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Review Article **Pharmacy**

Ginger: A Herbal Medicine for Numerous Ailments

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Abstract

Ginger (*Zingiber officinale* Roscoe), a popular herbaceous plant, has been generally used as a flavoring agent and herbal medicine for centuries. The main components of ginger rhizome are corbohydtrates, lipids, essential oils, terpenes and phenol compounds such as shogaol and gingerol. This systematic review aims to provide a comprehensive discussion in terms of the clinical effects of ginger in all reported areas. Clinical applications of ginger with an expectation of clinical benefits are receiving significant attention. The consumption of the ginger rhizome is a typical traditional remedy to relieve common health problems. Ginger shows the wide range of pharmacological and biological potential in the prevention and treatment of various diseases, like colds, nausea, arthritis, migraines, diabetes, allergy and hypertension.

Keywords: Ginger, Shogaol, Gingerol.

INTRODUCTION

India has a rich culture of medicinal plants, which includes about more than two thousands of species and has a huge geographical region with highly possible abilities for Ayurvedic, Unani, Siddha traditional medicines. Human beings have used plants for the treatment of various diseases for thousands of years. Rural areas of many developing countries still depend on traditional medicine for their primary health care requirements and have found a place in day to day life. These medicines are comparatively safer and cheaper than synthetic or modern medicine. Herbal medicines are in dominant requirement in both developed and developing countries as a source of primary health care owing to their quality having wide biological and medicinal activities, high safety margins and lesser costs. Ginger contains fresh or dried roots of *Zingiber officinale*. The English botanist William Roscoe gave the plant name *Zingiber officinale* in an 1807 publication (Banerjee, *et al*., 2011). Ginger is used universally as a cooking spice, flavoring agent and herbal remedy. The Chinese have used ginger for at least 2500 years for digestive support and antinausea remedy, and to treat bleeding disorders and rheumatism. It was also used to treat alopecia, toothache, snakebite, and respiratory conditions. In Traditional Chinese Medicine, ginger is considered a pungent, dry, warming, yang herb to be used for diseases activated by cold, damp weather. Ginger is used extensively in Ayurveda, the traditional medicine of India, to block excessive clotting (heart disease), reduce cholesterol and fight arthritis. In Arabian medicine, ginger is considered a stimulant. Some Africans believe that eating ginger regularly will help repel mosquitos. The Greeks wrapped ginger in bread and eat it after meals for digestive support. Subsequently, ginger was included directly into bread and confections such as gingerbread. Ginger was so valued by the Spanish that they established ginger plantations in Jamaica in the 1600s. The Eclectic physicians of the 19th century depend on ginger to induce sweating, raise the hunger and cure nausea, and as a topical ointment. Recently, ginger is extensively cultivated from Asia to Africa and the Caribbean and is used universally as a nausea remedy, as an anti-spasmodic and to promote warming in case of chills. Ginger is also extensively consumed as a flavoring agent; it is approximate that in India, the individual average daily consumption is 8-10 gm of fresh ginger root. The German commission E has also approved the use of ginger root as a treatment for indigestion and prophylactic against motion sickness (Moghaddasi and Kashani, 2012). Ayurveda medicine refers to osteoarthritis as sandhivata from the Sanskrit ‘sandhi’ for joint and vata for vata dosha. Ginger is believed to be a plant with properties to rebalance symptoms of osteoarthritis. Ginger has been taken internally and used externally in China, frequent as a compress, patch or in combination with moxibustion (Therkleson, 2012). Flavour and pungency can vary

considerably but it is not just cultivar that contributes to this as environmental factors such as soil type, season, climate, cultivation practice, location, maturity and postharvest processes have also been shown to contribute to differences in these properties. In general the genetic diversity within ginger is actually considered to be limited. Many types of molecular markers have been used to evaluate levels of polymorphism in ginger, and in general the results show only low to moderate variation with just a few exceptions. The ginger rhizome contains carbohydrates, proteins, fats, fibre, water, and essential oils. In addition to its nutritional and flavour aspects, it has long been considered to have potential for multiple health benefits as illustrated by its use as a traditional medicine against headache, nausea, colds, and arthritis for as long as a thousand years by traditional people in Asia. More recent evaluations by health scientists have shown that ginger may have a role in reducing certain cancers, diabetes, and high blood pressure and also have anti-inflammatory properties. However, there are still a few, albeit uncommon, minor adverse effects resulting from the consumption of ginger; these include slight gastrointestinal distress, heartburn, and oral irritation. Ginger has been shown to act as an antimicrobial agent where it has been shown to inhibit growth of *Escherichia coli*, *Proteus* spp., *Staphylococci*, and *Salmonella* in vitro assays. It has also been shown to have antifungal properties, inhibiting growth of *Aspergillus* spp., *Saccharomyces* spp., *Mycoderma* spp., and *Candida* spp. Despite its antimicrobial properties, ginger is still a host of at least 24 known plant pathogens including viruses, bacteria, *Oomycota* and fungi (Le, *et al*., 2014).

Fig 3.2: Ginger rhizome with fresh shoot

Fig 3.3: Young ginger rhizome

1. Taxonomic classification

Scientific name:	*Zingiber offficinale* Roscoe
Kingdom:	Plantae
Subkingdom:	Tracheobionta
Superdivision:	Spermatophyta
Division:	Magnoliophyta
Class:	Liliopsida
Subclass:	Zingiberidae
Order:	Zingoberales
Family:	Zingiberaceae
Genus:	Zingiber Mill.
Species:	*Zingiber offficinale*

2. Synonymes: Zingiberis, Ginger, Sonth.

Names in international language		**Names in regional language**	
African-	Gemmer	Hindi-	Adhrak
Indonesian-	Jahe	Urdu-	Adrak
Latin-	Giniberi	Marathi-	Ala
Turkish-	Zecefil	Gujarati-	Adu
Spenish-	Jegibre	Bengali-	Ada
Romanian-	himbir	Tamil-	Ellam, Inji
German-	Ingwer	Telgu-	Allamu
Dutch-	Gember		
French-	Gingembre		
Irish-	Ginger		

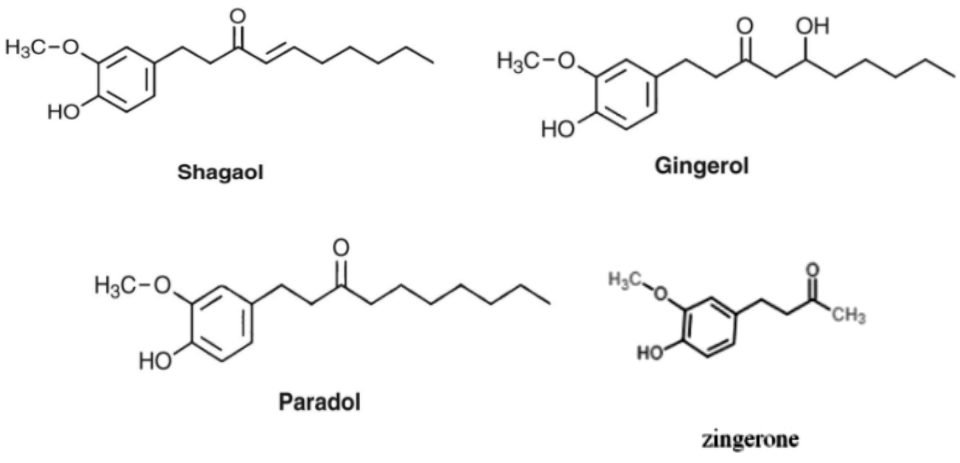
Italian-	Zenzero
Portuguese-	Gengibre

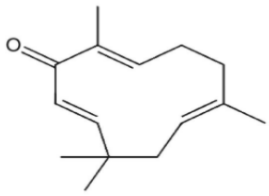
3. Description and distribution

Zingiber officinale Roscoe belongs to family Zingiberaceae (Ginger), which has 1300 species of which about 90 comprise the zingiber species. Ginger is cultivated in South East Asia, Caribbean island, Africa, Australia, Mauritius, Jamaica, Taiwan and in almost all states of India, especially in Kerala, Assam, Himachal Pradesh, Orissa, West Bengal and Karnataka. More than 35% of the world's production is from India. Ginger needs warm humid climate and is cultivated in areas with heavy rainfall, even at sea level but grow best at an altitude of 1000 to 1500 meter. Ginger is cultivated by showing rhizomes in the month of June. Externally it is buff colored, agreeable and aromatic in odor and pungent taste. Rhizomes of ginger are about 5 to 15 x 1.5 to 6.5 cm, bearing short flat, ovate and oblique branches on the upper side, with bud at the apex. Longitudinal striations and the occasional projecting fibres are present on the surface of ginger. Transversely cut surface shows well marked endodermis and stele. Ginger is produced in almost all of the states of India and ranks first among ginger producing countries of the world. There are one dozen large scale oleo resin producing industries in India at present with total installed capacity of 900 tonnes. 404.8 tonnes of spice oleoresins were exported during 1995-1996. Most of the exports are to U.S., U.K., France, West Germany, Netherland and Yugoslavia (Kokate, *et al*., 2010).

