Chapter 5
Traditional Uses, Phytochemistry, and Pharmacological Properties of *Zingiber officinale* Essential Oil and Extracts

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ABSTRACT

Ginger (Zingiber officinale) has been traditionally employed in south East Asia as well as India and China for treatment of nausea, asthma, fever, vomiting, cough, constipation, pain, arthritis, inflammation, etc. This chapter discusses the phytochemical composition and pharmacological studies of ginger extracts, ginger essential oil (GEO), and active bioactive constituents. The essential oil of fresh and dry ginger was ranged between 0.2% - 2.62% and 0.72% - 4.17% respectively. The bioactive constituent zingiberene, β-sesquiphellandrene, curcumene, β-bisabolene, β-farnesene, camphene, and gingerol and shogal are the major constituents in ginger extracts. These compounds are chief bioactive substances responsible for pharmacological activities such antioxidant, antidiabetic, anticancer, anticoagulant, antiradiation, anti-inflammatory, gastrointestinal, antimicrobial, cardiovascular, anti-obesity, and weight loss effects. Future research needs to investigate the suitable duration, maximum dosage of ginger, concerns of over-dosage, and its side effects in animal models and humans.

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INTRODUCTION

Ginger (*Zingiber officinale* Roscoe) belongs to the family Zingiberaceae and it was used in traditional medicine to treat illness almost 5000 years ago (Bode and Dong, 2004). The word ginger originated from the English word *gingivere*, while in Tamil it is known as *Ingii*, in Hindi, *adarakah*, in Chinese, *jiang* and in Arabic, *zanjabli*. Ginger is widely grown in the tropics with foremost exporting countries such as India, Nigeria, Australia, China and Jamaica. In India, ginger is cultivated in the states of Kerala, Karnataka, Orissa, Arunachal Pradesh, West Bengal, Sikkim and Madhya Pradesh. Kerala is the largest ginger producing state, which accounts for 30-40% of total production in India. Indian ginger has two popular varieties in the global market, namely Cochin Ginger and Calicut Ginger (Kubra and Rao, 2012). Dry ginger is mostly used for export purposes and fresh ginger as a vegetable.

The ginger rhizomes have a potent aroma and are extensively used as a spice and as medicine. Ginger and its extract are extensively used in beverage, food, and confectionery industries for manufacturing products such as ginger beer, ginger wine, pickles, Jam and biscuits (Wohlmuth et al., 2005). Ginger essential oil(GEO) and oleoresins are also used in several food products, especially in soft beverages and likewise various sorts of pharmaceutical formulations. It has various potential pharmacological effects in modern medicine such as anti-inflammatory, antifungal, and anticancer activities (Khan et al., 2010). In traditional medicine, ginger has been used for curing several diseases which includes cough, cold, asthma, nausea, travel sickness, morning sickness arthritis and gastrointestinal complaints (Grontved et al., 1988; Bone et al., 1990; But and Sultan, 2011; Khaki and Fathiazad, 2012).

The world health organization (WHO) has projected that nearly 80% of the global population depended on plant-based preparations as medicines to cure their health problems (WHO, 1991).

Plant-based food products are storehouses of various bioactive components like phenolics, flavonoids, carotenoids (Ashokkumar et al., 2013; Muthukrishnan et al., 2014; Ashokkumar et al., 2014; Ashokkumar et al., 2015; Ashokkumar & Shunmugam, 2016; Ashokkumar et al., 2018a; Ashokkumar et al., 2008b), folates (Jha et al., 2015; Ashokkumar et al., 2018c), terpenes (Ashokkumar et al., 2019b). These constituents have been evaluated for their potential biological effects. However, the dried ginger rhizomes contain 5 - 8% of oleoresin, and 1.5 - 3% essential oil depends upon the variety, country of origin, and quality (Zarate and Yeoman, 1996; Kayaardi et al., 2005). Also, the ginger rhizome possess significant concentration of essential nutrients, minerals and bioactive compounds such as flavonoids, terpenoids, carotenoids, essential oils, gingerols, zingiberene,zingerone, shogaolsand paradols(But and Sultan, 2011; Baliga et al., 2011; Ashokkumat et al., 2019). The pungency of ginger rhizome is mainly due to the presences of gingerols and shogaol, are key bioactive constituents of fresh ginger and it has various pharmacological effects including anticancer activity (Wohlmuth et al., 2005).However, zingiberene (10.5-16.6%), e-citrol (7.4 - 12.0%), ar-curcumene (2.9-9.8%),β-farnesene (5.1 - 8.4%), camphene (4.9 - 7.6%), β-sesquiphellandrene(5.8 - 7.2%) and citrol (5.3 - 7%) arethe major essential oil compoundsin dry ginger (Raina et al.,2005). The concentration of these compounds differs significantly depending upon the storage, country of origin, maturity stage of rhizome and preparation of ginger extract/product. The aim of this chapter is to highlight the key phytochemicals and pharmacological applications of ginger extracts and ginger essential oil (GEO) on human health.

