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Phytochemical and pharmacological properties of *Curcuma aromatica* Salisb (wild turmeric)

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ABSTRACT

Curcuma aromatica Salisb. (*C. aromatica*) is commonly known as wild turmeric. *Curcuma aromatica* is an essential herbal plant and it has been extensively used in traditional medicine for centuries. It has been used for the treatment of gastrointestinal ailments, arthritic pain, inflammatory conditions, wounds, skin infections, and insect bites. This article aims to review the phytochemical and pharmacological aspects of *C. aromatica* and to provide a guide and insight for further studies. Electronic repositories, including Web of Science, Google Scholar, ProQuest, Science Direct, Scopus, and PubMed, were searched until December 2019 to identify studies relating to *C. aromatica*. A systematic analysis of the literature on pharmacognostical, physicochemical, and nutritional contents, bioactive compounds, and biological activities of *C. aromatica* was carried out, and ideas for future studies were also coined. A total of 157 articles concerning *in vitro* or *in vivo* (or both) researches on *C. aromatica* have been evaluated. Analyses of the data showed that *C. aromatica* consists of various classes of compounds, including alkaloids, flavonoids, curcuminoids, tannins, and terpenoids, that formed the bases of its pharmacological activities. The reviewed data also revealed that *C. aromatica* possessed the pharmacological effect of anticancer, antidiabetic, antioxidant, anti-inflammatory, antimicrobial, antitussive, antiepileptic, analgesic, wound healing, and insect repellent activities. This review has systematically compiled and summarized the literature related to the nutritional values and bioactive compounds, as well as the biological activities of *C. aromatica*. To the best of our knowledge, this is the most comprehensive review reported on *C. aromatica*.

INTRODUCTION

Curcuma aromatica Salisb. (*C. aromatica*) is known as "vanaharidra" in Ayurveda, wild turmeric in English, "jangli haldi" in Hindi, and "Yu Jin" in Chinese. It is commonly used as a coloring and flavoring agent, as well as in many traditional medicines in Southeast Asian countries (Kanase and Khan, 2018). Therapeutically, it possesses a strong antimicrobial effect and has been used since ancient times as a remedy against various microbial infections (Ahmed *et al*., 2008). The rhizomes of *C. aromatica* are used in traditional medicine for eliminating blood stasis, delaying the ageing process, pain relief, and protecting against liver diseases (Dosoky and Setzer, 2018). Also, the rhizomes of *C. aromatica* are used internally as a tonic and carminative, while being topically applied for various skin ailments, sprains, bruises, as an antidote for snake venom, and also to enhance complexion (Ahmad *et al*., 2011; Dosoky and Setzer, 2018; Preethi *et al*., 2010; Xiang *et al*., 2017). Villagers in the northeastern part of India are using aqueous extracts and paste (with milk) of *C. aromatica* rhizomes and leaves for the treatment of indigestion, rheumatism, wound healing, and dysentery and also in the prevention of helminth infections (Sikha *et al*., 2015). In Thailand, the rhizome and roots of *C. aromatica* are often used in cosmetics and spas for skincare (Choochote *et al*., 2005). The traditional uses of *C. aromatica* rhizome extract as medicine are now being explored in modern scientific research for the possible development of modern medicine including but not limited to antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, antiangiogenic, antitussive, antiobesity, antiacne,

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antiallergic, and wound healing (Pant *et al*., 2013; Preethi *et al*., 2010; Revathi and Malathy, 2013).

The rhizome of *C. aromatica* has been reported to be rich in medically essential phytochemicals, such as alkaloids, flavonoids, curcuminoids, tannins, and terpenoids (Anoop, 2015; Kanase and Khan, 2018). As this plant has considerable therapeutic potential, the extraction and characterization of the essential bioactive compounds with vital medicinal properties may provide opportunities relating to pharmaceutical applications. Therefore, in this review, we have compiled and critically analyzed the reported studies on the phytochemical and pharmacological properties of *C. aromatica* rhizomes, leaves, and its essential oil. We hope this will provide future insight into the medical application of *C. aromatica* for the treatment of various diseases.

Botanical description

Curcuma aromatica, commonly known as wild turmeric, belongs to family Zingiberaceae and genus *Curcuma*. The genus *Curcuma* consists of 70–100 species that are generally rhizomatous herbs and are well known for their therapeutic potential (Ahmed *et al*., 2008). The most commonly found species are *Curcuma longa* Linn., *C. aromatica* Salisb., *Curcuma amada* Roxb., *Curcuma angustifolia* Roxb., *Curcuma caesia* Roxb., and *Curcuma zedoaria* Rosc. found in various regions of the world (Sikha *et al*., 2015). *C. aromatica* is only second to *C. longa* (turmeric) as the crucial species of the family (Ahmed *et al*., 2008; Shivalingu *et al*., 2016). *C. aromatica* is widely distributed in tropical and subtropical regions and mostly cultivated for its rhizomes mainly in India, China, and Japan (Ahmed *et al*., 2008; Sikha *et al*., 2015). *Curcuma aromatica* is an annual, erect herb with a characteristic light yellow aromatic rhizome and camphoraceous smell (Anoop, 2015). The plant develops clumps of erect, unbranched leaf stems that on full growth can reach a height of about 1 m from the stout, underground rhizome and with enlarged colored bracts tipped with pink. The inflorescences usually appear from the base of the rhizomes (Fig. 1A) before the leaves are produced in early spring. The flowers are fragrant and pinkish-white with an orange lip. The plant grows fast, wild, and vigorously in the monsoon season. The foliage dries in late autumn and the rhizomes remain dormant in winter; the rhizome (Fig. 1B), when mature, possesses a characteristic fragrance (Schultes, 1991).