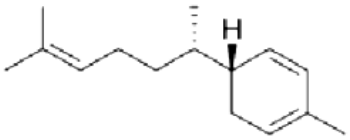
4. Chemical constituents

Ginger consists of volatile oil (1-4%), starch (40-60%), fat (10%), fibre (5%), inorganic material (6%), residual mixture (10%), and acrid resinous matter (5-8%). Ginger oil is constituted of monoterpene hydrocarbons, sesquiterpene hydrocarbons, oxygenated mono and sesquiterpenes, and phenyl propanoids. Sesquiterpenes hydrocarbon content of all types of ginger oil from different countries is found to be same and include α-zingibrene, β-bisabolene, α-farnesene, β-sesquiphellandrene and α-curcumene. Aroma and flavor are the main characters of ginger. Aroma is due to fragrant principles of volatile oil while the flavor, pungency and pharmacological action is exerted by phenolic ketones of oleo-resins. Various components of volatile oil like isometric terpenic aldehydes like geranial and citral, which cause the fine and lemony aroma. Few sesquiterpene oil hydrocarbons are believed to exert spicy note (Kokate *et al*., 2010). At least 31 gingerol associated constituents have been isolated from the methanolic crude extracts of fresh ginger rhizome. Ginger has been extracted into at least fourteen biologically active compounds, including 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerol, 6-paradol, 14-shogaol, 6-shogaol, 1-dehydro-10-gingerdione, 10-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4′ hydroxyl-3′ methoxyphenyl)-5-methoxyhepthan-3-one, and methoxy-10-gingerol (Bode and Dong, 2011). Terpene components of ginger include zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene, while phenolic compounds include gingerol, paradols, and shogaol. These gingerols (23-25%) and shogaol (18-25%) are found in higher quantity than others. Besides these, amino acids, raw fiber, ash, protein, phytosterols, vitamins (nicotinic acid and vitamin-A), and minerals are also present. The aromatic constituents include zingiberene and bisabolene, while the pungent constituents are known as gingerols and shogaols. Other gingerol or shogaol related compounds (1-10%), which have been reported in ginger rhizome, include 6-paradol, 1-dehydrogingerdione, 6-gingerdione and 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 8-gingerdiol, and 10-gingerdiol, and diarylheptanoids. The characteristic odor and flavor of ginger are due to a mixture of volatile oils like shogaols and gingerols (Prashad and Tyagi, 2015).





Zerumbone



Gingerbene

5. Medicinal uses

Ginger shows the wide range of pharmacological activity such as analgesic activity (Hitomi, *et al*., 2016; Mahani, *et al*., 2012), anti-allergic activity (Park, *et al*., 2016), anthelmentic activity (Lin, *et al*. 2010), anti-bacterial activity (Gull, *et al*., 2012; Vijendra, *et al*., 2014), anti-cancer activity (Cheng, *et al*., 2011; Manju and Nalini, 2005), anti-coagulant activity (Tjendraputra, *et al*., 2003), anti-convulsant activity (Hosseini and Mirazi, 2014), anti depressant activity (Yi, *et al*., 2009), anti-diabetic activity (Daily, *et al*., 2015; Kazeem, *et al*., 2015), anti-emetic activity (Hajbaghery and Hosseini, 2015), anti-fungal activity (Yamamoto-Ribeiro, *et al*., 2013; Ojaghian, *et al*., 2014), hepatoprotective activity (Heeba and Abd-Elghany, 2010; Kazeem, *et al*., 2015), anti-hypercholesterolemia activity (Akinyemi, *et al*., 2015), anti-hyperlipidemic activity (Matsuda, *et al*., 2009), anti-hypertensive activity (Akinyemi, *et al*., 2015), immunomodulator activity (Chakraborty and Sengupta, 2012), anti-inflammatory activity (Moussa, *et al*., 2012; Breemen, *et al*., 2011), memory enhancing activity (Lim, *et al*., 2014; Moon, *et al*., 2014), neuroprotective activity (Sharma, *et al*., 2012; Ha, *et al*., 2012), anti-obisity activity(Misawa, *et al*., 2015), anti-oxidant activity (Li, *et al*., 2016; Zhao, *et al*., 2011), anti-parasitic activity (Choi, *et al*., 2013; Levy, *et al*., 2015), proteolytic activity (Hashim, *et al*., 2011; Huang, *et al*., 2011), anti-respiratory disorder activity (Mangprayool, *et al*., 2013; Ahui, *et al*., 2008), renoprotective activity (Shirpoor, *et al*., 2016), anti-teratogenic activity (Farag, *et al*., 2010), anti-thrombotic activity (Hemalatha and Prince, 2016), anti-ulcer activity (Rashidian, *et al*., 2014; Abd-Allah, *et al*., 2015) and many others.

6. Pharmacological activity

1. Analgesic activity

6-gingerol and 6-shogaol, two components of a processed ginger extract, considerably inhibited voltage activated Na^+ currents. These two constituents diminished the stimulant induced release of substance-P and action potential generation in cultured rat sensory neurons. A submucosal injection of a mixture of 6-gingerol and 6-shogaol increased the mechanical withdrawal threshold in healthy rats. In a rat oral ulcerative mucositis induced mechanical pain was reduce 30 minutes after the swab application of hangeshashint. A swab application of a three mixture of 6-gingerol and 6-shogaol induced sufficient analgesia of oral ulcerative mucositis induced mechanical or spontaneous pain when co-applied with a ginseng extract containing huge quantity of saponin. The ginseng extract revealed an acceleration of substance permeability into the oral ulcer tissue without an analgesic effect. These findings indicate that Na^+ channel blockage by gingerol/shogaol plays an essential role in hangeshashint related analgesia of oral ulcerative mucositis induced pain. This pharmacological mechanism provides scientific proof supporting the use of this herbal medicine in patients suffering from oral ulcerative mucositis induced pain (Hitomi, *et al*., 2016). Study displayed that chronic morphine injected rats showed tolerance to the analgesic effect of morphine as well as morphine dependence. Ginger completely prevented the development of morphine tolerance. In addition, morphine induced L-type calcium channel over expression in spinal cord was reversed by ginger (Mahani, *et al*., 2012). The extract of ginger exhibited analgesic activity for its central and peripheral activities in mice, by inhibiting the hot plate test and acetic acid induced writhing. Analgesic activity of ginger extract against acute pain was moderate in contrast to the potent inhibitory activity of Ibuprofen. It is established that nonsteriodal anti-inflammatory drugs such as ibuprofen inhibits the synthesis of prostaglandin which increases the sensitivity of nociceptor and perception of pain. Prostaglandin and bradykinin were recommended to play an important role in the pain process. Therefore, it is likely that ginger extract might suppress the formation of these substances and show its analgesic activity in hot plate test and acetic acid induced writhing test. In both methods, ginger extract showed high analgesic activity. Recommended its peripheral and central analgesic activity. The analgesic activity may be due to the presence of total polyphenols, flavanoids and tannins in ginger extract (Chyad, *et al*., 2016).

2. Anti-convulsant activity

The study showed that the ginger extract has anticonvulsant effects. Ginger treatment significantly increased the seizure threshold. Ethanolic extract of ginger significantly increased the onset time of myoclonic seizure significantly prevented generalized clonic and increased the threshold for the forelimb tonic extension seizure two and 24 hours before induction of pentylenetetrazole compared with control group. Based on the results the ethanolic extract of ginger has anticonvulsant effects, possibly through an interaction with inhibitory and excitatory system, antioxidant mechanisms, oxidative stress and calcium channel inhibition (Hosseini and Mirazi, 2014). Study revealed

that ethanolic extract of ginger rhizome has dose dependent anticonvulsant activity. The ethanolic extract of ginger rhizome was administered orally in swiss albino rats and the effects were compared with phenytoin as standard. The ginger rhizome has shown significant decrease in the duration of tonic hind limb extension suggesting anticonvulsant effect (Venkatanarayana, *et al*., 2013).