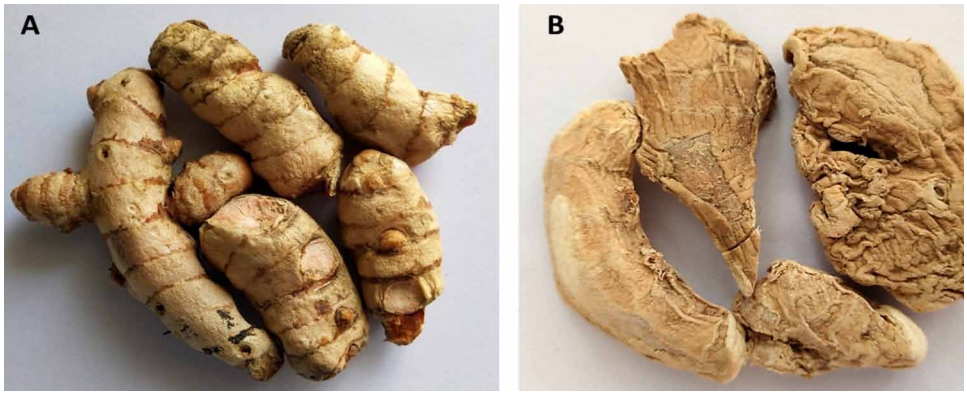
BOTANICAL DESCRIPTION OF GINGER

Ginger (*Zingiber officinale* Roscoe), belongs to the Zingiberaceae family. The basic chromosome number x=11 and somatic chromosome number is 2n=22, it is sterile diploid in nature. The botanical classification of ginger has been shown in Table 1. Ginger is a perennial, herbaceous, rhizomatous plant and has an erect stem, grown up to 1 meter in height. It has a fibrous root and aerial shoots. Leaves are simple, alternate, linear-lanceolate, and sheathing at the base. Shoots are originated from multiple bases and wrap around one another. Moreover, the leaf type of ginger is narrowed lanceolate to linear-lanceolate, and leaves die each year (Toader, 2014). The inflorescence is spiked; irregular and bisexual flowers are densely arranged and subtended by a persistent bract. Flowers have three yellowish-orange petals with a lip-like structure (Ravindran et al., 2005). Calyx is tubular 3 lobed, bilabiate corolla; 3 stamens in one whorl; tricarpel ovary,syncarpous; inferior; axile placentation; filiform style, subglobose type stigma. The rhizome is brown, thick lobed, branched with scaly structures. The morphological differences between the fresh and dried rhizome of ginger were shown in Figure 1.

Table 1. Botanical classification of ginger

Kingdom		**Plantae**
Sub-kingdom	:	Tracheobionta – Vascular plants
Division	:	Angiosperms (Seeded plants)
Class	:	Monocotyledons
Sub class	:	Zingiberidae
Order	:	Zingiberales
Family	:	Zingiberaceae (Ginger family)
Genus	:	*Zingiber*
Species	:	*officinale*

Figure 1. The fresh and dried rhizomes of ginger (Zingiber officinale Roscoe)



Traditional Uses of Ginger

In India, the ginger rhizome has been used for folk medicine from the Vedic period (Vasala, 2004). Ginger is an essential part of the preparation of various medicinal formulations in Ayurveda medicine. The rhizome of ginger and its extracts plays a key role in Ayurvedic, Chinese, African and Arabic folk medicines to cure headaches, cough, colds, flu, nausea, rheumatism, arthritis, muscular discomfort and inflammation (Baliga et al., 2011; Dehghani et al., 2011; Khaki and Fathiazad, 2012; Semwal et al., 2015). Several traditional medicines reported that ginger is a potential agent for antiinflammatory, carminative, antispasmodic, diaphoretic, appetite and peripheral circulatory stimulant (Vasala, 2004; Ali et al., 2008).

In Burma, peoples used to cure the flu by consumption of a mixture of ginger and palm tree juice. Ginger beer has been used to settle stomach upsets. However, in Colombia, ginger mixed with hot panela was used for the treatment of colds and flu (Semwal et al., 2015). In China, powdered ginger with scrambled eggs is taken as a home remedy to relieve a cough. Mango juice added with ginger is considered a panacea (medicine to cure all) in Congo. External application of ginger paste to cure headaches and oral administration to reduce colds in India and Nepal (Khaki and Fathiazad, 2012). Ginger is believed to reduce fatigue and increase digestion in Indonesia. Philippians had taken ginger to sooth asore throat, while the Japanese used ginger to improve blood circulation. In India, the southern states of Tamil Nadu and Kerala crushed ginger rhizomes and boiled it with tea and water to impart a pleasant aroma to tea, which is locally called "*Ingi tea*(ginger tea)" and which has been used to relieve tiredness and depression. The powdered ginger rhizome mixed with pulverized cloves, cardamom and caraway has been used for digestive ailments (Ashokkumar et al., 2020).

CHEMICAL COMPOSITION

Proximate and Mineral Composition

The proximate composition of fresh and dry ginger rhizome was summarized in Table 2. It includes moisture, ash, crude protein, crude fat, crude fiber, vitamin C, ascorbic acid and carbohydrates. The crude protein content of fresh and dried ginger rhizome was ranged between 3.1 - 12.3% and 7.9 - 34.1%, respectively (Agu et al., 2016;Sultan et al., 2005;Shahid and Hussain, 2012; Latona et al., 2012). Fresh ginger has significant level of crude fat and fibre with 2.1-11.7% and 1.4 -15% correspondingly (Ajayi et al., 2013;Sultan et al., 2005;Onimawo et al., 2019). Dry ginger has 1.04 -3.75%, in vitamin-C and 68.2 - 72.8% (Latona et al., 2012; Shahid and Hussain, 2012).