Nutritional and physiochemical contents

Rhizomes are the main edible portions of *C. aromatica*. They are well known for their high nutritional value and are particularly rich sources of carbohydrates, proteins, alkaloids, flavonoids, vitamin C, beta-carotene, polyphenol, fatty acid, and essential oils (Ravindran *et al*., 2007). The rhizomes of *C. aromatica* are mainly used as a spice and food flavoring, as well as a coloring agent in food preparation due to their pleasant aroma and taste (Rajkumari and Sanatombi, 2018). The nutritional compositions of the rhizomes are crude protein (19.44%), lipid (2.5%), and carbohydrate (97.5%). The rhizomes also have a moisture content of 19% and an ash content of 3.21% (Jain and Parihar, 2017). Other physicochemical parameters reported elsewhere were ash content (16.6% total ash, 2.8% acid insoluble ash, and 3.93% water-soluble ash), extractive values (0.4% alcohol soluble extractive value and 0.8% water-soluble extractive value), and moisture content (3.14%) (Jain *et al*., 2016).

Phytochemical constituents

Qualitative and quantitative phytochemical analyses on different parts of *C. aromatica* are obtained via various extraction methods, and solvents are reported to commonly contain several essential classes of phytochemical compounds, including alkaloids, terpenoids, flavonoids, steroids, saponins, tannins, phenols, phytosterols, glycosides, protein amino acids, and volatile oils (Patil *et al*., 2019; Promod, 2018; Srividya *et al*., 2012).

The total phenolic content of the rhizome extracts of *C. aromatica* is reported in the range of 151.33 ± 13.9 µg/mg eq to gallic acid (Jain and Parihar, 2017) to 265 ± 1.08 mg/g of ascorbic acid (Srividya *et al*., 2012), and the total flavonoids content ranges

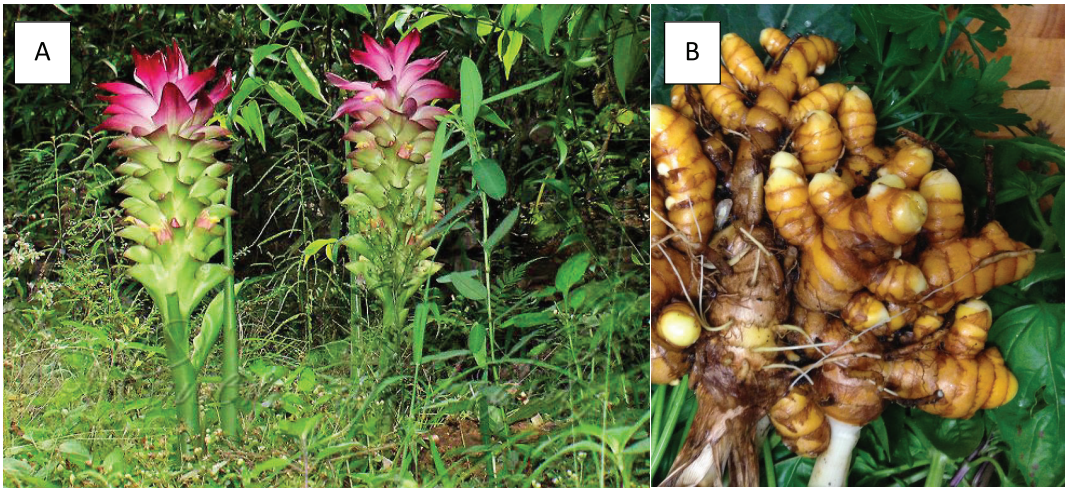

Figure 1. (A) Flowering cone of *C. aromatica* in its natural habitat (source: http://www.flowersofindia.net/catalog/slides/Wild%20Turmeric.html) and (B) fresh rhizomes of *C. aromatica* (source: https://www.gardentara.com/growing-organic-turmeric/).

from 106.8 ± 2.76 µg/mg eq to quercetin (Jain and Parihar, 2017) to 175 ± 1.56 mg/g of rutin (Srividya *et al*., 2012).

Thus, the presence of the above-mentioned phytochemicals shows the protective and disease preventive nature of the plant. It is also noteworthy to mention that there are not many phytochemical studies on the leaves of *C. aromatica* compared to other *Curcuma* species (i.e., *C. caesia*, *C. longa*, *C. amada*, and *Curcuma xanthorrhiza*) (Neha *et al*., 2013; Saxena and Sahu, 2012; Seema and Kaur, 2016).

Bioactive compounds

The bioactive compounds isolated and identified from the extracts and essential oils of *C. aromatica* obtained from different extraction methods are tabulated in Table 1 and 2, respectively. The chemical structures of some of the main bioactive compounds are shown in Figure 2. From the last three decades (1987–2019), a total of 79 major compounds have been identified from the leaves, rhizomes, and essential oils of *C. aromatica*. Most of the major compounds belong to alkaloids, flavonoids, curcuminoids, tannins, and terpenoids. Interestingly, there is no significant difference between the compounds found in the extracts of the leaves and rhizomes or their essential oils of *C. aromatica* grown either in the same or in different regions. A total of 37 (Table 1) compounds have been isolated and identified in the solvents extracts of leaves and rhizomes of *C. aromatica*. An additional 42 compounds were isolated and identified in the essential oils from the leaves and rhizomes (Table 2). The essential oils were also reported to have more potent antimicrobial, antioxidant, anticancer, and anti-inflammatory activities than the solvent extract counterparts (Xiang *et al*., 2018).

