ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

Antimicrobial and Anticarcinogenic Compounds from Endangered Plant *Curcuma zedoaria* (White Turmeric) and Pharmacological Activities – A Review

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Abstract

Around 80% of human population in the world relies on herbal or phytomedicines for their primary health care needs. The treatment of many diseases and disorders with phytomedicines is considered and observed as very safe with no or minimal side effects. Many medicinal plants and their preparations are practised at home as remedies for treating and preventing various diseases and disorders. *Curcuma* is a genus of about 100 accepted species in the family *Zingiberaceae*. Few known species of *Curcuma* with reported pharmacological activity are *Curcuma longa, Curcuma aeruginosa, Curcuma pseudomontana, Curcuma aromatica, Curcuma xanthorrhiza, Curcuma zedoaria, Curcuma angustifolia*. For the past few decades, extensive work has been done to establish the biological activities and pharmacological actions of Curcuma species and its extracts. *Curcuma zedoaria* (White turmeric) is a perennial herb found in tropical and sub-

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

tropical countries such as India. The medicinal properties of *C. zedoaria* has been used from ancient times globally in both Ayurvedic and Unani system of medicine. Hence in the present review of literature we mainly aimed to describe and delineate on the antimicrobial and anticarcinogenic compounds of medicinal plant *C. zedoaria* and its pharmacological activities.

Keywords: *Curcuma Zedoaria*,White turmeric, Curcumin, Antimicrobial, Anticancer

Introduction

Although modern medicine has been routinely used in the treatment of various diseases, it is 100 years old. The genus was first established by Carl Linnaeus in 1753. The name Curcuma is derived from the Arabic word kurkum, meaning "yellow," which refers to the color of the rhizome. Traditional medicine, in comparison, has served mankind for thousands of years and is quite safe and effective. The mechanism or the scientific basis of traditional medicine, however, is less well understood. Throughout the Orient, Curcuma species is traditionally used for both prevention and therapy of diseases. Modern *in-vitro* studies reveal that Curcuma species is a potent antioxidant, anti-inflammatory, antimicrobial, and anticancer agent.[1]

India is popularly known as the "Spice Bowl of the World" as a wide variety of spices with premium quality is grown in the country since ancient times. However, among all those ancient spices, one which is virtually associated and intertwined with all individuals in issues related to food as well as life, so far as aroma, taste, flavor, color, society, religion, economy, ecology, and emotion is concerned, which is turmeric. Turmeric not only adds golden grace but also considered as the golden spice and grown almost all over the world, especially in India, Bangladesh, Burma, China, Indonesia, Myanmar, Nigeria, Pakistan, Sri Lanka, Taiwan, etc. Among these countries, India occupies the first position in area (2,22,000 ha) and in production

(11,32,000 MT). Extensively cultivated in Southeast Asia specifically Bengal, China, Taiwan, Sri Lanka, Indonesia. Among these compounds, curcumin, which is mainly found in *Curcuma longa*, is the most widely investigated. In the past several decades, this compound has been studied in numerous comprehensive reviews examining its structure, synthesis, derivatives, and biological activities. Many species of the genus *Curcuma caesia, Curcuma rubescens, Curcuma amada, Curcuma leucorrhiza, Curcuma montana, Curcuma aromatica, Curcuma zedoaria, Curcuma angustifolia, Curcuma pseudomontana, Curcuma longa*, etc. are there with huge diversity and enormous medicinal usage.[2]

In present time, we all are well aware with the clinical importance of yellow turmeric mentioned as Haridra (*Curcuma longa* Linn.) of *Zingiberaceae*family in Ayurvedic texts. Its use is widely seen in every household and is seen as an effective medicinal herb used traditionally since ancient times in various diseases. The medicinal properties of white turmeric which belongs to the same family as Haridra, are almost similar to yellow turmeric. *Curcuma zedoaria*also goes by the name Kachur in Ayurvedic texts has been used from ancient times globally in both Ayurvedic and Unani system of medicine. It is native to tropical and sub-tropical humid forests along with eastern Himalayas and can be both wild or cultivated.[3,4]With these viewpoints in the present narrative review of literature we mainly aimed to describe and delineate on the antimicrobial and anticarcinogenic compounds of medicinal plant '*Curcuma zedoaria*' and its pharmacological activities.