3. Anti-depressant activity

Ginger has anti depressant like effect in the mouse forced swimming test and tail suspension test. The combination of an ineffective dose of ginger oils with mixture of honokiol and magnolol was the most effective and produced a synergistic action on behaviors after two week treatment. Significant increase in serotonin and synergistic increase in noradrenaline in prefrontal cortex were observed after co-administration of mixture of honokiol and magnolol with ginger oils. Compatibility of mixture of honokiol and magnolol with ginger oils was suggested to exert synergistic antidepressant actions by attenuating abnormalities in serotonergic and noradrenergic system functions (Yi, *et al*., 2009). Ethanolic extract of ginger shows significant antidepressant activity in tail suspension test and forced swim test model of depression. In both the test tail suspension test and forced swimming test extract shortened the immobility period and shows the dose dependent antidepressant activity. The extract is found to be effective nearly similar to that of conventional drug imipramine (Singh, *et al*., 2012). Ginger powder could act as serotoninergic antidepressant medicine in order to decrease depression presentation in exposed subjects to 50 Hz electromagnetic fields. Results revealed electromagnetic fields exposure increase immobility but reduce locomotor function of swimming and climbing in comparison. Rats that had been fed with ginger powder showed decrease in immobility score and increase in swimming, but not in climbing scores significantly (Khaki, *et al*., 2013). Dehydrozingerone is a phenolic compound isolated from ginger rhizomes and shows antidepressant effect. The results revealed that dehydrozingerone has a potent antidepressant effect, which seems to involve the serotonergic and noradrenergic systems. The effect of dehydrozingerone on immobility time in the tail suspension test was statistically significant. Study showed that dehydrozingerone administered orally significantly decreased the immobility time of mice in the TST, suggesting an antidepressant like effect (Martinez, *et al*. 2014).

4. Memory enhancing activity

Study revealed that ginger extract enhancing the memory in a model of scopolamine induced memory impairment and in normal animals by performing a novel object recognition test. Administration of ginger extract significantly improved the ability of mice is recognize novel objects, indicating improvements in learning and memory. Ginger extract administration led to elevated nerve growth factor in both the mouse hippocampus and rat glioma C6 cells. Ginger extract administration also showed phosphorylation of extracellular signal regulated kinase and *cyclic-adenosine monophosphate* response elevated binding protein. Ginger treatment significantly increases pre and post synaptic markers, synaptophysin and postsynaptic building blocks, which are related to synapse formation in the brain. Ginger has a synaptogenic effect via nerve growth factor induced extracellular signal regulated kinase/cAMP response element binding protein activation, resulting in memory enhancement (Lim *et al*., 2014). 6-shogaol reduced microgliosis and astrogliosis in intrahippocampal amyloid-β oligomer injected mice, ameliorated oligomer and scopolamine induced memory impairment, and elevated *nerve growth factor* levels and pre- and post-synaptic marker in the hippocampus. All these results suggest that 6-shogaol may play important role in inhibiting glial cell activation and reducing memory impairment in animal models of dementia (Moon, *et al*., 2014). 6-shogaol shows the effects on the cysteinyl leukotriene-1 receptor, a major factor in Alzheimer's disease pathogenesis. Cysteinyl leukotriene-1 receptor and cathepsin-B are upregulated by amyloid-β, and that cysteinyl leukotriene-1 receptor activation induces cathepsin-B. 6-shogaol mediated inhibition of cysteinyl leukotriene-1 receptor downregulates cathepsin-B in both in vitro and in vivo models. 6-shogaol mediated inhibition of cysteinyl leukotriene-1 receptor/cathepsin-B decrease the amyloid-β deposition in the brain and reform behavioral deficits in APPSw/PS1-dE9 Tg mice. Results indicate that 6-shogaol is a cysteinyl leukotriene-1 receptor/cathepsin-B inhibitor and is a novel potential therapeutic agent for the treatment of different neurodegenerative diseases, including Alzheimer's disease (Na, *et al*., 2016). Ginger pharmacopuncture improve cognitive function and oxidative stress following cerebral ischemia. Male Wistar rats were induced by right middle cerebral artery occlusion and subjected to ginger pharmacopuncture. Rats subjected to ginger pharmacopuncture at governing vessel-20 indicate enhanced spatial memory, and the activities of catalase and glutathione peroxidase were improved in both cerebral cortex and hippocampus. Elevation of superoxide dismutase activity was observed only in the hippocampus. The cognitive enhancing effect of ginger pharmacopuncture is likely to be at least partially attributable to decreased oxidative stress (Jittiwat and Wattanathorn, 2012).

5. Neuroprotective activity

Ethanolic extract of ginger shows the neuroprotective effects against 3-nitro propionic acid induced neurotoxicity. Intraperitoneal administration of 3-nitro propionic acid significantly, increased lipid peroxidation, nitrite and acetylcholinestrease level. Chronic treatment with ginger root extracts dose dependently improved 3-nitro propionic acid induced

behavioral, biochemical, and enzymatic changes (Sharma, *et al*., 2012). 6-shogaol shows the effects on microglia activation in BV-2 and primary microglial cell cultures. 6-shogaol significantly inhibited the release of nitric oxide and the expression of inducible nitric oxide synthase induced by lipopolysaccharide. 6-shogaol suppressed the microglial activation induced by lipopolysaccharide both in primary cortical neuron glia culture and in an in-vivo neuroinflammatory model. 6-shogaol showed significant neuroprotective effects in-vivo in transient global ischemia via the inhibition of microglia (Ha, *et al*., 2012). Study investigate the neuroprotective effect of fermented shogaol enriched extract, which is converted to 6-paradol by *Aspergillus niger*. Amyloid-β oligomer and amyloid-β plaque exposure reduced the hippocampal cell viability. Fermented shogaol enriched extract increased cell viability and inhibite the acetylcholinesterase activity, which was similar to tacrine (Park, *et al*., 2016). Neuroprotective effect of the extract of ginger was investigated against monosodium glutamate induced neurotoxicity. Daily dose of ginger root extract for 30 days and subsequent withdrawal caused a significant increased in epinephrine, norepinephrine, dopamine and serotonin. This is may be due to inhibition of 5HT-3-receptor effects at the same time the extract blockade of Ca^{+2} channels, as result the release of neurotransmitter is decreased and the content is increased. After the extract withdrawal, the increase in monoamine levels remained in brainstem, striatum and hippocampus, this may be due to the region specific effect of the extract. The co-administration of monosodium glutamate and ginger extract caused increased in monoamine content in most of the tested brain regions. This is may be due to partly attributable to an antagonistic action of ginger root extracts on monosodium glutamate effect, so the monoamines content was increased (Waggas, 2009).

6. Anti-hypertensive activity

Study revealed that the effect of ginger an ectonucleotidases, adenosine deaminase and acetyl cholinesterase activities in synaptosomes of cerebral cortex from N-nitro L-arginine methyl ester hydrochloride induced hypertensive rats. N-nitro L-arginine methyl ester hydrochloride increased the ATP and AMP hydrolysis as well as adenosine deaminase and acetyl-cholinesterase activities of cerebral cortex synaptosomes in rats. Pretreatment with ginger rhizome prevented these alterations by decreasing ATP and AMP hydrolysis and adenosine deaminase and acetyl cholinesterase activities in cerebral cortex with a related increase in nitric oxide level, this study revealed that ginger rhizomes interfere with the purinergic and cholinergic neurotransmission in cerebral cortex of hypertensive rats (Akinyemi, *et al*., 2015). In hypertensive animals, ginger has a generally dose dependent hypotensive effect. In addition ginger caused vasodilation in rats and rabbits, following induced vasoconstriction, and exhibited calcium channel blocking activity similar to verapamil. The only human trial to address hypertension found a synergistic effect between ginger and nifedipine. Animal studies have shown that ginger accelerates the Ca^{+2}-pumping rate without affecting its efflux, through activating Ca^{+2}ATPase sarcoplasmic reticulum. This effect was specifically revealed in guinea pig atrial muscle. Ginger can also promote the positive inotropic effect of adrenaline by stimulating its release from the adrenals (Nicoll and Henein, 2007).