Table 1. Major compounds isolated from solvent extracts of leaves and rhizomes of *C. aromatica*.

Compounds isolated (≥ 5%)	Extraction method	References
n-Heneitriacontan-14-one	SE	Ahmad *et al*. (2011)
Stigmasterol		
n-Nonacosan-1-ol		
n-Pentatriacontan-5-one		
Curcumapentadecanol		
Curcumin	CM	Bamba *et al*. (2011); Tsai *et al*. (2018)
Isozedoarondiol		
Zedoarondiol		
Aerugidiol		
Demethoxycurcumin		
Epiprocurcumenol		
Isoprocurcumenol		
13-hydroxy-germacrone		
(2S)-2-hydroxycurdione		
(4S,5S)-(+)-germacrone4,5-epoxide		
Procurcumenol		
Curcumenone		
Curdione	SE	Huang *et al*. (2000)
Neocurdione		
Curcumol		
(R)-(+)-1,2-hexadecanediol		
Tetramethylpyrazine		
Curcumene	CM	Choochote *et al*. (2005)
1H-3a,7–methanoazulene		
Aromaticanoid (A to E)	SE	Dong *et al*. (2018)
Germacrone	CM	Pintatum *et al*. (2020)
Dehydrocurdione		
Zederone	CM	Pant *et al*. (2001)
β-Sitosterol		
β-Sitosterol-3-*O*-β-D-glucopyranoside	SE	Pant *et al*. (2013)
Vatirenene	SE	Revathi and Malathy (2013)
Androstan-17-one-3-ethyl-3-hydroxy(5à)		

SE = Soxhlet extraction; CM = cold maceration.

Pharmacological activities of *C. aromatica*

Various studies have been reported on the pharmacological activities of *C. aromatica* as summarized below and in Table 3.

Anticancer activity

Cancer is a disease characterized by an uncontrollable growth of cells in the human body, forming tumors of malignant cells (Greenwell and Rahman, 2015). Cancer is a major public health problem and the second leading cause of death in both developed and developing countries (Moraes *et al*., 2017). The current regimen, including surgery, chemotherapy, and radiotherapy, is often expensive and associated with severe side effects (Greenwell and Rahman, 2015). Hence, the focus has shifted to identifying new, safe, and cost-effective alternative treatment against cancer, preferably from natural sources. Bioactive compounds, including 1,8-cineole, ar-curcumene, ar-turmerone, β-elemene, camphor, curcumol, curdione, germacrone, linalool, xanthorrhizol, and zingiberene, from the essential oil of *C. aromatica* have been proven to possess anticancer properties.

Xiang *et al*. (2018) studied cytotoxic activities of essential oils extracted from the rhizomes of *C. aromatica* by colorimetric MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide] assay against prostate cancer cells line [lymph node carcinoma of the prostate (LNCaP)] and human hepatoma cells line (HepG2). The essential oils showed significantly higher anticancer activity against LNCaP (IC_{50} of 1.14 ± 0.02 µg/ml) than the HepG2 (IC_{50} of 168.94 ± 1.93 µg/ml). In another study, the infusion of essential oils via the hepatic artery exhibited rapid therapeutic effects in patients with primary liver cancer and transplanted hepatoma rat model, respectively (Cheng *et al*., 1999). The essential oils were also reported to have a protective effect against intestinal metaplasia and esophagoduodenal anastomosis in a rat model (Li *et al*., 2009). On the other hand, Hou *et al*. (2011) investigated the inhibitory effect of curdione isolated from the rhizome of *C. aromatica* on CYP3A4 using 1α,25-(OH)(2)-D(3)-treated Caco-2 clone cells. The results revealed that curdione showed the best inhibitory activity with IC_{50} of 3.9 µg/ml after 72 hours of treatment with no cytotoxic effect. Hence, it was concluded that the inhibitory activity of curdione accelerates the degradation of CYP3A4. The molecular mechanisms of apoptotic activity of curcumin