Geographical and Botanical Description of *C. Zedoaria*

C. zedoaria is indigenous to tropical and sub-tropical humid regions of countries like India, China, Bangladesh, Thailand, Indonesia, Japan (South-east Asia). It can also grow up to an altitude of 900m with a humid climate having 100-120cm of rainfall. It generally requires loam

ISSN PRINT 2319 1775 Online 2320 7876
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or red soil to grow. Flowering can be seen in summers and later on fruits start to grow. In India, it grows wild in Eastern Himalayas, moist deciduous forests of the Coastal tract of Kanara and hilly regions of Orissa. Also, it is widely cultivated throughout India especially in Bengal for its tuber which is a source of Shoti starch, given as a substitute for barley and arrowroot.[3,4]

C. zedoaria is a tuberous herb which generally grows to a height of 45cm and closely resembles to *Curcuma longa* (Yellow Turmeric) but has a less intense aroma ranging in between turmeric and mango. Root stocks are large and ovoid with many sessile tubers pale yellow or whitish from inside and 1 inch diameter. Leaves are large, 30-60cm long, oblong, glabrous, acuminate, narrow at the bottom, with purple from the middle. The petiole is green and longer than the blade. The flowers are pale yellow and shorter than bracts of the coma which is bright red in color overlapping the flower. Capsules ovoid, trigonous, smooth; vernal spikes; Calyx obtusely toothed, whitish and half as long as the funnel-shaped Corolla tube (Figure 1). The rhizome/fruits are triangular, elliptical, smooth with 3-valved capsules, and seed are white, oblong, arillate.[3,5]

Figure 1: Showing *C. zedoaria* plant

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Figure 2: Showing rhizome of *C. Zedoaria*

Phytochemical constituents of *C. Zedoaria*

*C. Zedoaria*is found to possess different types of primary and secondary metabolites. The main components of plant are starch, curcumin, essential oil and Arabic gums. The rhizome of the plant is found to possess more than 10 sesquiterpenes which include curcumin (1), ethyl p-methoxycinnamate (2), β-turmerone (3 and 4), β-eudesmol (5), zingiberene (6), dihydrocurcumin (7), furanodiene (8), α-phellandrene (9), 1,8 cineole (10), β-elemene (11) and germacrone (12) as shown in Figure 3.[6]