The serving of 100g dried ginger rhizome contains substantial levels of calcium (34.5- 280 mg), phosphorus (26.7 mg), Sodium (39 mg), manganese (18.9 mg) and other micronutrients with traces amount (Latona et al., 2012; Ogbuewu et al., 2014; Adel and Prakash, 2010; Onimawo et al., 2019), (Table 2). These are essential mineral elements for normal day-to-day physiological activities of humans. Ashokkumar et al. (2019) reported nutritionally important metabolites including flavonoids (catechin and myricetin,) and carotenoids (lutein and β-carotene) in rhizomes of fresh ginger (Table 2).

Table 2. Proximate, mineral and metabolite content of fresh and dry rhizome of ginger

	Fresh	Dry	Reference
Proximate composition (%)			
Moisture	70.1 - 89	6.4 - 13.7	Aguet al. (2016); Sultan et al. (2005); Otunola et al. (2010); Latona et al. (2012)
Ash	0.81 - 2.54	1.74 - 7.64	Onimawo et al. (2019); Odebunmi et al. (2010); Shahid and Hussain (2012); Latona et al. (2012)
Crude protein	3.1 – 12.3	8.6 – 34.1	Aguet al. (2016); Sultan et al. (2005); Shammari (2018);Latona et al. (2012)
Crude fat	2.1 – 11.7	4 – 6.4	Ajayi et al. (2013); Onimawo et al. (2019); Latona et al. (2012); Shammari (2018)
Crude fibre	1.4 - 15	0.9 - 3.2	Onimawo et al. (2019); Sultan et al. (2005);Otunola et al. (2010)
Vitamin- C	-	1 – 3.8	Latona et al. (2012); Shahid and Hussain (2012)
Carbohydrates	2 – 16.7	68.2 – 72.8	Onimawo et al. (2019); Ajayi et al. (2013); Otunola et al. (2010); Shammari (2018)
Minerals (mg/100g)			
Calcium	88.4 -182.7	34.5 - 280	Latona et al. (2012); Ogbuewu et al. (2014); Adel and Prakash (2010); Onimawo et al. (2019)
Phosphorus	174	26.7	Adel and Prakash (2010);Ogbuewu et al. (2014)
Sodium	7.3	39	Onimawo et al. (2019); Ogbuewu et al. (2014)
Iron	8 – 9.7	1.59	Adel and Prakash (2010); Onimawo et al. (2019); Ogbuewu et al. (2014)
Copper	0.55	0.86	Ogbuewu et al. (2014); Adel and Prakash (2010)
Manganese	9.1	18.9	Ogbuewu et al. (2014); Adel and Prakash (2010)
Zinc	5	4.2	Ogbuewu et al. (2014); Adel and Prakash (2010)
Metabolites (µg/g)			
Flavonoids			
Catechin	757.9	-	Ashokkumar et al. (2019)
Myricetin	35.5	-	Ashokkumar et al. (2019)
Total flavonoids	793.4	-	Ashokkumar et al. (2019)
Carotenoids			
Lutein	0.2	-	Ashokkumar et al. (2019)
β-carotene	0.5	-	Ashokkumar et al. (2019)
Total carotenoids	0.7	-	Ashokkumar et al. (2019)

Ginger Essential Oil (GEO) and its Composition

The yield of GEO varied from 0.2% - 2.62% and 0.72% - 4.17% on a wet and dry basis, respectively, depending on the variety and extraction methods summarized in Table 3. Recent studies claim that the yield of dry ginger essential oil (GEO) was greater when using a hydro-distillation method (1.10% - 4.17%) compared to steam distillation (2.1%) and Ionic liquid based microwave assisted extraction (0.72%) methods (Pinoet al. 2004; Kiran et al., 2013; Stoyanova et al., 2006; Stoyanova, et al., 2006;

Guo et al., 2017). Among the hydro-distillation extraction, dry ginger yielded higher oil content than fresh ginger (Table 3).

Table 3. Yield of essential oil from ginger rhizomes by various extraction methods

Technique or method	Rhizome	Oil yield (%)	References
Ionic liquid-based microwave assisted extraction	Dry	0.72	Guo et al. (2017)
Steam distillation	Dry	2.1	Stoyanova et al. (2006)
Super critical fluid extraction	Fresh	0.24 - 2.62	Mesomoet al (2013)
Hydro-distillation	Dry	1.10- 4.17	Raina et al. (2005); Pino et al (2004); Kiran et al. (2013); Stoyanova et al. (2006)
Hydro-distillation	Fresh	0.20- 1.79	Gurib-Fakim et al. (2002); Mesomo et al. (2013); Héritier et al. (2018)

Figure 2. Molecular structures of major bioactive molecules isolated from ginger essential oil and extracts