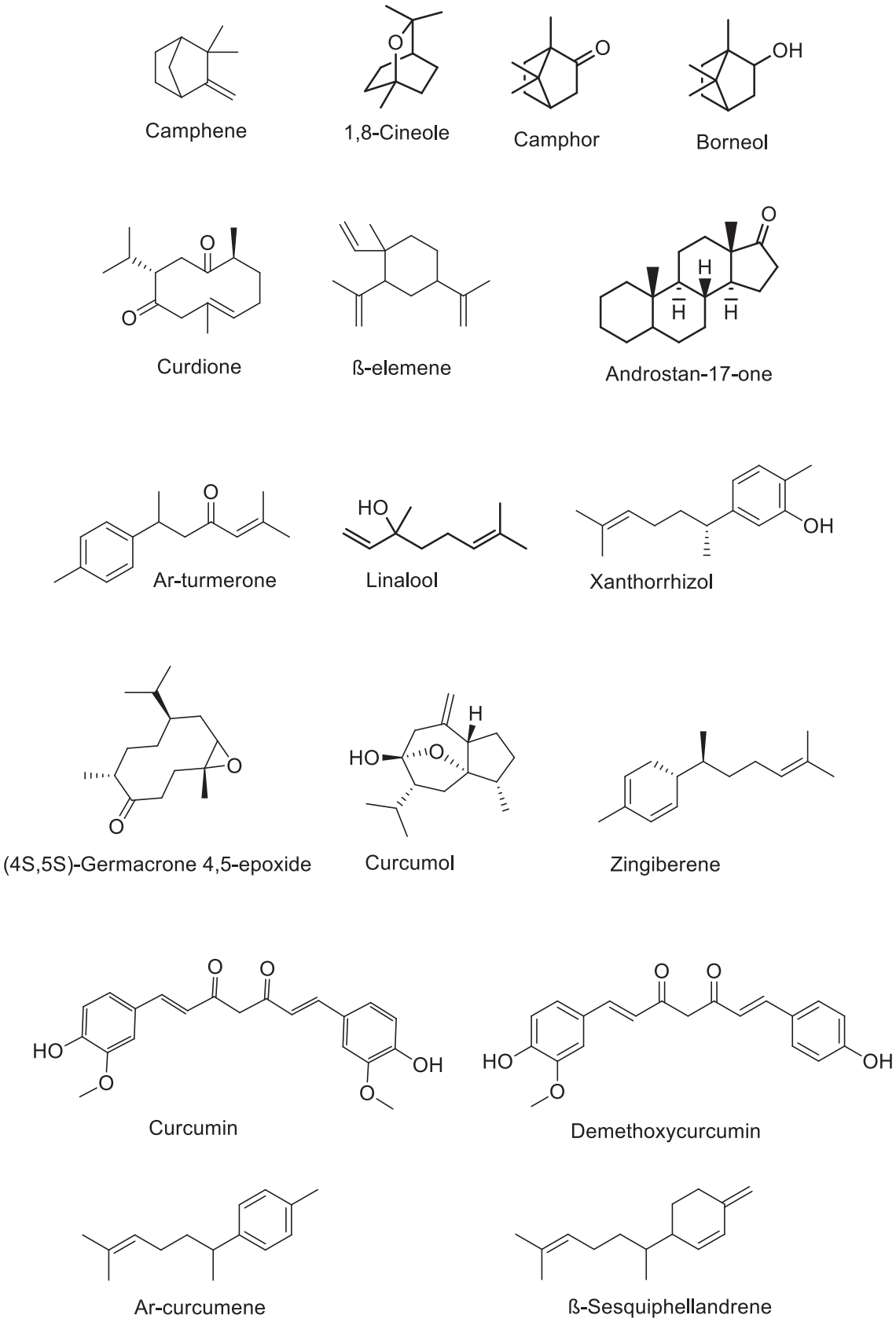

Figure 2. Chemical structures of some of the main bioactive compounds from extracts and essential oils from the leaves and rhizomes of *C. aromatica.*

Table 2. Major compounds isolated from the essential oils of leaves and rhizomes of *C. aromatica*.

Compounds isolated (≥ 5%)	Extraction method	References
Ar-curcumene	SD	Xiang *et al*. (2018)
β-curcumene		
Curzerene		
Curzerenone		
Zingiberene		
Camphor	HD	Choudhury *et al*. (1996); Gopichand *et al*. (2006); Kasai *et al*. (2019); Priyanka *et al*. (2019)
1,8-cineole		
Germacrone		
Isoborneol		
Camphene		
Limonene		
ar-turmerone	SD	Tsai *et al*. (2011)
Humulene oxide		
β-selinene		
P-cymene	HD	Singh *et al*. (2002)
α-terpineol		
2-oxabicyclo (3,2,1) octane-1-,4-dimethyl-8-methylene		
Curcumene	SD/HD	Choochote *et al*. (2005); Jarikasem *et al*. (2005)
1H-3a, 7–methanoazulene		
Caryo-phyllene oxide	HD	Al-Reza *et al*. (2010)
Patchouli alcohol		
Elsholtzia ketone		
Borneol	HD	Al-Reza *et al*. (2011)
Vinyldimethylcarbinol		
Cubenol		
Cucumber alcohol (2,6-Nonadien-1-ol)		
Linalool	SDE	Tsai *et al*. (2011)
Humulene oxide		
Curcumol		
Eucalyptol	SD	Chai *et al*. (2012)
Neocurdione		
Curdione	HD	Feng *et al*. (2013)
β- elemene		
Eugenol		
Isoledene	HD	Angel *et al*. (2014); Lee *et al*. (2014)
Bergamol		
Agarospirol		
α-caryophyllene		
β-guaiene		
β-sesquiphellandrene	SD	Herath *et al*. (2017); Xiang *et al*. (2018, 2017)
Ermanthin		
8,9-dehydro-9-formyl-cycloisolongifolene		

HD = hydrodistillation; SD = steam distillation; SDE = simultaneous steam distillation and solvent extraction.

isolated from *C. aromatica* were examined on human hepatoma SMMC-7721 cells (Yu *et al*., 2011). The curcumin significantly inhibited the growth of SMMC-7721 cells in a concentration-dependent manner and also induced apoptosis by modulation of apoptotic proteins (bax/bcl-2) in SMMC-7721 cells (Yu *et al*., 2011). A similar study by Dai *et al*. (2013) investigated the antiproliferative mechanism of the apoptotic effect of β-elemene isolated from *C. aromatica* on a HepG2 which revealed that β-elemene effectively inhibited the proliferation of HepG2 cells in a time- and dose-dependent manner. The induction of apoptosis in hepatoma HepG2 cells was by the upregulation of Fas/FasL expression.