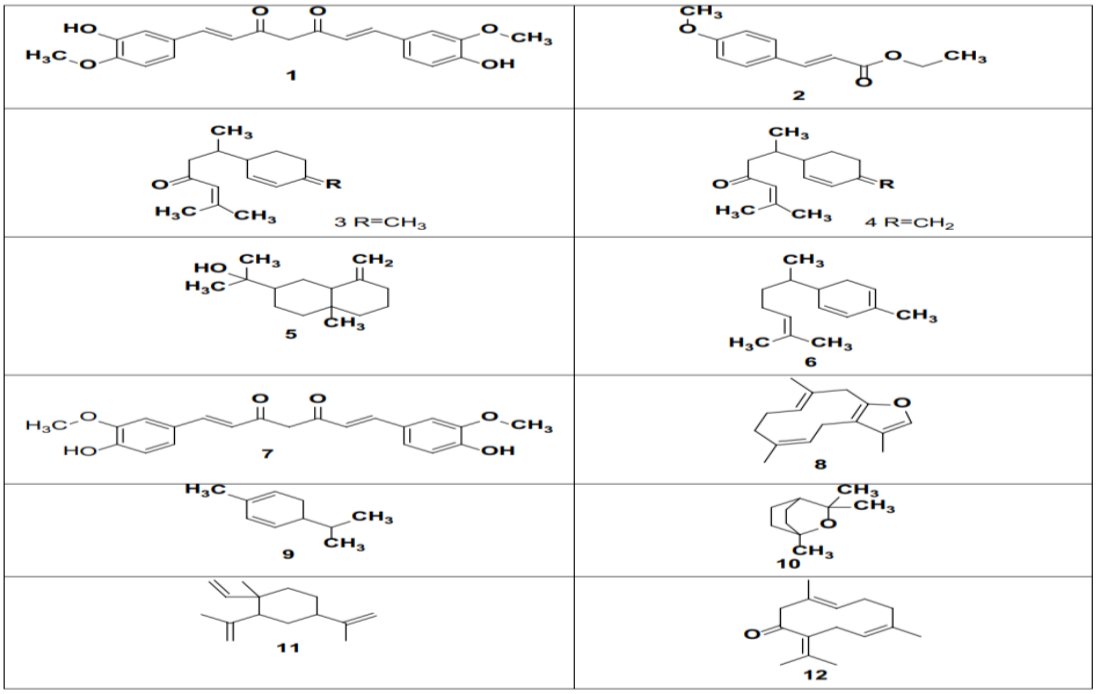

Figure 3: Showing chemistry of active phytoconstituents of *C. Zedoaria*
[Curcumin (1), ethyl Para-methoxycinnamate (2), β-turmerone (3 and 4), β-eudesmol (5), zingiberene (6), dihydrocurcumin (7), furanodiene (8), α-phellandrene (9),1,8 cineole (10), β-elemene (11) and germacrone (12)]

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Furthermore, the biological activities of chemical constituents of *C. Zedoaria*were as represented in Table 1.

Table 1: Chemical constituents of *C. Zedoaria* and their biological activities

S. No.	Biological Activity	Chemical Constituent of *C. zedoaria*	Reference
1	Analgesic& Antinociceptive activities	Curcumenol	Christiane *et al.*, (2006)[7]
		Dihyrocurdione	
2	Anti-allergic activity	Curcumin	Matsuda *et al.*, (2004)[8]
		Dihydrocurcumin	
		Tetrahyrodemothxycurcumin	
		Tetrahydrobismethoxycurcumin	
3	Cytotoxic activity	A-Curcumene	Saetung*et al.*, (2005)[9] Myoungae *et al.*, (2003)[10]
		b-tumerone	
		Zerumbone	
		Zerumboneepoxide	
		Diferuloylmethane	
		Di-p-coumaroylmethane	
4	Anticancer activity	Curcumin	Syu*et al.*, (1998)[11]
		Demothxycurcumin	
		Bisdemothxycurcumin	
5	Hepatoprotective activity	Furanodiene	Matsuda *et al.*, (1998)[12]
		Germacrone	
		Curdione	
		Neocurdione	
		Curcumenol	
		Isocurcumenol	
		Aerugidiol	
		Zedoarondiol	
		Curcumenone	
		Curcumin	
6	Anti-inflammatory activity	Curzenone	Makabee*et al.*, (2006)[13]
		Dehydrocurdione	

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Traditional Applications of *C. zedoaria*

The decoction prepared from fresh rhizome of *C. zedoaria* was traditionally beneficial in cold when taken with cinnamon, black pepper and honey,[3] and used as a blood purifier. The juice of fresh rhizome Rubbed in mother's milk and given to infants suffering from diarrhea due to teething or exposure to cold. Tuber starch of *C. zedoaria* is source of shoti starch which resembles closely to arrowroot starch and is used as a baby food and convalescents, especially those recovering from chronic stomatitis.[4]

According to the traditional Chinese medicine, *C. zedoaria* rhizomes contain several specific sesquiterpenes that are effective against flatulent colic, debility of the digestive organs, amenorrhea, hepatocirrhosis, cancer, oxidation, and human blood aggregation.[14-19]

Compounds and Pharmacological Activities

Antimicrobialactivities

Ethanolic extract of *C. zedoaria* was tested against various pathogenic bacteria and fungi. The results obtained are based on antibacterial and antifungal activity as shown by essential oil of C. zedoaria on various organisms. Ethanolic extracts showed excellent activity against *Staphylococcus aureus* and *Trichophyton mentagrophytes*.[20]

The antimicrobial activity of extracts of *C. zedoaria* tubers was tested against six bacterial and two fungal strains using the agar well diffusion and broth dilution methods. Petroleum ether, hexane, chloroform, acetone and ethanol extracts exhibited antibacterial as well as antifungal activity. Acetone and hexane extracts of the tubers showed comparable antimicrobial activity as indicated by minimum inhibitory concentration (MIC) values. The MIC values for different strains and extracts ranged from 0.01 to 0.15 mg/ml. The findings also

support the use of C. *zedoaria* tubers in traditional medicine for the treatment of bacterial and fungal infections.[21]