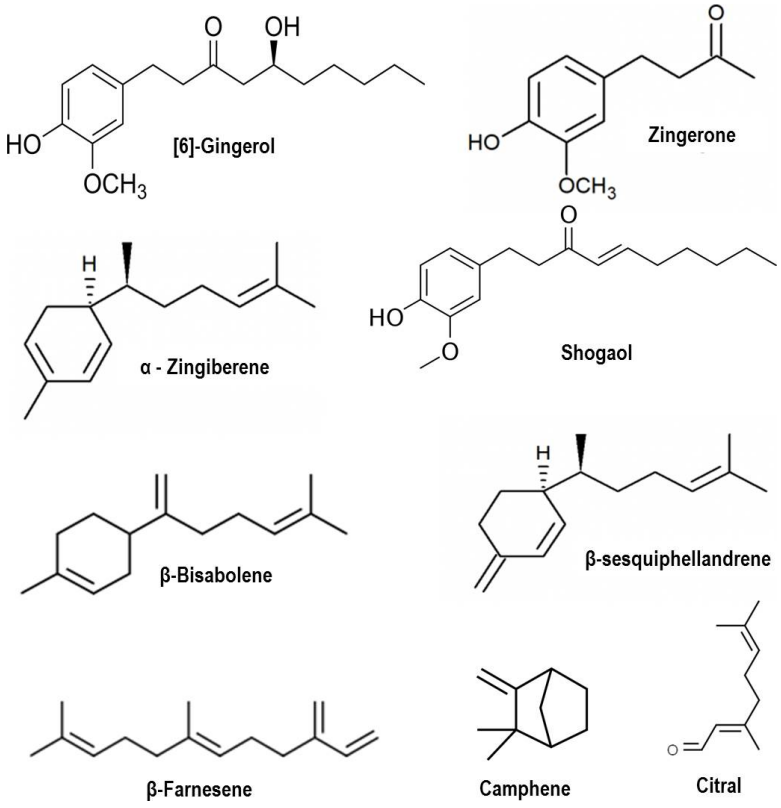


Table 4. Major essential oil constituents of ginger from various origins

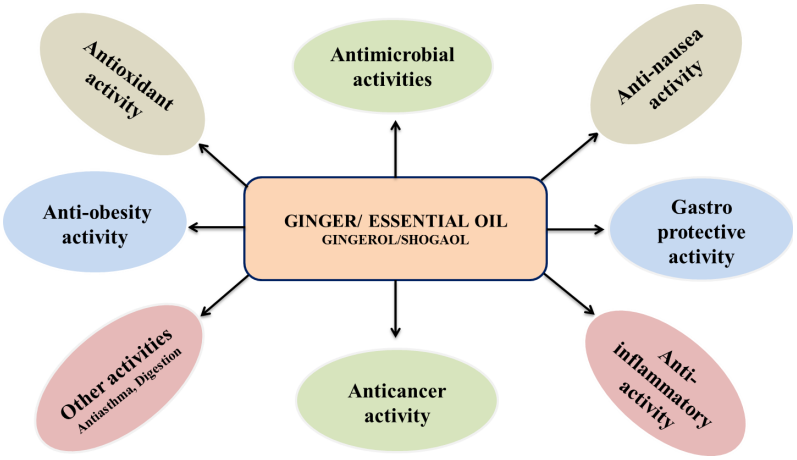
Origin	Rhizome	Constituents	Yield (%)	Authors
Nigeria	Dry	Zingiberene	29.54	Onyenekwe & Hashimoto (1999)
		β-Sesquiphellandrene	18.42	
		Farnesene	6.46	
China	Fresh	Zingiberene	22.76	An et al. (2016)
		β-phellandrene	12.40	
		Geranial	14.50	
		b-Sesquiphellandrene	7.01	
		β-Bisabolene	3.25	
Mauritius	Fresh	Geranial	16.3	Gurib-Fakim et al. (2002)
		Neral	10.3	
		Zingiberene	9.5	
		p-sesquiphellandrene	6.3	
		ar-Curcumene	5.1	
India, North East	Dry	Zingiberene	20.98	Kiran et al. (2013)
		Geranial	12.36	
		Camphene	8.49	
		β-sesquiphellandrene	7.96	
		Neral	4.95	
India	Fresh	Zingiberene	46.71	Sharma et al. (2016)
		Citronellyl n-butyrate	19.34	
		Valencene	7.61	
		β-phellandrene	3.70	
Cuba	Dry	ar-Curcumene	22.1	Pino et al. (2004)
		Cadina-1,4-diene	12.5	
		Zingiberene	11.7	
		β-bisabolene	11.2	
India, North	Semi dry	Zingiberene	10.5-16.6	Raina et al. (2005)
		e-Citral	7.4- 12.0	
		ar-Curcumene	2.9-9.8	
		β-Farnesene	5.1 - 8.4	
		Camphene	4.9- 7.6	
		β-Sesquiphellandrene	5.8 - 7.2	
		z-Citral	5.3- 7.0	
Vietnam	Dry	ar-Curcumene	12.6	Stoyanova et al. (2006)
		α-Zingiberene	10.3	
		β-Bisabolene	8.1	
		β-Sesquiphellandrene	7.4	

The chemical composition of major ginger essential oils across the countries and regions is presented in Table 4. The EO of fresh ginger from India predominantly exhibited zingiberene (46.71%), citronellyl n-butyrate (19.34%), valencene (7.61%) and β-phellandrene (3.70%), (Sharma et al., 2016). Kiran et al. (2013) indicated that rhizomes of dry ginger collected from across the ginger growing region of north east India chiefly contain zingiberene, geranial, camphene, β-sesquiphellandrene and neral with percentages of 20.98, 12.36, 8.49, 7.96, and 4.95, respectively (Table 4). Profiling of EO of fresh ginger rhizomes from China showed zingiberene (22.76%), β-phellandrene (12.40%), geranial (14.50%) and sesquiphellandrene (7%) as principal compounds (An et al., 2016). The molecular structure of major bioactive constituents isolated from gingeressential oil and extracts is shown in Figure 2. The yield of minor constituents of GEO from fresh ginger includes, 1,8-cineole (5.08%), camphor (0.16%), δ-3-carene (0.03%), citronelly lacetate (0.58%), copanene (0.21%), α-elemene (0.12%), β-elemene (0.30%), 2-farnesene (0.13%), myrcene (1.75%), sabinene (0.17%), terpinolene (0.29%)and 2-undecanone (0.40%),(Qin and Xu, 2008).