Table 3. Biological activities of the main bioactive compounds in the extracts and essential oils of *C. aromatica*.

Bioactive compounds	Biological activity	References
1,8-Cineole	Analgesic	Takaishi *et al*. (2012); Zheng *et al*. (2019)
	Anticancer	Murata *et al*. (2013); Sampath *et al*. (2017)
	Antioxidant	Miri (2018); Torres-Martínez *et al*. (2017)
	Insect repellent	Obeng-Ofori *et al*. (1997)
Androstan-17-one	Antiepileptic	Kaminski *et al*. (2005)
Ar-Turmerone	Anticancer	Kim *et al*. (2013); Park *et al*. (2012); Schmidt *et al*. (2015)
	Antidiabetic	Lekshmi *et al*. (2012)
	Anti-inflammatory	Jantan *et al*. (2012); Oh *et al*. (2014); Rana *et al*. (2015)
	Antimicrobial	Amaral *et al*. (2014); Lee (2006)
	Antimutagenic	Jayaprakasha *et al*. (2002)
	Antivenom	Ferreira *et al*. (1992); Melo *et al*. (2005)
	Chemopreventive	Yue *et al*. (2010)
	Insect repellent	Ajaiyeoba *et al*. (2008); Ali *et al*. (2015)
	Neuroprotective	Hucklenbroich *et al*. (2014)
Ar-Curcumene	Anticancer	Schmidt *et al*. (2015)
β-Elemene	Anticancer	Jiang *et al*. (2016, 2017); Zhao *et al*. (2015)
	Antiangiogenic	Chen *et al*. (2011)
	Hepatoprotective	Liu *et al*. (2011)
β-Sesquiphellandrene	Antioxidant	Zhao *et al*. (2010)
Borneol	Analgesic	Xiong *et al*. (2013)
	Anti-inflammatory	Almeida *et al*. (2013)
Camphene	Analgesic	Quintans-Júnior *et al*. (2013)
	Hypolipidemic	Vallianou *et al*. (2011)
Camphor	Analgesic	Adams (2012)
	Anticancer	Wu *et al*. (2016); Zhang *et al*. (2019)
	Antimicrobial	Peng *et al*. (2012); Rahman *et al*. (2016)
	Antitussive	Kumar *et al*. (2012); Laude *et al*. (1994)
	Insect repellent	Chen *et al*. (2018); Fu *et al*. (2015)
Curcumin	Anticancer	Allegra *et al*. (2017); Vallianou *et al*. (2015)
	Anti-inflammatory	Bagad *et al*. (2013); Chandran and Goel, (2012)
	Antimicrobial	
	Antidiabetic	De Oliveira *et al*. (2018); Tyagi *et al*. (2015)
		Chuengsamarn *et al*. (2012); Roxo *et al*. (2019); Widowati *et al*. (2018)
	Antiplatelet	Liu *et al*. (2013); Perrone *et al*. (2015)
	Wound healing	Mirzahosseinipour *et al*. (2020); Mohanty and Sahoo (2017); Nguyen *et al*. (2019)
Curcumol	Anticancer	Ning *et al*. (2016); Zhang *et al*. (2011)
	Antidiabetic	Raafat and Omar (2016)
Curdione	Anticancer	Li *et al*. (2014)
	Neuroprotective	Li *et al*. (2017)
	Antimicrobial	Naz *et al*. (2010)
Demethoxycurcumin	Anti-inflammatory	Ramkumar *et al*. (2018)
	Neuroprotective	Ramkumar *et al*. (2017)
Germacrone	Anticancer	Wu *et al*. (2020); Ye *et al*. (2017)
	Antimicrobial	Diastuti *et al*. (2014)
	Antioxidant	Hamdi *et al*. (2015); Hossain *et al*. (2015)
	Antiproliferative	Lim *et al*. (2016); Zhang *et al*. (2020)

continued

Bioactive compounds	Biological activity	References
Linalool	Anticancer	Iwasaki *et al*. (2016); Rodenak-Kladniew *et al*. (2018); Sun *et al*. (2015)
	Antiepileptic	Bahr *et al*. (2019); Souto-Maior *et al*. (2017)
	Anti-inflammatory	Kim *et al*. (2019a); Lee *et al*. (2018)
	Antioxidant	Jabir *et al*. (2018)
	Antimicrobial	Wu *et al*. (2019)
	Insect repellent	Campos *et al*. (2018); Fujiwara *et al*. (2017); Pajaro-Castro *et al*. (2017); Tabari *et al*. (2017)
Xanthorrhizol	Anticancer	Nurcholis *et al*. (2018)
	Antidiabetic	Kim *et al*. (2014)
	Antihypertensive	Campos *et al*. (2000)
	Anti-inflammatory	Kim *et al*. (2014)
	Antimicrobial	Kim *et al*. (2019b); Yanti *et al*. (2009)
	Antioxidant	Liao *et al*. (2019); Oon *et al*. (2015)
	Antiplatelet	Jantan *et al*. (2008)
Zingiberene	Anticancer	Chen *et al*. (2019); Chopra *et al*. (2019)
	Antioxidant	Togar *et al*. (2015)
	Antiulcer	Ko and Leung (2010)
	Insect repellent	Eigenbrode and Trumble (2019)

