 68.6 ± 1.8%), respectively ($p<0.05$) (Maizura et al. 2011).

Alongside lowering production of ROS (reactive oxygen species) *in vivo*, it also inhibits hydrogen peroxide induced damage in cells like keratinocytes, NG 108-15 cells and fibroblasts. Moreover, curcumin reduces oxidized proteins of amyloid pathology in Alzheimer's transgenic mice. Two methoxylated phenols and an enol form of β-diketone, a unique conjugated structure of curcumin traps radicals by acting like a chain breaking antioxidant (Chattopadhyay et al. 2004). Thus, turmeric or curcumin is also very much effective in arthritis, healing wounds, reducing acne owing to their ability to eliminate free radicals (Verma et al. 2018).

Anti-inflammatory activity

Sandur et al. (2007) reported that curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the active compounds in *C. longa* that inhibit TNF-induced NF-κB activation. *Curcuma longa* essential oil showed anti-inflammatory activity in carrageenan induced, dextran induced and formaldehyde induced paw edema in female Balb/C mice. In carrageenan induced acute models, inflammation was reduced in the 3rd hour by 61.1%, 50% and 33.3% in 1000, 500 and 100 mg/kg b. weight, respectively compared to diclofenac 10 mg/kg control group which was 55.56%. The action is mediated by inhibition of prostaglandins, proteases and scavenging of superoxides. While in dextran models, inflammation was reduced in the 3rd hour by 58.8%, 47.1% and 35.3% in 1000, 500 and 100 mg/kg b. weight, respectively compared to the control group of diclofenac 10 mg/kg which was 52.94%. Histamine and serotonin released from mast cells are inhibited here. Moreover, inflammation is also reduced by inhibition of histamine, prostaglandins, serotonin and bradykinin in formaldehyde induced models. Since a lot of chronic illnesses like diabetes, cardiovascular and pulmonary diseases produce inflammation, *C. longa* essential oil has the potential to treat these diseases (Kuttan et al. 2011). A study by Uchio et al. (2021) investigated the effects of *Curcuma longa* extract on serum inflammatory markers, mental health, and mood disturbances in healthy overweight individuals, showing potential improvements in these areas.

Alongside acute models, *Curcuma longa* has been equally effective in the case of chronic inflammatory models like cotton pellet induced granuloma. Even though there is a considerable amount of debate regarding which constituent is responsible behind this, a synergistic action between curcumin analogues can be assumed, even though triethyl curcumin is being considered the most potent one. It was also found out curcumin can also cure acute inflammation (diethylnitrosamine induced) and hepatotoxicity (carbon tetrachloride induced) in livers in concentrations as low as 200 or 600 mg/kg body weight. It is assumed that presence of β-dicarbonyl system along with conjugated dienes is responsible for this activity while the dienes provide a significant lipophilicity for skin penetration as well (Araújo and Leon 2001).

Turmeric has also been significant in the local eye application as well, corresponding to a study of 25 cases of inflammation and bacterial conjunctivitis. Symptoms like burning sensation and eye redness were alleviated from day three and 23 patients were completely relieved by day six. Curcumin also has the potential to treat chronic inflammation in obesity by suppression of adipocyte macrophages and inhibition of MCP-1 release from them. Inhibition of G protein mediated phospholipase D (PLD) and inhibition of prostaglandins and leukotrienes owing to presence of hydroxyl and phenolic groups in molecules are two working theories regarding the cause of anti-inflammatory action of curcumin (Niranjan and Prakash 2008).

Interestingly, a study found out the superiority of *C. longa* crude extract compared to pure curcumin. At histamine H_4 receptors, which are responsible for chemotaxis, inflammation and autoimmune disorders, it was seen that methanolic extract of *C. longa* inhibited more than 70% of radioligand binding at 10 µg/mL. By purification of the extract, curcumin, demethoxycurcumin, and bis-(4-hydroxy-cinnamoyl) methane were found. The presence of complex carbohydrates, glycosides and polyphenols might be responsible behind a more potent activity (Frank et al. 2017).