7. Anti-respiratory disorder activity

Ginger oil suppressed rat tracheal contraction induced by carbachol. Propranolol, indomethacin and N-Nitro-L-arginine methyl ester were used to block the inhibitory effects of ginger oil in which propranolol reversed bronchodilatory effects of ginger oil, suggesting that a possible mechanism involved in myorelaxing effect is β-adrenergic receptor (Mangprayool, *et al*., 2013). Ginger can exert effect in mouse model of T-helper2 mediated pulmonary inflammation. Intraperitoneal injections of aqueous ginger extract before airway problem of ovalbumin sensitized mice resulted in a marked decrease in the entry of eosinophils to the lungs as attested by cell counts in broncho alveolar lavage fluids. Resolution of airway inflammation induced by ginger extract was accompanied by a suppression of the Th2 cell driven response to allergen in-vivo. Interleukin-4, 5 and eotaxin levels in the lungs as well as specific immunoglobulin-E titres in serum were clearly diminished in ginger treated mice after allergen sensitization. Ginger can suppress Th2 mediated immune responses and might thus provide a potential therapeutic approach in allergic asthma (Ahui, *et al*., 2008). Ginger and its active components induce bronchodilation by altering intracellular calcium in airway smooth muscle. In isolated human airway smooth muscle, ginger caused significant and rapid relaxation. Three purified ingredients of ginger, 6-gingerol, 8-gingerol, and 6-shogaol, were subsequently tested for airway smooth muscle relaxant properties in both guinea pig and human tracheas: induced rapid relaxation of pre-contracted airway smooth muscle. In human airway smooth muscle cells, exposure to 6-gingerol, 8-gingerol, and 6- shogaol, blunted subsequent Ca21 responses to bradykinin and S-(2)-Bay K 8644. In A/J mice, the nebulization of 8-gingerol, 15 minutes before methacholine challenge, significantly reduce airway resistance. These data show that ginger and its isolated active components, relax airway smooth muscle, and 8-gingerol reduce airway hyper responsiveness, in part by modulating intracellular calcium regulation. (Townsend, *et al*., 2013). *Zingiber officinale* extract was studied on clonidine induced mast cell degranulation and OVA albumin induced airway inflammation model. Ginger extract at dose of 250 mg/kg showed significant protection of mast cell degranulation as compared to standard sodium cromoglycate, while at doses of 62.5 and 125 mg/kg showed marked inhibition of total cells, eosinophils,

neutrophils, lymphocytes, whereas in case of macrophages and monocytes an inhibition was observed at 125, 250 mg/kg along with the inhibition of immunoglobulin-E. The results suggest that bronchodilatory activity of extract may be due to the mast cell stabilizing potential, suppression of immunoglobulin-E and inhibition of release of inflammatory mediators (Dongre, *et al*., 2015). Extracts of fresh and dried gingers on human respiratory syncytial virus was tested by plaque reduction assay in both human upper (HEp-2) and lower (A549) respiratory tract cell lines. Fresh ginger dose dependently inhibited human respiratory syncytial virus induced plaque formation in both HEp-2 and A549 cell lines. In contrast, dried ginger didn't show any dose dependent inhibition. Fresh ginger was more effective when given before viral inoculation, particularly on A549 cells. Fresh ginger of high concentration could stimulate mucosal cells to secrete interferon-β that possibly contributed to counteracting viral infection (Chang, *et al*., 2012).

8. Anti-allergic activity

6-gingerol, a major compound of ginger, display anti-allergic effect in mouse allergy model and primary/cell line culture system. Oral administration of ginger reduce the severity of sneezing and nasal rubbing by nasal sensitization of ovalbumin and suppressed infiltration of mast cells in nasal mucosa and secretion of ovalbumin specific immunoglobulin-E in serum. 6-Gingerol inhibited the expression of T-helper cytokines in ovalbumin sensitized spleen cells. Accordingly, 6-gingerol suppressed in-vitro differentiation of both Th1 cells and Th2 cells from naive T-cells. In addition, 6-gingerol suppressed both superantigen staphylococcal enterotoxin-B and anti-cluster of differentiation-3 induced T-cell proliferation. 6-Gingerol also revoke phorbol 12-myristate 13-acetate, ionomycin and staphylococcal enterotoxin-B induced interleukin-2 production in T-cells, suggesting that 6-gingerol affected T-cell receptor mediated signal transduction rather than the antigen-presentation process. 6-gingerol significantly inhibited the phosphorylation of mitogen activated protein kinases, calcium release and nuclear localization of c-fos and nuclear factor-κβ by phorbol 12-myristate 13-acetate and ionomycin stimulation. Thus, results demonstrate that 6-gingerol suppresses cytokine production for T-cell activation and proliferation, thereby not causing β-cell and mast cell activation and resulting in prevention or reduction of allergic rhinitis symptoms (Kawamoto, *et al*., 2015). 6-shogaol inhibits allergic dermatitis like skin lesions and their underlying mechanism in-vivo and in-vitro. In-vivo, 6-shogaol inhibited the development of 2,4-dinitrochlorobenzene induced allergic dermatitis like skin lesions and scratching behavior, and showed significant reduction in Th2 and Th1 mediated inflammatory cytokines, immunoglobulin-E, tumor necrosis factor-α, interferon-γ, thymus and activation regulated chemokine, interleukin-1, 4, 12, and 13, cyclooxygenase-2, and nitric oxide synthase levels. In vitro, 6-shogaol inhibited reactive oxygen species and mitogen activated protein kinases signaling, and increased the levels of total glutathione, heme oxygenase-1, and quinine-1 via nuclear factor erythroid-2 related factor-2 activation. 6-shogaol can reduce allergic dermatitis like skin lesions by inhibiting immune mediators via regulating the reactive oxygen species/mitogen activated protein kinases/nuclear factor erythroid-2 related factor-2 signaling pathway, and may be an effective alternative therapy for allergic dermatitis (Park *et al*., 2016).

9. Anti-cancer activity

Aqueous extract of ginger interacts directly with cellular microtubules and disrupts its structure and induces apoptosis of cancer cells. The effect of ginger extract determined from cell viability experiment on human non-small lung epithelium cancer (A549) cells and human cervical epithelial carcinoma (HeLa). It has been found that the apoptosis of A549 cells by ginger extract is mediated by up regulation of tumor suppressor gene p53 and alteration of the normal Bax/Bcl-2 ratio followed by down regulation of cellular pro-caspase3. The morphological change of cells upon ginger extract treatment has also been demonstrated. Both the structural and functional properties of tubulin and microtubule were lost (Choudhury, *et al*., 2010). The anti proliferative effect of fresh, dried and steamed gingers was examined using human Hela cancer cells. The antiproliferative effect of steamed ginger at 120^{o}C for four hours was higher than that of dried and fresh ginger. The decreased concentration of gingerols and increased levels of shogaols contributed to the improved anticancer potential of the steamed ginger (Cheng, *et al*., 2011). 6, 8 and 10-gingerol inhibited the proliferation of MDA-MB-231 tumor cell line. These substances also inhibited human fibroblasts cell proliferation (Silva, *et al*., 2012). 6-dehydroshogaol had quinone reductase inducing activity of comparable potency to the well known cancer preventive agent, curcumin. 6-Shogaol, 6-dehydroshogaol and curcumin were also potent inhibitors of nitric oxide synthesis, inhibiting nitric oxide evolution inactivated macrophages (Imm, *et al*., 2010). 6-gingerol enhanced the tumor necrosis factor related apoptosis inducing ligand (TRAIL) induced viability reduction of gastric cancer cells while 6-gingerol alone affected viability only slightly. 6-gingerol accelerates TRAIL induced apoptosis by increasing TRAIL induced caspase-3/7 activation. 6-gingerol was shown to down regulate the expression of cellular inhibition of apoptosis protein-1, which suppresses caspase-3/7 activity, by inhibiting TRAIL induced nuclear factor-κβ activation. 6-shogaol alone reduced the viability of gastric cancer cells. 6-shogaol was shown to damage microtubules and induce mitotic arrest (Ishiguro, *et al*., 2007). Zingerone and its derivative have synergistic effect of on epithelial mesenchymal transition. Transforming growth factor-β1 induces the epithelial mesenchymal transition to