Antidiabetic activity

Diabetes mellitus is a chronic, life-threatening systemic disease leading to multiple complications, such as blindness, kidney failure, amputations, strokes, and heart attacks (Meral *et al*., 2001). Diabetes mellitus causes oxidative destruction of cellular membranes and redox imbalance (within the cells) called oxidative stress (Cheeseman, 1993), which leads to an increased production of free radicals and a decreased antioxidant defense mechanism in the body. Hence, it has been hypothesized that, in diabetes mellitus, free radical production increases due to the increased oxidative stress and decreased antioxidant production (Ahmad *et al*., 2014; Meral *et al*., 2001). Thus, the increased production of free radicals could be considered as one of the significant complications of diabetes mellitus (Meral *et al*., 2001). *Curcuma aromatica* possesses compounds such as 1,8-cineole (Miri, 2018; Saito *et al*., 2004), ar-turmerone (Lekshmi *et al*., 2012), curcumin (Chuengsamarn *et al*., 2012; Roxo *et al*., 2019; Widowati *et al*., 2018), curcumol (Raafat and Omar, 2016), demethoxycurcumin (Jayaprakasha *et al*., 2006), germacrone (Hamdi *et al*., 2015; Hossain *et al*., 2015; Makabe *et al*., 2006), and xanthorrhizol (Kim *et al*., 2014) that have been well reported to have antioxidant and antidiabetic properties. Besides, Srividya *et al*. (2012) reported that the toluene extract of rhizomes of *C. aromatica* significantly decreased the glucose level from 278.53 to 116.5 mg/dl, increased protein level from 3.09 to 5.78 mg/dl, decreased cholesterol level from 292.33 to 134.50 mg/dl, and reduced the triglyceride level from 85.66 to 64.16 mg/dl upon oral administration at a maximum single dose of 400 mg/kg in streptozotocin-induced diabetic rats.

Antioxidant activity

An antioxidant is a molecule that scavenges and neutralizes free radicals by donating an electron, thus reducing the damaging power of free radicals (Halliwell, 1995). Methanol and aqueous extracts of *C. aromatica* rhizomes have been proven to have comparable potency to *L*-ascorbic acid, a well-known antioxidant with IC_{50} less than 60 µg/ml. In another study, Xiang *et al*. (2017) studied the antioxidative activity of the essential oils of *C. aromatica* rhizomes from 12 different locations in China using the 2,2diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging assay. The results again proved the antioxidative potency of *C. aromatica* with IC_{50} ranging from 1.57 to 21.36 µg/ml, which was indeed better than the control, Trolox C (IC_{50} 8.82 µg/ml).

Similarly, Al-Reza *et al*. (2010) studied the chemical composition and antioxidative activity of both essential oil and organic extracts of *C. aromatica* leaves. The antioxidant properties were evaluated by DPPH and superoxide radical-scavenging assays. The essential oil extract showed potent antioxidative activity (IC_{50} = 14.45 µg/ml), followed by the methanol extract (IC_{50} 16.58 µg/ml), and both possessed better activity than the reference compound, butylated hydroxyanisole with an IC_{50} value of 18.27 µg/ml. The activity was associated with the presence of antioxidant compounds such as 1,8-cineole (Miri, 2018; Saito *et al*., 2004), germacrone (Hamdi *et al*., 2015; Hossain *et al*., 2015), xanthorrhizol (Liao *et al*., 2019; Oon *et al*., 2015), and β-sesquiphellandrene (Zhao *et al*., 2010).

Antimicrobial activity

Microbial contamination and resistance are a few of the significant challenges in the food, beverage, and pharmaceutical industries. For instance, antimicrobial agents, including food preservatives, have been used to inhibit the growth of food-borne bacteria and prolong the shelf life of processed foods (Rahimi-Nasrabadi *et al*., 2013). Many plant derivatives, including those of *C. aromatica*, have been shown to possess antimicrobial properties.

A study conducted by Revathi and Malathy (2013) revealed that crude hexane extract of *C. aromatica* was effective against Gram-positive bacteria and ineffective against the tested Gram-negative bacteria. The phytochemical analysis identified that the antimicrobial activity was attributed to germacrone.

It should be noted that germacrone has also been reported to possess other biological activities, including anti-inflammatory, antitussive, antitumor, and antifungal properties (Wu *et al*., 2017). On the other hand, the essential oil extracted from the fresh rhizomes of *C. aromatica* has been shown to inhibit the growth of both Gram-positive and Gram-negative bacteria (Ahmed *et al*., 2008). Curcumin (diferuloylmethane) was then isolated and found to be active against *Staphylococcus aureus* strains and *Saccharomyces cerevisiae*. In another study, the essential oil of *C. aromatica* was also reported to have higher antifungal activity against *S. cerevisiae* (183.18 µg/ml) than the essential oils from other *Curcuma* species, including *Curcuma nankunshanensis*, *Curcuma elata*, *Curcuma kwangsiensis var. nanlingensis*, *Curcuma yunnanensis*, *Curcuma rubescens*, and *Curcuma sichuanensis* (Xiang *et al*., 2018).