Inflammatory mediators like phospholipase, COX-2, thromboxane, elastase, MCP-1, nitric oxide, IL-12, lipoxygenase, leukotrienes, prostaglandins, collagenase, hyaluronidase, interferon-inducible protein are effectively inhibited through curcumin. Besides, in sepsis, curcumin has been shown to reduce inflammation through PPAR-gamma upregulation, which leads to pro-inflammatory cytokine suppression and TNF-α expression and release. However, many studies showed that bisdemethylcurcumin is a better anti-inflammatory agent than curcumin due to suppression of TNF induced NF-κB activation and thus, more effective in inhibiting ROS. It also promotes wound healing in diabetic mice and rats (Chattopadhyay et al. 2004).

Antimicrobial activity

Several researchers have evaluated the antimicrobial activity of curcumin against various bacterial strains, including *Salmonella paratyphi*, *Trichophyton gypseum*, *Staphylococcus aureus*, *Streptococcus mutans*, and *Mycobacterium tuberculosis* (Tajbakhsh et al. 2008, Maghsoudi et al. 2017). The extract demonstrated antimicrobial efficacy against *Trichophyton longifusus*, *Microsporum canis*, and *Staphylococcus aureus*, and showed toxicity against *Lemna minor*. In a study involving rabbits treated with *C. longa*, the group exhibited significantly greater wound contraction, reduced inflammation, and increased collagen formation. Additionally, the ethanol extract of *C. longa* showed activity against *Shigella flexneri*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Lactobacillus*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, and *Salmonella typhi* (Oghenejobo and Bethel 2017). In a study concerning effectiveness of *Curcuma longa* essential oil against eye infecting pathogens namely *S. aureus, P. aeruginosa, C. Albicans* and *A. niger*, dose dependent inhibition was noticed with the MIC being 1-6 µL/mL in tube dilution method and 2.5 µL/disc in agar plate technique. The essential oil was bactericidal against *S. aureus* since it was killed just after 15 mins possibly due to cell wall synthesis inhibition (Gupta et al. 2015) while others took more than 24 hours (Singh et al. 2011). Besides, another study also showed inhibition of *S. aureus* growth at conc. 1-5000 ppm. Moreover, a study further showed antimicrobial activity of *Curcuma longa* extracts against *S. aureus*. The methanolic extract had the highest zone of inhibition at 19 mm at concentration 50 mg/mL while benzene extract had the least active one, 9 mm at 50 mg/mL (Gupta et al. 2015). Antifungal activity was also observed against *C. krusei*, C*. parapsilosis*, dermatophytes isolates, yeast as well as pathogenic molds (Niranjan and Prakash 2008). Ar-turmerone is credited for the antimicrobial activity. Turmeric extract also managed to hinder growth of intestinal lactobacilli. Thus, *C. longa* could be a good replacement of generally side effects causing antibiotics (Singh et al. 2011). Etemadi *et al.* (2021) found that *Curcuma longa* aqueous extract and chitosan exhibit significant synergistic antibacterial activity at concentrations of 512 µg/mL and 1,024 µg/mL against multidrug-resistant (MDR) pathogens. These include methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas*, carbapenem-resistant Enterobacteriaceae, AmpC-producing Enterobacteriaceae, and antibiofilm producers.

In vitro, curcumin is reported to prevent growth of *H. pylori* CagA+ strains (Verma et al. 2018). Curcuminoids were also found to be effective against spore germination in *C. coccodes, C. acutatum, C. gloeosporioides*. Bisdemethoxycurcumin was found to be the most effective one, which inhibited 100% of spores at 20 µg/mL. Interestingly, when it came to *in vivo* antifungal activity, only demethoxycurcumin showed activity, at concentration 500-1000 µg/mL with control values 92-97%, respectively which was comparable to Dithianon. *C. longa* leaves can also be used as an antidermatophytic agent owing to its fungicidal effect (Krup et al. 2013).