promote hepatocellular carcinoma metastasis, including migration and invasion. Zingerone derivatives and 6-hydroshogaol significantly increased expression of the epithelial marker E-cadherin and repressed Snail upregulation and expression of the mesenchymal marker N-cadherin during initiation of the transforming growth factor-β1 induced epithelial mesenchymal transition. Zingerone derivatives inhibited the transforming growth factor-β1 induced increase in cell migration and invasion of SNU182 hepatocellular carcinoma cells. Zingerone derivatives significantly inhibited transforming growth factor-β1 regulated matrix metalloproteinase-2/9 and activation of Smad2/3. Zingerone derivatives also inhibited nuclear translocation of nuclear factor-κβ, activation of p42/44 mitogen activated protein kinase/activator protein-1 signaling pathway in the transforming growth factor-β1 induced transforming growth factor (Kim, *et al*., 2017). Synthetic novel shogaol analogue 3-phenyl-3-shogaol has the anti-cancer potential. At non-toxic concentrations, 3-phenyl-3-shogaol suppressed cancer cell invasion in MDA-MB-231 and MCF-7 breast carcinoma cells through inhibition of phorbol 12-myristate 13-acetate activated matrix metalloproteinases-9 expression. At similar concentrations, 3-phenyl-3-shogaol reduced expression of the inflammatory mediators nitric oxide, inducible nitric oxide synthase, cyclooxygenase-2 and prostanglandin-E2 in RAW 264.7 macrophage-like cells. Inhibition of cancer cell invasion and inflammation by 3-phenyl-3-shogaol were mediated through suppression of the nuclear factor-κβ signaling pathway. The 3-phenyl-3-shogaol also demonstrated cytoprotective effects by inducing the antioxidant response element driven genes NADPH quinone oxidoreductase-1 and heme oxygenase-1. Cytoprotection by 3-phenyl-3-shogaol was achieved at least partly through modification of cysteine residues in the E3 ubiquitin ligase substrate adaptor Kelch-like ECH-associated protein 1, which resulted in accumulation of transcription factor nuclear factor-E2 p45-related factor 2 (Gan, *et al*., 2013). Nanoparticle made from ginger derived lipids that can serve as a delivery platform for the therapeutic agent doxorubicin to treat colon cancer. Nanoparticles created from ginger and reassembled their lipids into ginger derived nanovectors. Which efficiently taken up by colon cancer cells and exhibited excellent biocompatibility. Ginger derived nanovectors were capable of loading doxorubicin with high efficiency and showed a better pH-dependent drug release profile than commercially available liposomal doxorubicin. Modified ginger derived nanovectors conjugated with the targeting ligand folic acid mediated targeted delivery of doxorubicin to colon-26 tumors in vivo and enhanced the chemotherapeutic inhibition of tumor growth compared with free drug (Zhang, *et al*., 2016). 6-shogaol and 6-gingerol from ginger were found to be most effective in preventing methylglyoxal induced cytotoxicity in the human retinal epithelial cells. These compounds could act by modulating key regulative detoxifying enzymes via modifying nuclear factor-erythroid 2-related factor 2 functions. Methylglyoxal induced cytotoxicity led to increased levels of advance glycation ends products causing increase in Nε-carboxymethyl lysine and glutathione levels and over expression of receptor for advanced glycation end products. Results also showed that translocation of nuclear factor-erythroid 2-related factor 2 from cytosol to nucleus were inhibited, which decreased the expression of detoxifying enzyme like heme oxygenase-1. The most potent bioactive compounds scavenged dicarbonyl compounds, inhibited advance glycation ends products formation and significantly reduced carbonyl stress by nuclear factor-erythroid 2-related factor 2 related pathways and restoration of heme oxygenase-1expression (Sampath, *et al*., 2015).

10. Anti-diabetic activity

Administering of ginger powder lowered fasting serum glucose levels and glycated haemoglobin levels in patients with type-2 diabetes. The supplementation of ginger regular lower fasting serum insulin levels and HoMA-IR (Homeostatic model assessment for insulin resistance: an index of insulin resistance), but they were not significantly different in type-2 diabetic patients. Ginger supplementation improves glucose homeostasis in type-2 diabetic patients possibly by lowering insulin resistance (Daily *et al*., 2015). Administration of the ginger extracts to the diabetic rats, significantly reduced serum glucose and increased serum insulin and HoMA for cell dysfunction while the level of creatinine and Homeostatic HOMA-IR were not affected (Kazeem *et al*., 2015). Study shows the hypoglycemic effect of ginger aqueous extract on alloxan induced diabetic rats. Ginger treated rats showed significant reduction in serum glucose level (Jafri *et al*., 2011). Study shows the effect of raw and cooked ginger extracts on serum insulin in normal rats, streptozotocin induced and high fat diet induced diabetic rats. Type-1 diabetes mellitus was induced with intraperitoneal injection of streptozotocin and Type-2 with twelve weeks high fat diet consumption. Raw and cooked ginger extracts administer orally for four weeks. Raw and cooked ginger extracts and glibenclamide increased serum insulin significantly in streptozotocin induced diabetic rats but this parameter reduced significantly in high fat diet induced diabetic group. This is confirmed that raw and cooked ginger extracts enhanced insulin secretion and reduced hyperinsulinemia in high fat diet induced diabetic rats (Adeniyi *et al*., 2014). Serotonin inhibits insulin release from insulin-1 cells which is reversed by tropisetron, a 5-HT3 receptor antagonist and an oily extracts of ginger. The in-vitro data with respect to ginger are confirmed by in-vivo data on glucose loaded rats showing that blood glucose is reduced and plasma insulin is increased. It may be concluded that serotonin and in particular the 5-HT3 receptor channel system are involved in modulating insulin release and that

tropisetron and various ginger extracts can be used to improve a diabetic situation (Heimes *et al*., 2009). The diabetic rats exhibited lower activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase and reduced glutathione content and higher level of malondialdehyde in hepatic and renal tissues as compared with normal rats. The activities of all parameters were found to be increased, except malondialdehyde in ginger treated diabetic rats, in hepatic and renal tissues. Ginger supplementation to diabetic rats, resulted in significant dose dependent hypoglycaemic and antioxidant activities. These results suggest that ginger treatment exerts a therapeutic protective effect in diabetes by decreasing oxidative stress, and hepatic and renal damage (Shanmugam *et al*., 2011). The study demonstrates that ethanol extract of ginger produced significant hypoglycemic effect in the fasting state of type-2 diabetic model rats. Significant hypoglycemic effect that was found in the fasting state of type-2 model rats indicated that the blood glucose lowering effect of the ethanol extract of ginger is probably due to enhanced insulin releasing activity (Shadli *et al*., 2014).

11. Anti-hyperlipidemic activity

Cholesterol enriched diet developed hepatic steatosis with hyperlipidemia and increased retinoid binding protein mRNA expression in the liver, as well as mRNA expression of retinoid binding protein, heart fatty acid binding protein, and cutaneous fatty acid binding protein in adipose tissue around the left kidney. These lipid metabolism genes are important indicators of hyperlipidemia. Ginger tends to reduce retinoid binding protein mRNA expression levels in the liver and visceral fat in hyperlipidemia, and may improve lipid metabolism (Matsuda, *et al*., 2009). Dietary supplementation of ginger rhizomes inhibited arginase activity and prevented hypercholesterolemia in rats. Study evaluates the effect of ginger on the arginase activity, atherogenic index, levels of liver thiobarbituric acid reactive substances, and plasma lipids in rats fed with a high cholesterol diet. Ginger caused significant decreases in arginase activity and the atherogenic index, and prevented hypercholesterolemia by decreasing the total cholesterol, triglycerides, and low-density lipoprotein cholesterol while increasing the high density lipoprotein cholesterol. Therefore, these activities of ginger represent possible mechanisms underlying its use in herbal medicine to treat several cardiovascular diseases (Akinyemi, *et al*., 2015). Study revealed a decrease in the levels of total cholesterol, and low density lipoprotein in the serum of rats that were treated by ginger extracts. Previous extracts were also able to cause reduction in low density lipoprotein to similar levels and that was the same effect of atorvastatin. Combined effect was clear between the act of ginger and atorvastatin; that levels of both total cholesterol and low density lipoprotein in animals which received atorvastatin combined with ginger extract was almost equal to levels in animals that received atorvastatin. Distinct reduce in triglyceride, and clear increase in high density liopprotein was also recorded in the ginger treated groups. Ginger was more active in hypothyroidism rats than in diabetic rats in reducing low density lipoprotein and total cholesterol (Al-Noory, *et al*., 2013).

12. Anti-obesity activity

Food derived peroxisome proliferator activated receptor-δ (PPARδ) stimulators represent potential treatment options for obesity. Ginger extract increased energy expenditure and attenuate diet induced obesity in C57BL/6J mice. Ginger extract also enhanced the number of type-I muscle fibers, better running tolerance capacity, and upregulated PPARδ targeted gene expression in skeletal muscle and the liver. 6-shogaol and 6-gingerol acted as specific PPARδ ligands and stimulated PPARδ dependent gene expression in cultured human skeletal muscle myotubes. Pretreating cultured skeletal muscle myotubes with ginger extract increased palmitate induced oxygen consumption rate, which suggested an increase in cellular fatty acid catabolism. 6-shogaol and 6-gingerol may be responsible for the regulatory effects of dietary ginger on PPARδ signaling (Misawa, *et al*., 2015). Ginger extract increase muscle mitochondrial biogenesis and serum high density lipoprotein-cholesterol level in high fat diet fed rats. Supplementation with ginger extract, reduced final body weight and epididymal adipose tissue mass without affecting energy intake. Ginger extract increased mitochondrial size and mitochondrial DNA content as well as key genes expression associated to mitochondrial biogenesis, including peroxisome proliferator activated receptor gamma coactivated-1α, nuclear respiratory factor-1 and transcription factor-α in skeletal muscle. Ginger extract also elevated serum high density lipoprotein-cholesterol along with upregulating ATP binding cassette transporter-α1, apolipoprotein-α1 and lecithin cholesterol acyltransferas mRNA in liver (Oh, *et al*., 2017). Administration of gingerol shows significant reduction in body weight gain, glucose and insulin levels, and insulin resistance, which affect the activity, expressions of lipid marker enzymes such as fatty acid synthase, acetyl Co-A carboxylase, carnitine palmitoyl transferase-1, hydroxymethylglutaryl Co-A reductase, lecithin choline acyl transferase and lipoprotein lipase and inflammatory markers in high fat diet fed rat which confirms that gingerol prevents high fat diet induced hyperlipidemia by modulating the expression of enzymes important to cholesterol metabolism (Naidu, *et al*., 2015). 6-gingerol shows the effect on adenosine monophosphate activated protein kinase nuclear factor-κβ pathway in high fat diet rats. 6-gingerol substantially enhanced phosphorylated adenosine monophosphate activated protein kinase-α1 and reduced the P65 via upregulation of sirtuin-6 and down regulation of resistin, and diminished the inflammatory molecules P65, free fatty acids and tumor necrosis factor-α (Hashem, *et al*., 2017). Ginger has a potent and unique