Apart from germacrone and curcumin, *C. aromatica* is also composed of other bioactive compounds, such as ar-turmerone (Dhingra *et al*., 2007; Lee, 2006), camphor (Kordali *et al*., 2005; Kotan *et al*., 2008; Viljoen *et al*., 2003; Zafar *et al*., 2019), curdione (Naz *et al*., 2010), linalool (Queiroga *et al*., 2007; Van Zyl *et al*., 2006), and xanthorrhizol (Hwang *et al*., 2000; Rukayadi and Hwang, 2007; Rukayadi *et al*., 2006), that are reported elsewhere to have an antimicrobial effect against both fungi (*Aspergillus flavus*, *Fusarium semitectum*, *Colletotrichum gloeosporioides*, *Colletotrichum musae*, *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*) and bacteria (*Escherichia coli*, *S. aureus*, and *Bacillus cereus*). Perhaps these findings are not surprising, as *C. aromatica* often is one of the ideal plant sources for the treatment of various infectious diseases in the conventional and Ayurvedic regime.

Anti-inflammatory activity

Inflammation has been described as a transitory biological tissue response to dangerous stimuli, for example, wounds, exogenic, and endogenic antigens, meant to clear or remove the stimulus and repair the wounded tissue that ultimately leads to tissue regeneration and normal homeostasis (Egger, 2012). Even though inflammation is an affirmative body defense mechanism, dysregulated and chronic inflammatory reactions have been well documented as underlying causes of many systemic diseases, including diabetes, asthma, atherosclerosis, obesity, cancer, and pain, thus contributing to the increased cost of healthcare to the society (Mizuno *et al*., 2011).

However, an undeniable fact is that most of the conventional nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and immunosuppressant drugs used to treat all kinds of inflammatory conditions are linked with unfavorable side effects, such as headache, ulceration, gastric irritation, perforation, hemolytic anemia, hyperglycemia, and many more (Bagad *et al*., 2013). Considering these drawbacks associated with these drugs, an alternative source especially from medicinal plants that are usually considered safe is incessantly being investigated for probable anti-inflammatory activity.

Xiang *et al*. (2017) studied the anti-inflammatory activity of the essential oils of *C. aromatica* rhizomes obtained from 12 different locations in China. In their study, ear edema was induced by 12-O-tetradecanolphorbol-13-acetate in mice. Different groups of mice received different essential oil treatments, and ibuprofen was used as a positive control. Generally, all the essential oils showed anti-inflammatory activity on a dose-dependent fashion from 20.56 to 61.34% and surprisingly superior to ibuprofen (17.84%–54.57%), which is known for its anti-inflammatory effect. The histological and immunohistochemical analysis further showed tissue relief from inflammation after treatment with both essential oils. Cytokine analysis showed a significant decrease in the expression of COX-2 and TNF-α in the essential oil-treated groups compared to the untreated group. However, the difference was not significant compared to the ibuprofen-treated group. The extracts of *C. aromatica* rhizomes were also reported to have a promising anti-inflammatory effect similar to prednisolone when tested on the inflamed paw of mice induced by carrageenan (Ahmed *et al*., 2008).

It is not surprising though that the extracts and essential oil of *C. aromatica* have a more anti-inflammatory effect than conventional drugs, as they contain and may have a synergistic effect of different potent anti-inflammatory compounds, such as ar-turmerone (Jantan *et al*., 2012; Oh *et al*., 2014; Rana *et al*., 2015), borneol (Almeida *et al*., 2013), curcumin (Bagad *et al*., 2013; Chandran and Goel, 2012), curdione (Oh *et al*., 2007), linalool (Peana *et al*., 2002), 1,8-cineole (Beer *et al*., 2017), and xanthorrhizol (Chung *et al*., 2007; Lee *et al*., 2002; Lim *et al*., 2005).

Antitussive activity

One study has reported on the antitussive activity of *C. aromatica*. Marina *et al*. (2008) revealed that the ethanol extract of the plant possessed a promising and comparable antitussive effect with codeine phosphate in a dose-dependent fashion. The extract inhibited 79% of cough at a concentration of 400 mg/kg body weight after 1.5 hours of oral administration, which is similar to codeine phosphate (87% at a concentration of 40 mg) in mice. The acute oral toxicity study of the ethanol extract showed no adverse effect up to the maximum dose of 4 g/kg.

Analgesic activity

The use of analgesic drugs, such as opiates and NSAIDs, for pain relief has been stagnated as these drugs are reported to have adverse side effects, including addiction and gastrointestinal disorders (Khokra *et al*., 2012; Maniyar and Sriraj, 2017). In an effort to find natural alternatives to these drugs, several plants, including *C. aromatica*, have been studied and have showed potent analgesic activity. Pranav Kumar *et al*. (2013) studied the analgesic effect of aqueous extract of *C. aromatica* rhizomes by Eddy's hot plate (55°C) method in rats to induce pain due to heat. The extract was administered orally at a concentration of 300 and 500 µg/kg and showed prolonged pain latency compared to the diclofenac sodium (10 mg/kg). In another study, a reduced number of writhes by mice were observed in the acetic acid-induced writhing test after the administration of aqueous extract of the rhizomes of *C. aromatica* (Huang *et al*., 2007). The analgesic activity of *C. aromatica* was attributed to the presence of 1,8-cineole (Takaishi *et al*., 2012; Zheng *et al*., 2019), linalool (Souto-Maior *et al*., 2017), borneol (Xiong *et al*., 2013), camphene (Quintans-Júnior *et al*., 2013), and camphor (Adams, 2012).