Moreover, turmeric extract was also effective against *Bacillus subtilis, Escherichia coli, Penicillium citrinin, Micrococcus* and *Streptococcus faecalis* at concentration of 1 mg/mL through determining zone of inhibition by agar well diffusion method. Even though the inhibition zone was smaller compared to antibiotics like

ampicillin and fungabacter, purified crude extract is surely to be more potent than standard antibiotics while providing a nutritional supplement as well (Ahamefula et al. 2014).

Antiviral activity

Interestingly, curcumin has also been found active against SARS-CoV-2, the reason behind the latest pandemic. In a randomized clinical trial study, patients who received curcumin with piperine as adjuvant showed faster symptomatic recovery (fever, cough, breathlessness, sore throat) and were able to maintain better oxygen saturation than the control group (Pawar et al. 2021). Moreover, it also acted as a prophylactic measure for cytokine storms within the patient's body by attenuating proinflammatory effects caused by angiotensin II-AT_1 receptors which decreased cytokines like TNF-α, IL-6 and ROS (Manoharan et al. 2020), while also preventing COVID coagulopathy due to inhibition of thrombin and FXa which reduces viscosity of blood (Pawar et al. 2021). In another *in vitro* study using vero E6 cells, curcumin provided a protective effect at a concentration 1.56-3.125 µg/mL. It is assumed that combination of curcumin extract with quercetin or naringenin could be very potent against SARS-CoV-2 (Leka et al. 2022). Regarding the mechanism, it was observed through an *in-silico* study that curcumin binds to both receptor-binding domain of S protein of virus as well as attachment sites of virus in ACE-2 receptor, thus working as an antagonist (Manoharan et al. 2020).

In vitro studies have also found out that Curcumin extracts have antiviral activity against Hepatitis B (Kim et al. 2019), Herpes Simplex Virus Type-1 (HSV-1) (El-Toumy et al. 2018), Dengue Virus Type-2 (DENV-2) (Ichsyani et al. 2017). Curcumin analogues like rosmarinic acid and dicaffeoylmethane have potential to be developed as anti-AIDS drugs since they can inhibit replication of HIV-1 and HIV-2 by blocking integrase protein (IC_{50}= 40µg/mL) as well as gene expression of HIV induced by UV light. Moreover, curcumin can also inhibit Epstein-Barr Virus (EBV) (Verma et al. 2018).

Antiprotozoal activity

In vitro studies against promastigotes using curcumin and methylcurcumin showed excellent results with the former having LD_{50} = 9 mg/mL and the latter showing better results with LD_{50} <5 µg/mL. *In vitro* studies have also proved efficacy of *C. longa* ethanolic extract against *P. falciparum, L. major* (Araújo and Leon 2001), African Trypanosomes (Niranjan and Prakash 2008), *L. amazonensis, Entamoeba histolytica* (Chattopadhyay et al. 2004) and against nematodes *Paramecium caudatum, Toxocara canis* (Araújo and Leon 2001). A synergistic action between the curcuminoids is assumed to be responsible behind the activity (Araújo and Leon 2001). *In vivo* studies in mice have reported 65.5% reduction in lesion size of footpad of animals along with no reported inflammation (Araújo and Leon 2001).

Anticancer activity

Annapurna et al. (2011) evaluated the prophylactic and therapeutic effects of *C. longa* in modulating N-methyl-N-nitrosourea-induced mammary cancer in rats over 24 weeks, using both oral and topical applications. They found that prophylactic topical application of *C. longa* at 200 mg/kg significantly reduced mean tumor volume compared to therapeutic topical application. This study was the first to demonstrate the anticancer activity of *C. longa* through topical application in a breast cancer model. Additionally, in an *in vivo* study involving CD-1 mice, the topical application of curcumin and dietary administration of 1% *C. longa* and 0.05% of its ethanol extract significantly reduced tumor incidence, tumor burden, and tumor volume in dimethyl benz[a]anthracene (DMBA)-initiated and 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumors (Huang et al. 1988). The pioneering work by Kuttan et al. (1985) first demonstrated curcumin's anticancer potential in both *in vitro* and *in vivo* experimental models. Research has also shown that circulating miR-21 levels are elevated in patients with hepatocellular carcinoma (HCC), suggesting its

potential as a diagnostic marker and therapeutic target, particularly due to its association with distant metastasis (Zhang et al. 2019). Li et al. (2020), demonstrated that in human hepatoma cell lines such as HepG2 and HCCLM3, the suppression of miR-21 enhances the anticancer effects of curcumin. This includes inhibition of cell growth, induction of apoptosis through upregulation of target genes, and increased TIMP3 expression, likely mediated by the inhibition of the TGF-β1/Smad3 signaling pathway.