pharmacological function in 3T3-L1 adipocytes via different mechanisms. Pretreatment with 6-shogaol and 6-gingerol significantly inhibited the tumor necrosis factor-α mediated downregulation of the adiponectin expression in 3T3-L1 adipocytes. 6-shogoal functions as a peroxisome proliferator activated receptors-c agonist with its inhibitory mechanism due to the peroxisome proliferator activated receptors-c transactivation, and 6-gingerol is an effective inhibitor of tumor necrosis factor-α induced c-Jun-NH2-terminal kinase signaling activation (Isa *et al*., 2008).

13. Anti-inflammatory activity

Ginger hexan extract display the inhibitory effect on the production of inflammatory mediators such as nitric oxide, prostaglandin-E2, and proinflammatory cytokines in lipopolysaccharide stimulated BV-2 cells, a mouse microglial cell line. Ginger extract significantly inhibited the excessive production of nitric oxide, prostaglandin-E2, tumor necrosis factor-a, and interleukin-1b in lipopolysaccharide stimulated BV-2 cells. In addition, ginger extract reduce the mRNA expressions and protein levels of inducible nitric oxide synthase, cyclooxygenase-2, and proinflammatory cytokines. The molecular mechanisms that underlie ginger extract mediated reduction are related to the inhibition of the phosphorylation of three mitogen activated protein kinases, extracellular signal regulated kinases 1 and 2, p38 mitogen activated protein kinases, and c-Jun N-terminal kinase, and the activation of nuclear factor-κβ. Results indicate that ginger exhibits anti-inflammatory properties by suppressing the transcription of inflammatory mediator genes through the mitogen activated protein kinases and nuclear factor-κβ signaling pathways. The anti-inflammatory properties of ginger may make it useful as a therapeutic candidate for the treatment of human neurodegenerative diseases (Moussa, *et al*., 2012). 6-shogaol showed its anti-inflammatory effects by inhibiting the production of prostaglandin-E2 and proinflammatory cytokines, such as interleukin-1b and tumor necrosis factor-α, and by downregulating cyclooxygenase-2, p38 mitogen activated protein kinase, and nuclear factor-κβ expression (Ha, *et al*., 2012). Methanolic extract of ginger roots for cyclooxygenase-2 ligands, and 10-gingerol, 12-gingerol, 8-shogaol, 10-shogaol, 6-gingerdione, 8-gingerdione, 10-gingerdione, 6-dehydro-10-gingerol, 6-paradol, and 8-paradol bound to the enzyme active site. Purified 10-gingerol, 8-shogaol and 10-shogaol inhibited cyclooxygenase-2. Therefore, 10-gingerol, 8-shogaol and 10-shogaol inhibit cyclooxygenase-2 but not cyclooxygenase-1, which can explain the anti-inflammatory properties of ginger (Breemen, *et al*., 2011). Ginger ingredients, 8-paradol and 8-shogaol, as well as two synthetic analogues, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl) decane and 5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) dodecane, showed strong inhibitory effects on cyclooxygenase-2 enzyme activity (Tjendraputra, *et al*., 2001). 6-dehydroshogaol, 6-shogaol and 1-dehydro 6-gingerdione potent inhibitors of nitric oxide synthesis inactivated macrophages and shows anti-inflammatory effects in lipopolysaccharide stimulated mouse macrophage cell. 1-dehydro-10-gingerdione, one of pungent isolates from ginger, suppress the lipopolysaccharide induced gene expression of inflammatory cytokines. 1-dehydro-10-gingerdione inhibited lipopolysaccharide binding to myeloid differentiation protein-2 with higher affinity than gingerol and shogaol from dietary ginger. 1-dehydro-10-gingerdione also down regulate the toll-like receptor-4 mediated expression of nuclear factor-κβ or activating protein-1 target genes such as tumor necrosis factor-α and interleukin-1b, as well as those of interferon regulatory factor-3 target interferon-β gene and interferon-c inducible protein-10 in lipopolysaccharide activated macrophages. So that myeloid differentiation protein-2 is a molecular target in the anti-inflammatory action of 1-dehydro-10-gingerdione (Park, *et al*., 2012). After three months of supplementation, ginger decreases serum concentration of nitric oxide and highly sensitive C-reactive protein. Ginger powder supplementation can reduce inflammatory markers in patients with knee osteoarthritis (Naderi, *et al*., 2015). Ginger essential oils shows the anti-inflammatory effect in female Lewis rats with streptococcal cell wall induced arthritis. Ginger oil prevented chronic joint inflammation in sites of streptococcal cell wall deposition in liver. Pharmacological dose of 17β estradiol elicited the same pattern of anti-inflammatory activity, suggesting that ginger oil could be acting as a phytoestrogen (Funk *et al*., 2016). *Zingiber officinale* extract showed significant anti-inflammatory activity. The anti-inflammatory activity may be due to the presence of sequiterpene, gingerol, oleoresin and flavanoids in extract. The result from this study showed the rhizome extract of ginger exhibits anti-inflammatory. The significant anti-inflammatory effect of ginger extract was compared to that of ibuprofen, which could be related to its histamine, serotonin, kinin and prostaglandin inhibitory activities (Chyad *et al*., 2016).

14. Immunomodulator activity

It is concluded that dietary intake of ginger increase the non specific host defenses against opportunistic infections. Polar fractions of ginger rhizomes boost the immune system by altering the cytokine milieu of the immunosuppressed macrophages. Carbon tetrachloride intoxication was found to affect the functional status of splenic macrophages. Carbon tetrachloride intoxicated mice also exhibit lower levels of cytokines tumor necrosis factor-α and interferon-c. Oral administration of polar fractions of ginger rhizomes reduces the affects of carbon tetrachloride (Chakraborty and Sengupta, 2012). Ginger extract is an effective dietary source that could potentiate the immune function of piglets by enhancing the antioxidant capacity and the level of

immunoglobulin in the sow colostrum. Total levels of antioxidant, phenolic compounds and Immunoglobulin-G concentrations were significantly increased in the plasma of the sows and piglets by ginger supplementation. Dietary ginger also increased the levels of total protein and most of amino acids in the sow colostrums (Lee, *et al*., 2013).