The antimicrobial activity of oils obtained from *C. zedoaria* in Nepal was examined using the Petri plate–paper disk method. The microorganisms tested were *Staphylococcus aureus*, *Corynebacterium amycolatum*, *Escherichia coli*, *Candida albicans*, and *Aspergillus ochraceus*. All the examined oils indicated antimicrobial activity at similar levels. Hence, it was revealed that oils produced in Nepal could be effectively applicable to a variety of uses in terms of antimicrobial activity.[22]Furthermore, Uechi *et al.*,reported that in the broth dilution method, the MIC of *C. zedoaria* against *Bacillus cereus* was found to be 0.035% v/v. In addition, the effect of heating the essential oils on their antibacterial activity was also examined. The activity against *B. cereus* remained unaffected after heating at 121ºC for 20 min.[23]

The antimicrobial activity of *C. zedoaria* extract against some oral microorganisms was compared with the anti-microbial activity of five commercial mouthrinses to evaluate the potential of the plant extract to be incorporated into the formulae for improving or creating antiseptic activity. The in-vitro antimicrobial efficacy of plant extracts and commercial products was evaluated against *Streptococcus mutans*, *Enterococcus faecalis*, *S. aureus* and *C. albicans* using a linear regression method to evaluate the microbial reduction obtained as a function of the exposure time, considering effectiveness as a 99.999% reduction in count of standardized microbial populations within 60 s. The results showed that the antimicrobial efficacy of *C. zedoaria* extract was similar to that of commercial products, and its incorporation into a mouthrinse could be an alternative for improving the antimicrobial efficacy of the oral product.[24]

Huang et al., carried out a research investigation to study the antiviral effect of compound of *C. zedoaria*volatile oil. Results delineated that compound of *C. zedoaria* volatile oil was

effective via the mechanisms including virus killing, virus inhibiting, the prevention of the virus spread, and the treatment of the virus-related injury in MDCK. *In-vivo* studies indicated that compound of *C. zedoaria* volatile oil prolonged the mean survival days of the chickens, showing significant preventive effect in the chickens.[25] Furthermore, *C. zedoaria* has shown antiviral activity on Hepatitis C, Influenza and H5N1 viruses.

Anticarcinogenic activities

Anticancer activity

Ethanolic extract of *C. zedoaria* showed an inhibitory effect against OVCAR-3 cells (human ovarian cancer).[11,26,27]A Study caried out by Seo *et al.*, demonstrated that the water extract of *C. zedoaria* may play an important role in the inhibition of cancer metastasis.[28]A study conducted by Hong *et al.*, found that the methanolic extract of *C. zedoaria* had both anticancer and anti-inflammatory activity.[29] The inhibitors of prostaglandin biosynthesis and NO production have been considered as potential anti-inflammatory and cancer chemopreventive agents. Methanolic extracts of *C. zedoaria* showed potent inhibition of COX-2 activity (> 80% inhibition at the testconcentration of 10 mg/ml). Snehna et al., reported active fraction isolated from *C. zedoaria* possess anti-cancer activity against lung cancer and lymphoma cells together with chemoprotective effects.[30] Furthermore, Fitriana et al., demonstrated the beneficial effects of ethanolic extract of *C. zedoaria*as a therapeutic agent for breast cancer.[31]

Antitumor activity

The compound isolated from the rhizomes of *C. zedoaria*, characterized as isocurcumenol by the MS and IR spectra, significantly inhibited the cell proliferation in human lung, leukemia, nasopharyngeal carcinoma, and murine lymphoma cells. The *in-vivo* studies suggested the non-toxic nature of the compound at low doses and its antitumor effects in the ascetic tumor

development comparable to the standard drug used to treat lymphoma and cyclophosphamide. The present study highlights the antitumor potential of isocurcumenol isolated from *C. zedoaria* to be exploited further to be developed as a good antitumor agent.[32]

Anti-ulcerogenic activity

The root powder of *C. zedoaria* at a dose level of 200mg/kg significantly reduced the gastric pH, free acid, total acid and ulcer index in pyloric-ligated rats and the results were comparable to that of standard drug omeprazole (30mg/kg, i.p.).[33]