C. longa has been evaluated against many cancer cell lines and positive results have been found for all of those. For example, in an *in vivo* study conducted with mice, Hepa1-6 cells were inoculated which formed liver tumors in all. However, in the group treated with *curcuma* oil, the size and weight of the tumors were reduced significantly, along with inhibition of metastasis both intrahepatic and peritoneal (Li et al. 2013). Besides, ethanolic extract of *C. longa* also showed dose dependent inhibition in human breast cancer cell line MDA-MB-231 with an IC_{50} 49± 2.08 µg/mL in 0.25% DMSO and 40 ± 1.03 µg/mL in 0.5% DMSO (Ahmad et al. 2016). *C. longa* extract has also been evaluated against cell lines A549, MCF-7, HT-29, HeLa which showed significant anticancer activity with IC_{50} values 5.18, 3.46, 2.73, and 7.66 g/mL, respectively (Panichayupakaranant et al. 2019). Curcumin also inhibits bone resorption, alongside apoptosis stimulation in rabbit osteoclasts (Araújo and Leon 2001). The induction of apoptosis and inhibition of cell-cycle prevents cancer cell growth in smooth muscle cells of aorta and colon carcinoma in rats (Verma et al. 2018). In Wistar rats, curcumin decreased the number of aberrant cells in cyclophosphamide induced chromosomal aberration at 100 and 200 mg/kg body weight. However, contradictory reports regarding enhancement of gamma-radiation induced aberration have been seen in Chinese hamster ovaries (Chattopadhyay et al. 2004). It is assumed that the anticancer activity is mediated through inhibition of tyrosine kinase as well as activation of caspase 9 and 3 for cell death (Chattopadhyay et al. 2004). Curcumin also promotes apoptosis in TK-10, UACC-62, HL-60, K562, scleroderma lung fibroblasts (SLF), PC-3, BxPC-3, Panc-1 cells and many more. A summarized picture of the mechanism of anticancer activity of *Curcuma longa* L. is given in Fig. 2.

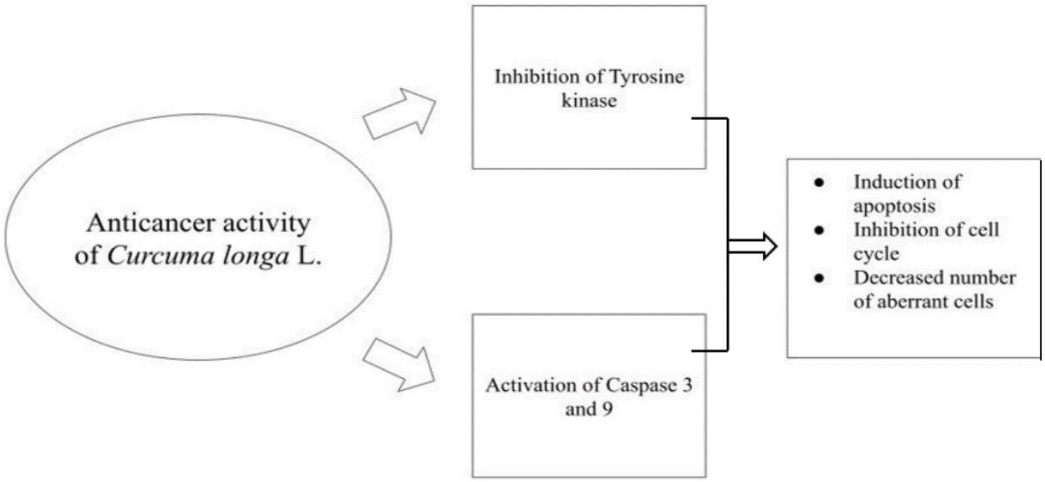


Fig. 2: Mechanism of anticancer activity of *Curcuma longa* L.