15. Anti-oxidant activity

The antioxidant effect of fresh, dried, stir-frying and carbonized gingers were evaluated by three assays [2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azinobis (3-ethyl benzthiazoline sulfonic acid) diammonium salt (ABTS) and ferric reducing antioxidant power (FRAP)]. Results revealed that antioxidant activity of dried ginger was the highest, because of its phenolic contents is higher than that of fresh, stir-frying and carbonized ginger (Li, *et al*., 2016). Supplementation of ginger powder increased the serum and egg yolk antioxidant enzymatic activities of laying hens. Dietary supplementation of ginger powder improved laying performance and serum and egg yolk antioxidant status and enhanced dietary oxidation stability in a dose dependent manner (Zhao *et al*., 2011). Study compares the protective properties of two varieties of ginger [red ginger (*Zingiber officinale* Rubra) and white ginger (*Zingiber officinale* Roscoe)] on Fe^{+2} induced lipid peroxidation in rat brain in-vitro. Aqueous extract from both varieties of ginger caused a significant decrease in the malondialdehyde contents of the brain in a dose dependent manner. Aqueous extract of red ginger had a significantly higher inhibitory effect on Fe^{+2} induced lipid peroxidation in the rat brain homogenates than that of white ginger. This higher inhibitory effect of red ginger could be attributed to its significantly higher phytochemical content, Fe^{+2} chelating ability, OH• scavenging ability and reducing power. Ginger (red and white) may protect the brain through their antioxidant activity, Fe^{+2} chelating and OH• scavenging ability (Oboh *et al*., 2012). The aqueous extract of ginger has detoxifying and antioxidant effects. Ginger significantly increase the total antioxidant capacity and glutathione peroxidase activity and decrease in the nitric oxide and malondialdehyde level in liver and brain in alcohol abuse mice. Ginger also decease the liver function enzymes such as L-c-glutamyl transpeptidase and butyrylcholinesterase activities (Shati and Elsaid, 2009). Ginger has protective effects on oxidative stress, DNA damage and bone marrow genotoxicity induced by streptozotocin in diabetic rats. Ginger powder exerted a protective effect against streptozotocin induced diabetes by modulating antioxidant enzymes and glutathione and down regulating lipid and protein oxidation and inhibition in genotoxicity (Kota *et al*., 2012). The CO_2 extract from ginger has high polyphenol content. It manifested a very good scavenging of DPPH and reduced its reducing capacity. The extract can be used as an antioxidant at an earlier stage of fat oxidation. The ginger extract showed an antioxidant activity comparable with that of butylated hydroxyl toluene in inhibiting the lipid peroxidation. The ginger extract also showed an inhibiting effect with regard to the hydroxyl radicals, better than that of quercetin. The antioxidant activity in a linoleic acid/water emulsion system determined by means of thiobarbituric acid reactive substances was highest at 37^{o}C when the formation of conjugated dienes was inhibited. At 80^{o}C the antioxidant activity at the highest concentration of a ginger extract was less efficient (Stoilova *et al*., 2007). Study shows antioxidant effects of ginger against lead acetate induced hematotoxicity. Ginger significantly decreases sulfhemoglobin percent, methemoglobin percent, carboxyhemoglobin percent, superoxide dismutase activity, malondialdehyde concentration, while it significantly increased oxyhemoglobin percent. Also ginger treatment significantly increased glutathione peroxidase activity of lead exposed rats (Attia *et al*., 2013).

16. Anti-coagulant activity

Anti-platelet activity of the ginger compounds was determined in vitro by the Chrono Log whole blood platelet aggregometer. Cyclooxygenase-1 inhibitory effect of 8-paradol and analogues was carried out using a cyclooxygenase-1 inhibitor assay kit. 8-gingerol, 8-shogaol, 8-paradol and gingerol analogues exhibited anti platelet activities. The cyclooxygenase-1 inhibitory activity of 8-paradol was more potent than the gingerol analogues. The findings show that gingerol constituent and their derivatives are more potent anti-platelet agents than aspirin under the conditions described in this study. 8-Paradol, a natural constituent of ginger, was found to be the potent cyclooxygenase-1 inhibitor and anti platelet aggregation agent. The mechanism underlying acetic acid induced platelet aggregation inhibition may be related to attenuation of cyclooxygenase-1/thromboxane synthase enzymatic activity (Tjendraputra, *et al*., 2003). Anticoagulant effect of ginger aqueous extract in different volumes was examined in-vitro in blood samples of normal individuals through measuring of prothrombin time. Ginger aqueous extract in different concentrations inhibited clot formation and increased prothrombin time. Ginger can be used as a supplementary anticoagulant agent to improve or prevent cardiovascular disorders (Taj *et al*., 2016).

17. Anti-thrombotic activity

Zingerone has anti thrombotic effect in isoproterenol induced myocardial infarcted rats. Rats were pretreated with zingerone and were then induced myocardial infarction with isoproterenol. Isoproterenol induced myocardial infarcted rats showed significant increase in the levels/activities of cardiac troponin-I, highly sensitive C-reactive protein, lysosomal hydrolases in the serum and concentration of heart lysosomal lipid peroxidation products. Reverse transcriptase polymerase chain reaction study revealed over expression of myocardial tumor necrosis factor-α,

interleukin-1β and interleukin-6 genes in the myocardial infarcted rats. Histopathology of heart and coronary artery revealed marked necrosis, inflammation and coronary thrombosis. Zingerone pretreatment significantly decreased serum cardiac troponin-I, highly sensitive C-reactive protein, lysosomal hydrolases and heart lysosomal lipid peroxidation and down regulated myocardial tumor necrosis factor-α, interleukin-1β and interleukin-6 genes and prevented coronary thrombosis in isoproterenol induced myocardial infarcted rats (Hemalatha and Prince, 2016).

18. Anthelmintic activity

6-gingerol, 10-shogaol, 10-gingerol, 6-shogaol and hexahydrocurcumin, a ingredients isolate from the roots of ginger display the anthelmentic activity for the parasite *Hymenolepis nana* and *Angiostrongylus cantonensis* in mice. The cetocidal and larvicidal activity to stop spontaneous parasite movement of ginger ingredients at different concentrations was reached in a time and dose dependent manner. Ginger at 1gm/kg exhibited cetocidal activity in-vivo of significantly reduced worms number and cytokines production by in-vitro concanavalin-A stimulated spleen cells showed that interferomn-gamma and interleukin-2 were significantly increase by ginger extract. interleukin-4, 5, 6, 10 and 13 were significantly decreases and murine-KC and interleukin-12 were not changes (Lin, *et al*., 2014). The crude powder of ginger showed moderate anthelmintic activity in sheep. The dose of 1.0 gm/kg showed a maximum reduction of eggs per gram while the higher dose showed a time dependent anthelmintic effect and significantly reduced the eggs per. The alcoholic extract of ginger has been studied in human against a specific helminth infestation (*Ascaris lumbricoides*) and found active (Iqbal, *et al*., 2006). Study evaluates the anthelminitic activity of ginger on the cestode *Raillietina cesticillus*. Regression of worms increased gradually in all concentrations. Also praziquantel showed the highest regression. The extract efficacy was exhibit as concentration time dependent mainly at higher concentrations (El-Bahy and Bazh, 2015).

19. Anti-bacterial activity

Antibacterial activity assays of ginger extracts has been investigated against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumoniae, Shigella sonnei, Staphylococcus epidermidis* and *Salmonella typhi* using the disc diffusion method. Three types of extracts of ginger including aqueous extract, methanol extract and ethanol extract had been evaluate separately. Methanol and ethanol extracts are most susceptible than aqueous extract (Gull, *et al*., 2012). Phenolic components of ginger viz. 6-gingerol, 6-shogaol and zingerone showed quorum sensing inhibitory activity against *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. The inhibitory activity of all the compounds was studied by zone of inhibition, pyocyanin, and violacein assay. All the compounds displayed good inhibition at 500 ppm. 6-Azashogaol, a new derivative of 6-shogaol, showed good quorum sensing inhibitory activity against *P. aeruginosa*. An isoxazoline derivative of 6-gingerol was prepared and it exhibited good quorum sensing inhibitory activity (Vijendra, *et al*., 2014). The ditch plate method was used to test effectiveness of ginger powder extracts against *Streptococcus* mutans in-vitro. There was significant difference in mean diameter of zone of inhibition ginger extract at different concentrations (Sharma, *et al*., 2014). The study revealed that ginger extract of both the plant and root have the highest antibacterial activity against *Staphylococcus aureus* and *Streptococcus pyogenes* while the three antibiotics used (chloramphenicol, ampicillin and tetracycline) were also active but at less extent compared to ginger extract (Sebiomo, *et al*., 2011). The antimutagenic potential of zerumbal and zerumbenone was tested against *Salmonella typhimurium* tester strains (TA98 and TA1538) by Ames test. They showed significantly higher antimutagenic activity against TA98 than zerumbone. At 156 µM concentration, zerumbone had weak activity but its derivatives showed strong activity and the same trend was also observed at higher concentrations. Zerumbenone showed significantly higher activity than zerumbal at 156 µM concentration and the effect was reversed at higher concentrations, where zerumbal showed higher antimutagenic activity. At 2500 µM concentration all the compounds showed 100% inhibition of mutagenesis. Ethanol extracts from the rhizome of ginger were reported to reduce the number of organism in different *Salmonella* tester strains (Kumar, *et al*., 2016). Natural spices of ginger possess effective anti-bacterial activity against multi drug resistant pathogens and can be used for prevention of drug resistant microbial diseases. Anti-bacterial potentials of the extracts of ginger rhizome were tested against five gram negative and two gram positive multi drug resistant bacteria isolates. All the bacterial isolates were susceptible to crude extracts. Except *Enterobacter* sp. and *Klebsiella* sp., all other isolates were susceptible when subjected to ethanolic extracts of ginger (Karuppiah and Rajaram, 2012). Study evaluate the antimicrobial effect of soybean oil extract of dried ginger powder, using agar diffusion assay, against isolates of food borne pathogens including *Escherichia coli, Pseudomonas aruginosa, Staphylococcus aureus, Vibrio cholerae, Klebsiella* sp. and *Salmonella* sp. Results showed the potent antimicrobial activity of the ginger extract against the all tested bacterial pathogens. Soybean oil extract of ginger showed highest zone of inhibition against Salmonella sp. and lowest zone of inhibition against *Escherichia coli*. Ginger extract also showed lower zone of inhibition against *Staphylococcus aureus* compared to the Gram-negative bacteria. Soybean oil extract of ginger at boiling temperature has potential antimicrobial activity and could be used in food preparation to get the synergistic effect of soybean and ginger (Islam *et al*., 2014).