Wound healing activity

Govindarajan *et al*. (2004) and Mukherjee *et al*. (2000) studied the wound healing properties of the powdered rhizomes of *C. aromatica* incorporated in an ointment of soft white paraffin. The ointment was topically applied to acute wounds on rabbits and resulted in significant wound contraction and complete epithelization within 9–11 days. Similarly, cream formulations of *C. aromatica* rhizome extracts also showed significant wound healing properties when applied externally on excision wounds of Swiss albino mice (Kumar *et al*., 2009).

Antiepileptic activity

Nonetheless, the plant also consists of compounds that possess antiepileptic effect which is including androstan-17-one (Kaminski *et al*., 2005) and linalool (Bahr *et al*., 2019; Souto-Maior *et al*., 2017), but the activity is yet to be evaluated using *C. aromatica* extracts or essential oils.

Insect repellent activity

Apart from pharmacological use, *C. aromatica* is also extensively studied as a potential insecticide. Lack of sufficient knowledge on plant-based oviposition deterrents lead to the current overuse of synthetic insecticides and insect growth regulators to monitor larval instars of mosquitoes, which are believed to cause resistance to insecticides, environmental contamination, and threats to humans and other species, thus representing significant limitations to their successful employment (Benelli, 2015). Recently, the use of some plant-derived products, such as essential oils, has shown to provide safer and effective alternatives to synthetic pesticides and repellents (Alshebly *et al*., 2017).

A study conducted by Singh *et al*. (2002) showed that the essential oil of *C. aromatica* possesses a better insecticidal effect against *Odontotermes obesus* Rhamb. (a pest of sugarcane) than the commercial synthetic insecticides, Thidon and Primoban-20. At a dose of 3 µl and 6 µl, the essential oils of *C. aromatica* showed a percentage mortality rate of 50% and 100%, respectively, after 2 hours of exposure, whereas Thidon showed a mortality rate of 10% and 20%, and Primoban-20 showed 10% and 30% under the same dose and exposure time, respectively.

Pitasawat *et al*. (2003) showed that the ethanol extract could provide repellence against *Aedes togoi* mosquito on human volunteers with ED_{50} and ED_{95} values of 0.061 and 1.55 mg/cm^2, respectively. The biting protection lasted for 3.5 hours when the extract was applied topically at a concentration of 25% (w/w). Neither dermal irritation nor adverse effect was reported on the human volunteers. The ethanolic extract was further shown to provide a protective effect against other mosquito species, including *Armigeres subalbatus*, *Culex quinquefasciatus*, and *Cx. tritaeniorhynchus* under field conditions.

Choochote *et al*. (2005) also investigated the antimosquito effects, including larvicidal, adulticidal, and repellent activities, of the hexane rhizome extracts and essential oil of *C. aromatica* against *Aedes aegypti* mosquitoes. The essential oil showed a significantly higher larvicidal activity (LC_{50} of 36.30 ppm) against the 4th instar larvae of *A. aegypti* than that of the hexane extracts (LC_{50} of 57.15 ppm). On the other hand, the adulticidal activity of the hexane extract was found to be slightly more effective (LC_{50} of 1.60 µg/mg) against female *A. aegypti* than the essential oil (LC_{50} of 2.86 µg/mg). However, these two products showed a significant repellent activity against female adult *A. aegypti*. The hexane extract showed higher repellent period (total protection time of 1 hour) when applied at a concentration of 25% than that of the essential oil (0.5 hours). The phytochemical analysis revealed the presence of xanthorrhizol, 1H-3a, 7-methanoazulene, curcumene, germacrone, and camphor as the major constituents, with the exception of germacrone and camphor that are present only in the essential oils.

CONCLUSION

This review spotlighted important findings of *C. aromatica* as one of the most medically crucial plant species of the genus *Curcuma*. The review also justifies the reason for the use of this plant in traditional medicines in India, China, and other Southeast Asian countries. However, scientific findings are still lacking on the *in vivo* toxicity, clinical trials, and nutritional content of this plant. These findings are crucial to providing immense opportunities for the development of new *C. aromatica*-based products in pharmaceutical industries and cosmetics.

RECOMMENDATIONS

It should be emphasized that the medicinal value of *C. aromatica* has not been scientifically and extensively studied as compared to *C. longa*, which is regular turmeric. This could be due to improper farming practices, habitat destruction, deforestation, and the high demand of the pharmaceutical industry for wild plant sources which make this plant one of the most endangered plant species in many South Asian countries, hence leading to the limited supply of the plant. If these hurdles can be mitigated satisfactorily, *C. aromatica* has the potential to be used for the treatment of various diseases. We believe that both conservation and sustainable use of this plant should not be underestimated. We recommend that conservation strategies, such as *in situ* and *ex situ* conservation strategies, should be adequately taken into consideration for the sustainable use and proper harvesting of this medicinal plant. Also, biotechnological approaches, such as micropropagation, molecular marker-based approaches, and tissue culture, are promising alternative approaches to produce high-value medicinal plants, including *C. aromatica*. These methods may shorten the breeding time of the plant.

Although *C. aromatica* has been extensively used in traditional medicine for the treatment of various ailments and scientifically studied for medicinal use, to our understanding, no commercial product is currently available in the market. This could be due to the safety concern on the systemic administration of *C. aromatica*. Hence, more safety studies are required to prove the medicinal value of *C. aromatica*. We strongly believe that these problems can be extenuated through systematic investigation of the whole plant, including toxicity and clinical studies for safety assessment.

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CONFLICT OF INTEREST

Authors declared that there are no conflicts of interest.

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