Hypolipidemic activity

In a study conducted with streptozotocin induced diabetic rats, 0.5% dietary curcumin was associated with significant decrease in LDL-VLDL fraction with the values 76.3±7.23 and 50.9±6.04 in control and curcumin group, respectively. While in blood triglycerides, the values were 242±19.3 mg/dL and 145.9±13.8 mg/dL in the control and curcumin group, respectively. The increased level of enzyme cholesterol 7 alpha-hydroxylase was noticed after inclusion of curcumin in diet and is assumed to be responsible behind the hypolipidemic activity (Babu and Srinivasan 1997).

Besides, in another study conducted with triton induced hyperlipidemic rats, feeding of 50% ethanolic extract of *C. longa* elevates the HDL-total cholesterol ratio with values 0.420 ± 0.031 compared to control group 0.290 ± 0.015 after 24h. A reduction of 88.6% was also seen in LDL cholesterol levels after 48h (Dixit et al. 1988). Moreover, concentration dependent increase in LDL-receptor-mRNA was seen after curcumin treatment in a study depicting the effect of it in hepatic gene expression using HepG2 cell lines (Niranjan and Prakash 2008). These can be potentially very useful in preventing atherosclerosis, which is also backed by a study in which mice fed with a turmeric incorporated diet had 20% less blockage in arteries compared to control group over an interval of 4 months (Krup et al. 2013). This prevention of atherosclerosis is also credited to the increase of alpha-tocopherol in the plasma after ingestion of turmeric. So, there is a possibility of interaction between curcumin and tocopherol which might increase bioavailability of Vitamin E and reduce cholesterol levels. Even though, curcumin has a positive effect on heart since it can cure defective Ca^{2+} in cardiac muscles by improving calcium transport from sarcoplasmic reticulum (Chattopadhyay et al. 2004) as well as preventing blood clots in the walls of arteries (Verma et al. 2018), the prevention of atherosclerosis is of much more credit.

Effect as a gastrointestinal agent

According to Ammon and Wahl (1990), it has been demonstrated that curcumin enhances the secretion of gastrin, secretin, and bicarbonate, as well as increases the production of gastric wall mucus and pancreatic enzymes. Additionally, research by (Rafatullah et al. 1990) indicates that it inhibits intestinal spasms and the formation of ulcers induced by stress, alcohol, indomethacin, pyloric ligation, and reserpine, while also alleviating symptoms in patients with dyspepsia. In a phase II clinical trial conducted on patients suffering from peptic ulcer, the administration of 2 capsules (300 mg each) containing turmeric, five times daily, healed ulcer at 48% (12 cases), 72% (18 cases) and 76% (19 cases) after 4, 8, 12 weeks, respectively. Moreover, 19 of 25 patients had no more ulcers after 12 weeks. It is assumed that ar-turmerone or curcumin is responsible for this anti-ulcer activity. Turmeric may impart a local anesthetic action on the stomach which inhibits secretion of gastrin. Although this trial had no adverse effects, interestingly it is also known that high doses of curcumin at 100 mg/kg body weight can cause ulcer itself. Although the mechanism is not known yet, it is assumed that increase in gastric acid and/or pepsin secretion as well as mucin reduction is responsible for this. Besides, curcumin was also reported to stimulate mucin secretion in rabbits also which protected against ulcer and prevented gastric necrosis induced by HCl in rats. Another way it prevents ulcers is through its anti *H. pylori* activity by inhibiting NF-kappa-β activation and IL-8 induction (Prucksunand *et al.* 2001). This inhibition also ameliorated gastric injury in NSAIDS induced gastropathy in rats (Krup et al. 2013).