Biological Activities

The GEO and ginger extracts have various biological effects including antioxidant, antibacterial, anti-cancer insecticidal and other miscellaneous activities that are summarized in Table 5. The schematic representation of biological activities of ginger rhizome extract, GEO and active constitutes were presented in Figure 3.

Figure 3. Schema depiction of biological activities of ginger rhizome extract, essential oil, gingerol and Shogaol



Antioxidant Activity

Oxidative stress is one of the major health problems in humans, for which several therapies are utilized and where medicinal plants offer a favorable alternative. The rhizome of ginger possesses a rich source of antioxidants that are used to scavenge free radicals and associated health problems. Gingerols is the major bioactive metabolite, which has potent antioxidant activity determined by various antioxidant

Table 5. Biological activities of ginger rhizome extract, essential oil and bioactive compounds

Pharmacological activities	Studyextract/ GEO	In vitro/ In vivo	Target/ Model	IC 50/ Dosage	Control	Reference
Antimicrobial activity	GEO	*In vitro*	*Bacillus subtilis*	MIC:10.0µl/ml	Positive: Tetracycline Negative: DMSO	Sharma et al. (2016); Sasidharan, & Menon (2010)
Antimicrobial activity	GEO	*In vitro*	*Staphylococcus aureus*	MIC: 8.7 mg/ml	-	Bellik, (2014)
Antimicrobial activity	Aqueous extract	*In vitro*	*Helicobacter pylori*	MIC: 300µg/ml	Positive: Lansoprazole	Nanjundaiah et al. (2011)
Antimicrobial activity	Ethanol extract	*In vitro*	*E. col*	MIC: 75.6 µg/ml	Positive: Ciprofloxacin	Karuppiah, and Rajaram (2012)
	Ethanol extract	*In vitro*	*Klebsiella* sp.*Enterobacter* sp.	MIC: 185.6µg/ml	Positive: Ciprofloxacin	
	Ethanol extract	*In vitro*	*S. aureus* *Bacillus sp.* *Proteus sp.*	MIC: 68.4 µg/ml MIC: 74.5 µg/ml MIC: 70.2µg/ml	Positive: Ciprofloxacin	
Antimicrobial activity	Oleoresin	*In vitro*	*S. aureus*	MIC: 50 mg/ml	-	Bellik, (2014)
Antimicrobial activity	GEO	*In vitro*	*Vibrio vulnificus* *V. parahaemolyticus* *Pseudomonas aeruginosa &* *Yersinia enterocolitica*	MIC: 31.2 µl/ml MBC:31.3µl/ml MIC: 31.3µl/ml MBC:125 µl/ml MIC: 31.3 µl/ml MBC: 62.5 µl/ml	Positive: Ampicillin Negative: DMSO	Debbarma et al. (2013)
	GEO	*In vitro*	*Salmonella typhimurium* *S. paratyphi* *E. coli*	MIC: 62.5µl/ml	Positive: Ampicillin Negative: DMSO	
Antimicrobial activity	GEO	*In vitro*	*Candida albicans*	MIC:10.0µl/ml	Positive: Fluconazole Negative: DMSO	Sharma et al. (2016)
Antimicrobial activity	Ethanol	*In vitro*	*C. albicans*	MIC: 6.3 mg/ml MBC: 25 mg/ml	Negative: Sterile water	Lucky et al. (2017)
	Aqueous extract	*In vitro*	*C. albicans*	MIC: 6.3 mg/ml MBC: 25 mg/ml	Negative: Sterile water	Lucky et al. (2017)
Antimicrobial activity	Oleoresin	*In vitro*	*Penicillium*spp.	MIC: 2mg/ml	-	Bellik (2014)
Antimicrobial activity	GEO	*In vitro*	*Fusarium verticillioides*	MIC: 2500µl/ml	-	Yamamoto-Ribeiro et al. (2013)
Antimicrobial activity	GEO	*In vitro*	*Botrytis cinerea* *Alternaria panax* *F. oxysporum*	MIC: 0.3%	-	Hussein, & Joo (2018)
Antimicrobial activity	Methanol extract	*In vitro*	*E. coli* *S. aureus* *E. faecalis* *C. albicans* *M. smegmatis* *S. mutans*	MIC:125 mg/ml MIC:62.5mg/ml MIC: 250 mg/ml	-	Agrawal et al. (2018)
	Chloroform extract	*In vitro*	*E. faecalis* *S. mutans* *C. albicans* *M. smegmatis* *E. coli* *S. aureus*	MIC:125 mg/ml MIC: 62.5mg/ml MIC: 250 mg/ml	-	
	Ethyl acetate extract	*In vitro*	*S. aureus* *S. mutans* *E. faecalis* *C. albicans* *E. coli* *M. smegmatis*	MIC:125 mg/ml MIC: 250 mg/ml MIC: 62.5 mg/ml	-	
	Petroleum ether extract	*In vitro*	*S. aureus* *C. albicans* *S. mutans* *E. coli* *E. faecalis*	MIC:250 mg/ml MIC:125 mg/ml	-	