Anti-nociceptive activity

Using the acetic acid-induced abdominal constriction model in mice, the dichloromethane extracts from root, mother rhizome and rugous rhizome of *C. zedoaria* were collected in different seasons for studying its antinociceptive activity. At doses of 10mg/kg, the extracts obtained in autumn and winter season from mother rhizome caused considerable antinociceptive activity intraperitoneally inhibiting 91.1 and 93.4% of the abdominal constrictions, respectively. Also, curcumenol and dihydrocurdione compounds of *C. zedoaria* caused inhibitions of 64.0 and 46.0%, respectively, thus confirming that both compounds contribute towards antinociceptive and analgesic activity.[7]

Antimutagenic activity

Thirty-six commonly used anticancer crude drugs from Chinese herbs were studied for their antimutagenic activity, by using the Salmonella/microsomal system in the presence of picrolonic acid or benzo[a]pyrene to test whether they contained direct or indirect antimutagens. Each crude drug was extracted with boiling water for 2 h (i.e., the method commonly used by Chinese people to prepare the drug for oral intake). *C. zedoaria* was found to possess moderate activity against benzo[a]pyrene.[34]

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Antivenom activity

Aqueous extract of *C. zedoaria* was investigated for inhibitory activity by binding of anticobra venom antibody to antigen of cobra venom using the 96-well plate enzyme-linked immunosorbent assay method. In this study, the extract was allowed to react with immobilized venom before the addition of antivenom antibody. The extract of *C. zedoaria* showed clear inhibitory activity. It was found that the extract targeted neurotoxin and protein-degrading enzyme present in venom, thus suggesting the use of aqueous extract as antivenom.[35]

Anti-amoebic activity

Alcoholic extract of rhizome of *C. zedoaria* was able to inhibit the growth of Endamoeba histolytic at a concentration of 1–10 mg/ml.[33]

Anti-inflammatory activity

At a dose of 1µmol application, Curzenone and Dehydrocurdione compounds obtained from methanolic extract of the C. zedoaria rhizome suppressed 12-Otetradecanoyiphorbol-13-acetate (TPA) by 75% and 53% respectively and thus showed promising anti-inflammatory activity.[36]

Analgesic activity

From hydroalcoholic extract of rhizomes of *C. zedoaria* grown in Brazil different fractions like dichloromethane, ethyl acetate, methanol and curcumenol were prepared and tested for analgesic activity using several models of pain in mice in which Aspirin and dipyrone were used as standard drugs. Curcumenol showed promising analgesic effect as it came out to be several times more potent than the reference drugs when evaluated in the same experimental models. When given by the intraperitoneal route, dichloromethane extract presented a dose-dependent analgesic effect by inhibiting acetic acid induced writhing responses in mice.[37]

Anti-allergic activity

The 80% aqueous acetone extract of zedoaria rhizome cultivated in Thailand was found to inhibit the release of beta-hexosaminidase, as a marker of antigen-IgE-mediated degranulation in RBL-2H3 cells and passive cutaneous anaphylaxis reaction in mice. Four curcuminoids (Curcumin, Dihydrocurcumin, Tetrahyrodemothxycurcumin and tetrahydrobisdemethoxycurcumin) along with two bisabolane-type sesquiterpenes were isolated from the active fraction to study for degranulation. With a 50% inhibitory concentration (IC_{50}) of 5.3mM, curcumin showed the highest activity against beta-hexosaminidase release followed by bisdemethoxycurcumin (IC_{50} 11 mM).[8]

Hepatoprotective activity

Hepatoprotective sesquiterpenes were isolated from the aqueous acetone extract of the rhizome of *C. zedoaria*. Principal sesquiterpenes, furanodiene, germacrone, curdione,[23]neocurdione,[24]curcumenol, isocurcumenol, aerugidiol, zedoarondiol, curcumenone, and curcumin were found to show the potent protective effect on D-galactosamine (D-GalN)/lipopolysaccharide-induced acute liver injury in mice.[12]

Conclusion

In conclusion,*Curcuma* species are very promising medicinal plants with great pharmacological impact. *Curcuma zedoaria* is a well-known plant used in the Indian system of medicine. Traditionally, plant and its extracts have been used for management of various illnesses in human beings. Various parts of plant have been reported for the presence of complex phytoconstituents which include curcumin, ethyl p-methoxycinnamate, β-turmerone, β-eudesmol, zingiberene, dihydrocurcumin, furanodiene, α-phellandrene, 1-8 cineole, β-elemene and germacrone.

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