Curcumin is also effective on other parts of GIT except the stomach. In the intestine, curcumin imparts antiflatulent and antispasmodic activity tested in rats and guinea pigs, respectively while also enhancing sucrase, lipase and maltase activity (Chattopadhyay et al. 2004). In the liver, curcumin showed hepatoprotective activity in cultured rat hepatocytes against carbon tetrachloride, D-galactosamine, ionophore, peroxide, diethylnitrosamine and 2-acetylaminofluorene induced toxicity (Chattopadhyay et al.

2004). Moreover, powder of rhizome mixed with amla juice has also been effective in jaundice. It promotes apoptosis of damaged hepatocytes and its ability to scavenge free radicals and increase glutathione peroxidase levels is assumed to aid its ability in hepatic detoxification (Krup et al. 2013). In pancreas, curcumin is reported to increase bicarbonate levels and activities of pancreatic amylase, lipase, trypsin and chymotrypsin (Chattopadhyay et al. 2004).

Antidiabetic activity

In the management of diabetes mellitus, adding *C. longa* rhizome powder to Amla juice and honey proves especially advantageous. Curcuminoids, the active compounds in the rhizome, mitigate lipid peroxidation by maintaining elevated levels of superoxide dismutase, catalase, and glutathione peroxidase. Studies involving patients with type-II diabetes mellitus have shown that curcuminoids improve insulin resistance, lower glucose and insulin levels, increase adiponectin secretion, and reduce levels of leptin, resistin, interleukin (IL-6, IL-1β), and TNF-α (Hajavi et al. 2017). The antidiabetic activity of *C. longa* has been observed both *in vivo* and *in vitro*. In an *in vivo* study conducted with type-II diabetic mice, 0.2g/100g diet and 1g/100g diet of ethanolic extract showed significant hypoglycemic effect compared to the control group where both were administered for 4 weeks. This ethanolic extract also stimulated differentiation of adipocytes. This differentiation is assumed to be related with PPAR-gamma ligand binding of the extract which suppressed increase of blood glucose in the mice (Kuroda *et al.* 2005). In another study conducted with alloxan induced diabetic rats, methanolic extract showed superiority over aqueous and n-hexane at 400 mg/kg body weight for 4 weeks (Mohammed et al. 2015). Turmeric also augments effects of antidiabetic medications and lowers the body's resistance to insulin in order to prevent type-II diabetes (Verma et al. 2018). Freeze dried rhizome powder dissolved in milk also has antidiabetic potential with inhibitory action of pancreatic amylase, which reduces starch hydrolysis leading to low glucose levels (Krup et al. 2013).

Impact on nervous system

Curcuma oil mitigates the adverse effects of ischemia by reducing nitrosative and oxidative stress. Ischemia typically results in the collapse of mitochondrial membrane potential, the release of cytochrome c, alterations in the BAX: BCL-2 protein ratio, and activation of caspases, all of which sequentially trigger apoptosis. Curcuma oil significantly inhibits these processes. Consequently, evidence suggests that Curcuma oil offers neuroprotective benefits and possesses a broad therapeutic window for reducing ischemic brain injury (Dohare et al. 2008). Curcumin also showed significant neuroprotective activity in ethanol-induced brain damage. Ethanol, a powerful neurotoxin, is responsible for disruption of the central nervous system, leading to cognitive and behavioral impairment and can lead to cerebral edema and hemorrhage in toxic doses. In a study conducted with rats, it was seen that curcumin reduced the amount of cholesterol, phospholipid and free fatty acids after treatment of alcohol previously. The cholesterol, phospholipid and free fatty acid levels dropped to 1654.18 ± 41.70, 2011.49 ± 111.26, 39.865 ± 7.28 from 2031.08 ± 64, 2795.08 ± 146.26, 53.08 ± 6.95 respectively (mg/100g tissue) (Rajakrishnan et al. 1999). Curcumin can also act as a neuroprotective agent in Parkinson's disease pathogenesis. Conventionally, it is assumed that people of the Indian subcontinent have a lower prevalence of Alzheimer's and Parkinson's due to chronic consumption of spices like curcumin compared to Caucasian brains. Curcumin protects Parkinson's in a number of ways. Primarily, it was seen in rats that antioxidant activity of curcumin protects substantia nigra neurons, regulates iron metabolism and improves dopamine levels. It is worth mentioning that increased iron content is a major factor in pathogenesis of Parkinson's since it auto-oxidizes dopamine and also produces hydroxyl radicals. AP-1 binding, which plays a major role in oxidative stress, was dose-dependently inhibited by curcumin at 1 and 10 μM concentrations. Curcumin also reduces aggregation of α-synuclein, a protein associated with Parkinson's, by increasing its solubility, making it non-toxic. Compared to anti-Parkinson's drugs available in