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Table 5. Continued

Pharmacological activities	Studyextract/ GEO	In vitro/ In vivo	Target/ Model	IC 50/ Dosage	Control	Reference
Antimicrobial activity	Aqueous extract	*In vitro*	*K. pneumoniae* *Proteus vulgaris* *P. mirabilis* *B. subtilis* *C. albicans* *E. coli*	MIC:156.3 µg/ml MIC:39.1 µg/ml	Positive: Amracin (for bacteria) Nystatin (for yeast)	Švarc-Gajić et al. (2017)
	Subcritical extract	*In vitro*	*K. pneumoniae* *Proteus vulgaris* *P. mirabilis* *B. subtilis* *C. albicans* *E. coli*	MIC:78.1 µg/ml MIC:19.5 µg/ml	Positive: Amracin (for bacteria) Nystatin (for yeast)	Švarc-Gajić et al. (2017)
Antimicrobial activity	Methanol extract	*In vitro*	*B. subtilis* *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	MIC: 8.17µg/ml MBC:30.0 µg/ml MIC: 16.4µg/ml MBC:61.8µg/ml MIC: 20.5 µg/ml MBC:74.3µg/ml MIC: 18.2µg/ml MBC:64.5µg/ml MIC: 16.3µg/ml MBC:44.9µg/ml MIC: 26.3µg/ml MBC:86.5µg/ml	-	Chakraborty et al. (2014)
Antimicrobial activity	Ethanol extract	*In vitro*	*B. subtilis* *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	MIC: 10.6µg/ml MBC:36.8µg/ml MIC: 17.6µg/ml MBC:66.4µg/ml MIC: 23.5µg/ml MBC:83.2µg/ml MIC: 20.3µg/ml MBC:67.5µg/ml MIC: 18.9µg/ml MBC:52.8µg/ml MIC: 34.0µg/ml MBC:84.3µg/ml	-	Chakraborty et al. (2014)
	Acetone extract	*In vitro*	*B. subtilis* *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	MIC: 10.5µg/ml MBC:40.8µg/ml MIC: 21.5µg/ml MBC:77.8µg/ml MIC: 27.9µg/ml MBC:94.2µg/ml MIC: 28.2µg/ml MBC:75.9µg/ml MIC: 11.5µg/ml MBC:40.2µg/ml MIC: 13.3µg/ml MBC:50.5µg/ml	-	Chakraborty et al. (2014)
	Aqueous extract	*In vitro*	*B. subtilis* *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	MIC: 11.5µg/ml MBC:45.6µg/ml MIC: 15.8µg/ml MBC:42.7µg/ml MIC: 19.3µg/ml MBC:65.7µg/ml MIC: 13.1µg/ml MBC:45.7µg/ml MIC: 21.3µg/ml MBC:55.9µg/ml MIC: 20.2µg/ml MBC:78.2µg/ml	-	Chakraborty et al. (2014)
Antimicrobial activity	Ethanol extract	*In vitro*	*P. aeruginosa* *B. subtilis*	MIC:12.5 mg/ml MBC: 50mg/ml MIC: 6.3 mg/ml MBC: 25 mg/ml	Negative: Sterile water	Lucky et al. (2017)
Antifungal activity	GEO	*In vitro*	*Fusarium verticillioides*	MIC: 5000mg/ml	-	Yamamoto-Ribeiro et al. (2013)
Antifungal activity	GEO	*In vitro*	*Aspergillus niger* *M. hemalis* *F. oxysporum*	MIC: 70µg/ml MIC: 75µg/ml	-	El-Baroty et al. (2010)

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Table 5. Continued

Pharmacological activities	Studyextract/ GEO	In vitro/ In vivo	Target/ Model	IC 50/ Dosage	Control	Reference
Antifungal activity	GEO	*In vitro*	*Aspergillus flavus* *Penicillium expansum*	MIC: 500µg/ml	-	Sharma et al. (2013)
Antioxidant activity	Aqueous extract	*In vitro*	*Rats*	IC_{50}: 6.8 µg/ml	-	Nanjundaiah et al. (2011)
Gastro protective activity	Aqueous extract	*In vivo*	*Ulcer induced rats by ethanol/ swim stress*	200 mg/kg body weight	Positive: Lansoprazole	Nanjundaiah et al. (2011)
Gastro protective activity	Zingerone	*In vivo*	*Ethanol-induced gastric ulcers in rats*	200 mg/kg body weight	Positive: Ranitidine	Karampour et al. (2019)
Antidiabetic activity	Aqueous Extract	*In vivo*	Streptozotocin (STZ)-induced type I diabetic rats	4 ml/ kg, p.o. daily for 6 weeks	Negative: Sterile water	Akhani et al. (2004)
Antidiabetic activity	Ethanolic Extract	*In vivo*	STZ-induced diabetic rats	200 mg/kg p.o daily for 20 days	Positive: Gliclazide	Bhandari et al. (2005)
Cytotoxic activity	Subcritical water extracts	*In vitro*	Hep2c cells RD cells L2OBcells	IC_{50}: 9.82 µg/ml IC_{50}: 13.81 µg/ml IC_{50}: 6.88 µg/ml	-	Švarc-Gajić et al. (2017)
Cardioprotective activity	Ethanol extract	*In vivo*	Wistar rats	400 mg/kg body weight	-	Amran et al. (2015)
Antiproliferative activity	Aqueous extract	*In vitro*	A549 cells HeLa cells	IC_{50}: 239.4µg/ml IC_{50}: 253.4µg/ml	Control: Untreated	Choudhury et al. (2010)
Insecticidal activity	GEO	*In vivo*	*Culex theileri*	1 ml	-	Madreseh-Ghahfarokhi et al. (2018)