the market, curcumin can cross the blood-brain barrier more readily although its therapeutic application is limited by its poor availability. It is possible to develop curcumin as a novel drug for treatment of Parkinson's by solving its bioavailability issues through proper clinical and preclinical studies (Mythri et al. 2012). On the other hand, *C. longa* can also inhibit monoamine oxidase (MAO) and promote serotonin and dopamine production to healthy levels (Verma et al. 2018). A high dose of essential oil of *C. longa* (200 mg/kg) intraperitoneal served as an anxiolytic agent in mice and had more sedative effect than a standard diazepam dose (Oyemitan et al. 2017). In ischemic brain injury, curcumin played a significant protective role by decreasing oxidative and nitrosative stress. As a potential anti-Alzheimer's agent, curcumin can reverse the amyloid pathology while also decreasing inflammation and oxidation (Krup et al. 2013). Vascular dementia can be prevented by curcumin and complex manganese owing to its antioxidant activity (Chattopadhyay et al. 2004).

Other pharmacological actions

Apart from these, *C. longa* also exhibits other various pharmacological effects. For example, in a study conducted with asthmatic rats, it was observed that all concentrations of *C. longa* decreased total WBC, Immunoglobulin E, NO_2, bronchoalveolar lavage fluid (BALF) levels of phospholipase A_2, etc. (Boskabady et al. 2021). Furthermore, compared to dexamethasone, all concentrations of curcumin decreased total WBC count more effectively than it ($p<0.05$ upto $p<0.001$) (Shakeri et al. 2017). Curcumin can also act as a vaginal contraceptive. In an *in vitro* study conducted with incubated sperms, curcumin decreased sperm motility to 53.4±2.44, 4.1±1.41, 0 at 30, 100, 300 µg/L, respectively. The viability of sperms also decreased in a dose-dependent manner (Rithaporn et al. 2003). Ar-turmerone also acts as a potent anti-venom agent. In a study conducted with mice using *Bothrops jararaca* and *Crotalus durissus* venom, injection of 12.5 µg *Crotalus* venom saved 3/6 and 4/6 mice in whom 600 and 700 µg/mL ar-turmerone were injected i.p. It is assumed that ar-turmerone acts as an enzymatic inhibitor of venom enzymes having hemorrhagic activity (Ferreira et al. 1992). Moreover, in an ultraviolet-B induced skin aging assay, *Curcuma longa* essential oil showed anti-aging effects. It was observed that, epidermal hyperplasia and production of inflammatory cytokines such as IL-1β and TNF-α were decreased in mice treated with essential oil of *C. longa* compared to control group and ar-turmerone, curlone and β-turmerone were deemed as the major contributors (Zheng et al. 2020). In healing wounds from third-degree burns, the role of *C. longa* was also observed. In a study conducted with rabbits, a composite of nano ZnO and nano *C. longa* took the fastest time to heal third-degree burn wounds (average 24.25±0.5 days) compared to only nano ZnO (average 26.25±0.5 days), only *C. longa* (average 28±0.62 days) and control (36.25±0.5 days) (Bhutta et al. 2021). Against gamma-irradiation induced oxidative stress in rats, treatment of aqueous extract of *C. longa* for 21 days before and 7 days after exposure improved transaminase disorders, lipid peroxidation, release of TNF and IL-6, superoxide dismutase-1 and peroxiredoxin-1 protein levels compared to control group exhibiting a radioprotective effect (Nada et al. 2012). Interestingly, even though curcumin is known for its antioxidant properties, in presence of trace metals in cells like copper, curcumin can create ROS and cause DNA damage in HL60 cells, thus, acting as a prooxidant. The conjugated β-diketone structure of curcumin helps binding and reducing copper in this regard (Yoshino et al. 2004). Furthermore, in a study conducted with mouse regarding food allergy symptoms, it was observed that administration of turmeric extract (100 mg/kg) and curcumin (3 mg/kg or 30 mg/kg) reduced rectal temperature as well as anaphylactic response while also inhibiting IgE, IgG1, mMCP-1 levels which were increased at first by challenging mice with ovalbumin and alum. A significant balance of Type-1/Type-2 helper T cells was also achieved, although turmeric extract proved to be more useful than curcumin (Shin et al. 2015). Curcumin also has anticoagulant properties, being an inhibitor of both extrinsic and intrinsic pathways. In activated partial thromboplastin time (aPTT) assay and prothrombin time (PT) assay, the time taken for curcumin at 0.1 µm and 50 µm were 37.2 ± 1.3, 119.8 ± 0.9 (s) [aPTT] and 17.4 ± 0.3, 35.2 ± 0.4 (s) [PT] respectively, compared to heparin whose values were found >300 (s) at 1.5 µg/mL