Note: GEO, Ginger essential oil, MIC, Minimum inhibition concentration; MBC, Minimum bactericide concentration; $LC_{50,}$ Lethalconcentration; IC_{50}, Inhibitory concentration

studies (Kikusaki and Nakatani, 1993; Dugasani et al., 2010). Increasing antioxidant activity of the human body will undoubtedly protect against the oxidative stress (Shukla and Singh, 2007). Bellik, (2014) reported that ginger oleoresin has greater antioxidant activity (IC_{50} =1.82mg/ml) compared to essential oil (IC50 =110.14 mg/ml). The bioactive molecule [6]-Gingerol is the major pungent constituent that has considerable antioxidant activity. [6]-Gingerol have greater scavenging activity compared to ethanol extract of ginger against 1,1-diphenyl-2-picrylhydrazyl and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical at lower concentrations (<100 µg/ml). However, both the ginger extract and [6]-gingerol displayed same antioxidant potential at higher doses (100–1000 µg/ml) (Harliyansyah et al. 2007). Ginger extracts also protect the DNA from lipopolysaccharide-induced oxidation damage in rats (Tchombé et al., 2012). Ginger oil can act as a scavenger of oxygen radical and could be used as antioxidant (Yadav et al., 2016). The alcoholic extracts of ginger have shown effective antioxidant effects and can prevent lipid peroxidation (Shobana and Naidu, 2000).

Antimicrobial and Antifungal Activity

Ginger extracts have significant antimicrobial activity against *Bacillus subtilis*, *Escherichia coli,Staphylococcus aureus, Salmonella typhimurium, Bacillus cereus, Candida albicans*and*B. subtilis* (Thongson et al., 2005; Natta et al., 2008; Singh et al. 2008; Bellik, 2014) and antifungal activity against *Fusarium*sp., *Pseudomonas aeruginosa* and *Aspergillus Niger* (Sa-Nguanpuag et al., 2011;Auta et al. 2011; Bellik, 2014; Riaz et al., 2015).The active biomolecule [6]-gingerol and [12]-gingerol revealed potential antibacterial effects against gram negative bacteria, *Porphyromonas gingivalis,P. endodontalis* and *Prevotella intermedia.* However, another bioactive molecule, [10]-gingerol showed antibacterial

activity against *Mycobacterium avium* and *M. tuberculosis* (Hiserodt et al., 1998). Furthermore, several antimicrobial studies were summarized in Table 5.

Anticancer Activity

Worldwide, researchers are interested in identifying plant derived bioactive constituents that have the capacity to interfere with carcinogenic processes. Several spices and medicinal plants are known to possess an array of pharmacological properties including anticarcinogenic and antimutagenic activities. Tumor induction is strictly linked to oxidative stress, a constituent that exhibits antioxidant properties might be act as antitumorogenic agent. Masuda et al. (2004) isolated more than 50 antioxidants from the rhizomes of ginger. Among them topical application of [6]-gingerol to DMBA initiated skin cancer in SENCAR mice contributed a substantial protection against skin canceras reported by Katiyar et al. (1996). Glioblastoma multiforme (GBM) is the most lethal, destructive and malignant astrocytoma of primary brain tumors in adults. Lee et al., 2008 reported the [6]-Gingerol induced tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apoptosis of glioblastoma. The previous study reports noticed that the bioactive molecule [6]-gingerol had been induced apoptosis of gastric cancer cells by increasing caspase-3/7 activation (Prasad and Tyagi, 2015). The other bioactive constituent gingerdione has been demonstrated as a potential antitumor agent in human leukemia cells(Hsu et al., 2005).

In another study, the methanolic extract of ginger inhibited the growth of 19 *Helicobacter pylori* (HP) strains with a minimum inhibitory concentration (MIC) range of 6.25-50μg/ml (Mahady et al., 2003). Yusof et al. (2009) demonstrated that oleoresin of ginger has chemopreventive activity against liver cancer in rats. The ginger extract also remarked that suppression of cell cycle progression and prompted the death of human pancreatic cancer cell lines (Akimoto et al. 2015). Tahir et al. (2015) observed that fresh ginger extract contains a high level of gingerols, and it is used to induce cell death of colon cancer cells.

Anti-inflammatory Activity

The anti-inflammatory activity of ginger has been well known for centuries. However, the scientific evidence confirmed it mostly in animal models more than humans, Wei et al. (2005). Anti-inflammatory potential of gingerols was evidenced by the inhibitory effects of prostaglandins and leukotrienes synthesis in Rat Basophilic Leukemia -1 (RBL-1) cells (Kiuchi et al., 1982). The ginger rhizome contains bioactive constituents such as [6]-gingerol and [6]-paradol which has been reported to have durable anti-inflammatory effects and suppress the production of TNF α in TPA- treated female ICR mice (Surh et al., 1999).Ramadan et al. (2011) reported that oral administration of ginger (200 mg/kg) suppressed the incidence and severity of adjuvant-induced arthritis by increasing the production of anti-inflammatories and decreasing pro-inflammatory cytokines in rat.

OTHER ACTIVITIES

Anti-nausea Activity

The consumption of ginger may be a safe and effective option for the treatment of nausea and vomiting in the pregnancy period (Borrelli et al., 2005). Maitre et al. (2011) evaluated four randomized controlled trials (RCTs) on the use of ginger for pregnancy-induced nausea, and vomiting (PINV) which were sourced from MEDLINE, TRIP CINAHL, and the Cochrane library. All the trials noticed that orally administered ginger was significantly more effective for reducing vomiting and nausea. Additionally, in the U.K, the National Institute of Health and Clinical Excellence, has included a list of ginger acceptable therapies to cure nausea and vomiting during early pregnancy.

Anti-respiratory Diseases Activity

Ginger rhizome has been used for centuries in treating respiratory diseases. Gingerols remarkably reduced the eosinophils in the lungs of ovalbumin-sensitized mice and suppressed the allergen-induced Th2 cell-drivenn airway inflammation (Ahui et al., 2008). Ingestion of 6-, 8- gingerols, and 6-shogaol reduced asthma disease at doses ranged between 100 to 300 μM, by prompt relaxation of precontracted airway smooth muscle (Townsend et al., 2013).

Anti-diabetic and Anti-obesity Activity

The oral administration of ethanolic ginger extract significantly decreased fasting blood glucose levels in streptozotocin (STZ) - treated type 1 diabetic rat model (Ojewole, 2006). Okamoto et al. (2011) reported that [6]-gingerol reduce body weight and fat accumulation in mice. In another study, [6]-gingerol inhibits rosiglitazone-induced adipogenesis through suppressing oil droplet accumulation and reduces the oil droplet size in 3T3-L1 cells (Tzeng and Liu, 2013).

Cardio Protective and Lipid-Lowering Activity

Cardiovascular activity of ginger reported that ginger extract has an antioxidative potent, and it can scavenge the superoxide anion and hydroxyl radicals (Fuhrman et al., 2000). *In vitro* and *in vivo*, studies with animal models showed that ginger extract possessed antioxidant activity, and it might be triggering the anti-inflammatory response and protect against cardiovascular disease (Masuda et al., 2004). The ethanol extract of ginger at 400 mg/kg body weight of Wistar rats showed a significant decrease in all the cardiac enzyme activities. (Amran et al., 2015).The aqueous ginger extract also exhibited durable inhibitions against low-density lipoprotein (LDL) and platelet aggregation (Saputri and Jantan, 2011). Ethanolic *Zingiber officinale* extract (200 mg/kg)p.o. for 20 days is substantially lowering the lipids in streptozotocin (STZ) - induced diabetic rats (Bhandari et al., 2005).

Antithrombotic Activity

Earlier studies reported that ginger extract was found to possess antithrombotic activity as a result of inhibiting platelet aggregation and thromboxane-B2(TXB2)*in vitro.* Whereas, effect of *in vivo* experiments, oral administration of high doses of ginger extract in rats substantially reduced the level of TXB2andprostaglandin-E2 (PGE2) production (Srivastava and Mustafa, 1989;Thomson et al., 2002).

CONCLUSION

Nowadays, plant based nutraceutical compounds have increased wider acceptance as chosen alternatives to several synthetic medicines, mainly for cancer and diabetes. Also, people are aware that long term uses of synthetic drugs are connected with various side effects. The rhizome of ginger is well known for its medicinal value and flavor-enhancing agent. Gingerol is the key pungent constituent, it is a major bioactive compound accumulated in the rhizome of fresh ginger. Presently, ginger is mainly used for the prevention of travel sickness and chemoprevention of cancer. Several studies are extensively investigated for discovering the therapeutic potential of ginger extracts, GEO and its bioactive compounds such as α-zingiberene, gingerol and shogaol in humans and animal models.

Various results accounted that ginger has antibacterial, antifungal, anticancer, anti-inflammatory, antidiabetic, insecticidal, and other miscellaneous activities. Future research should focus on the genetic variability of GEO and bioactive constituents from various cultivated varieties as well as the country of origin. GEO contains major active constituents such as zingiberene, geranial, camphene, β-sesquiphellandrene, neral, citrol, farnesene, bisabolene, and ar-curcumene. The presence of these biologically active molecules as major constituents in ginger essential oil can be used in food, aroma, cosmetics and pharmaceutical domains. Additionally, future research needs attention on the influence of environmental factors attributed to ginger and its active compounds.

Further studies on determining the various pharmacological potential of the ginger extracts, GEO, gingerol, shogaol and other active compounds should include human intervention clinical trials to investigate the activity against humans from various diseases. Future research should also focus on the suitable duration, maximum dosage of ginger, concerns of overdosage and its side effects. Furthermore, future investigations also are required to study the genetic diversity of phytochemicals among various ginger germplasm lines grown across the world or country for improving GEO or particular bioactive constituents, which are essential for developing varieties with higher beneficial bioactive constituents.

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