[aPTT] and 61.5 ± 0.5 (s) at 15 µg/mL [PT]. Curcumin also increased the bleeding time compared to control, which were 102 ± 2 and 54.2 ± 8 (s) but was less than heparin (158.6 ± 4) (s) (Kim et al. 2012).

Toxicity

Various acute and chronic toxicity studies have been carried upon administration of *C. longa*. In a study conducted with mice, acute doses at 0.5, 1, 3 g/kg body weight and chronic doses 100 mg/kg/day were administered. Firstly, no mortality was observed at any of the animals, although some CNS stimulation was observed at 3 g dose. Secondly, it was seen that the levels of RBC and WBC dropped more than the control animals. Thirdly, chronic treatment was seen to increase the weight of heart, lungs and also sexual organs in case of male mice. Increased sperm motility and sperm count was also seen in male mice with no spermatic toxic effects (Qureshi et al. 1992). Besides, in other studies, curcumin up to 5 µg/mL didn't cause any toxic effects and was metabolized rapidly (Araújo and Leon 2001). In clinical trials, it was observed that administration of turmeric up to 2.2g daily by a 60 kg individual was safe and caused no toxic symptoms. But in extremely high doses (5% turmeric daily), it was observed that it showed hepatotoxicity in rats (Chainani-Wu 2003). Owing to its anticoagulant properties, caution should be maintained during administration if the patient is already taking anticoagulant drugs like Clopidogrel or low dose Aspirin. Thus, it can be concluded that administration of *C. longa* doesn't cause toxicity in normal or low doses, in general. But, a safe level of administration (2g/60 kg body weight) should be maintained.

Conclusion

Curcuma longa is regarded as a universal panacea among herbal remedies. This potent medicinal plant is rich in numerous chemical components, including starch, essential elements, proteins, vitamins, volatile oils, curcumin, and curcuminoids. Curcumin, in particular, has a long history of use as a culinary spice, food colorant, and a key component in Ayurvedic and Chinese medicine. Over the past fifty years, extensive clinical studies have explored curcumin's efficacy, safety, and pharmacokinetic properties. Curcumin exhibits a wide range of beneficial effects, including anti-inflammatory, anticancer, and antioxidant properties. Notably, research has indicated potential strategies for incorporating natural products like curcumin in combating COVID-19. Given its non-toxic nature and extensive pharmacological activities, daily administration of turmeric could prevent various diseases. With further research into its mechanisms of action, *Curcuma longa* holds significant promise as a novel therapeutic agent.

Authors' contribution

The original idea was first generated by MSA. AIK and FA extensively reviewed the literature, prepared the initial manuscript and arranged the references section. JAC, AAC and SK critically reviewed the overall activities. The whole activity was supervised by MSA. All the authors read the review article meticulously and agreed to submit the article.

Conflict of interest

There is no conflict of interest, according to the authors.

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