20. Anti-fungal activity

The antifungal activity of ginger essential oil was examined against *Fusarium verticillioides*. The effects of ginger oil on fumonisin and ergosterol production were evaluated at concentrations of 500-5000 µg/mL in mycelial disc of *F. verticillioides*. Ginger oil reduced ergosterol biosynthesis and production of fumonisin B1 and fumonisin B2. Thus, the inhibition of fungal biomass and fumonisin production was dependent on the concentration of ginger oil. These results suggest that ginger oil was able to control the growth of *F. verticillioides* and subsequent fumonisin production (Yamamoto-Ribeiro, *et al*., 2013). The in-vitro and in-vivo experiments were conducted to evaluate antifungal activity of crude extract obtained from ginger rhizomes against three isolates of *Sclerotinia sclerotiorum*, the causal agent of storage carrot root. Furthermore, all crude extracts were able to reduce carpogenic germination of sclerotia. At volatile phase, ethanol extracts of ginger reduced myceliogenic germination of sclerotia in three isolates. However, all plant extracts decreased the myceliogenic germination of sclerotia at contact phase. The results of in-vivo tests showed that all plant extracts are able to decrease disease severity of carrot root at the concentration (Ojaghian, *et al*., 2014). Research showed the potent antimicrobial activity of the ginger extract against the *Fusarium oxysporum* sp., using paper disc diffusion assay, by using chloroform, ethanol, acetone and petroleum ether as solvents. Chloroform extract of ginger showed highest zone of inhibition against tested pathogen. Whereas, other solvents showed, moderate to minimum antifungal activity (Rawal and Adhikari, 2016).

21. Anti-parasitic activity

Ginger also has a anti-parasitic activity against several parasites and can be used for prevention of drug resistant parasitic diseases. Ginger was found to have a significant antihelmintic activity against *Schistosoma mansoni, Toxocara canis, Dirofilaria immitis, Angiostrongylus cantonensis, Aniskis simplex, Hymenolepis nana* and hydatid cysts either in-vitro or in-vivo. Ginger has an anti-protozoal effect against *Toxoplasma gondii, Giardia lamblia, Trypanosoma brucei brucei* and *Blastocystis species*. Additionally, ginger was found to have insecticidal, molluscicidal and anti-leech effects (El-Sayed and El-Saka, 2015). Ginger has antiparasitic effect against *Toxoplasma gondii* (*T. gondii*) in-vitro and in-vivo. After *T. gondii* invasion, C6 cells induced the activation of caspase-3, bax, p53 and p21 related to programmed cell death, and ginger extract effectively suppressed the expression of caspase-3, bax, p53 and p21 causing cell death of the infected host cells. These results revealed that ginger has antiparasitic properties which inhibit inflammatory cytokine secretion in vivo (Choi *et al*., 2013). Ginger has activity against the monogenean parasite *Gyrodactylus turnbulli* in the guppy. Ethanolic extract of ginger is more effective than aqueous extract. The higher concentration of extract is effective as praziquantel. These results suggest that immersion in ginger extract offers an effective, alternative treatment against monogenean infection in fish (Levy, *et al*., 2015). Ginger has scolicidal effect against *Echinococcus protoscoleces* which collected aseptically from sheep livers containing hydatid cysts. Ginger extract showed the strongest scolicidal effect after twenty minutes at a concentration of 30 mg/ml and ten minutes at 50 mg/ml (Almalki *et al*., 2016). Ginger has an important anti-hydatic effect against *protoscoleces* and cyst wall in-vitro. This effect is amplified in the presence of interferon-gamma. Ginger may protect against host's cell death by reducing the high levels of nitric oxide. Ginger may act through the 6-gingerol. Data suggest the promising use of ginger in the treatment of *Echinococcus granulosus* infection (Amri *et al*., 2016). Study showed the anti-parasitic effect of ginger on *Limnatis nilotica* leech population. After treating the leeches with ginger and the positive controls; chloroform, formalin and savlon, the mean death time of *L. nilotica* was measured by disinfectant assay. The results offer an opportunity for using ginger plant as antiparasitic and disinfectant (Forouzan *et al*., 2012).

22. Anti-ulcer activity

Ginger volatile oil reduced colon weight/length ratio and the effects were similar to the prednisolone. Higher oral doses of volatile oil reduced ulcer severity, ulcer area and ulcer index. Determination of microscopic scores display that the volatile oil was effective to decrease inflammation severity and inflammation extent (Rashidian, *et al*., 2014). Study showed the role of serotonin and nuclear factor-kappa beta in the ameliorative effect of ginger in colitis. Administration of ginger ameliorated the effect of acetic acid induced colitis. These effects were reverse by down regulation of nuclear factor-kappa beta and reduction of colonic tumor necrosis factor-α, interleukin-10, total peroxidase and serum serotonin levels (Abd-Allah, *et al*., 2015). Ginger and its component zingerone has therapeutic effects against 2,4,6-trinitrobenzene sulphonic acid (TNBS) induced colitis in mice. Zingerone reduce TNBS induced colonic injury in a dose dependent manner. Zingerone significantly regulated cytokine related pathways. Nuclear factor- kappa beta and interleukin-1β were key molecules involved in the expression of ginger and zingerone affected genes. In-vitro imaging and immuno histochemical staining also verified that ginger and zingerone suppressed TNBS induced nuclear factor-kappa beta activation and interleukin-1β protein level in the colon (Hsiang *et al*., 2013). Study showed that the effect of ginger derived nanoparticles on colon targeting following oral administration. These nanoparticles contained high levels of lipids, a few proteins, ~125 micro RNAs, and large amounts of ginger bioactive constituents (6-gingerol and 6-shogaol). Nanoparticles were mainly taken up by intestinal epithelial cells and

macrophages, and were nontoxic. Nanoparticles reduced acute colitis, increase intestinal repair, and prevented chronic colitis and colitis related cancer. Oral administration of nanoparticles increased the survival and proliferation of intestinal epithelial cells and reduced the pro-inflammatory cytokines and increased the anti-inflammatory cytokines in colitis models, suggesting that nanoparticles has the potential to reduce damaging factors while promoting the healing effect (Zhang *et al*., 2016). Results showed that 6-gingirol exerts protective effects against ischemia reperfusion induced intestinal mucosa injury by inhibiting the formation of reactive oxygen species and p38 mitogen activated protein kinase activation. 6-gingirol significantly reduced malondehyde level and increased the levels of super oxide dismutase, glutathion, and glutathione peroxidase in ischemia reperfusion injured intestinal tissues. 6-gingirol significantly decreased the production of proinflammatory cytokines including tumor necrosis factor-α , interleukin-1β, and interleukin-6, and inhibited the expression of inflammatory mediators indicible nitric oxide synthase/nitric oxide in ischemia reperfusion injured intestinal tissues. The impaired intestinal barrier function was restored by using 6-gingirol in ischemia reperfusion injured rats and in both Caco-2 and intestinal epithelial cells-6 cells characterized by inhibiting p38 mitogen activated protein kinase phosphorylation, nuclear translocation of nuclear factor-κβ, and expression of myosin light chain kinase protein. 6-gingirol also reduced the generation of reactive oxygen species in both Caco-2 and intestinal epithelial cells-6 cells. In vitro transfection of p38 mitogen activated protein kinase siRNA mitigated the impact of 6-gingirol on nuclear factor-κβ and myosin light chain kinase expression (Li, *et al*., 2017).

23. Anti-emetic activity

Ginger essence inhalation has positive effect on post nephrectomy nausea and vomiting (PONV). Accordingly, ginger essence can be used as an effective antiemetic agent for managing PONV. Study limitations were that changes in respiratory patterns and olfactory system secondary to anesthesia might have affected the absorption of ginger aroma (Hajbaghery and Hosseini, 2015). Gingerol and shogaols have demonstrated in-vitro to extract 5-HT3 receptor antagonism which could benefit chemotherapy induced nausea and vomiting (Yamamoto-Ribeiro, *et al*., 2013).

24. Hepatoprotective activity

Histopathological study revealed that ginger extract cure liver lesions induced by atorvastatin. Administration of atorvastatin had major hepatotoxic effect and seems to cause liver injury. Ginger increases hepatic superoxide dismutase and catalase, lower serum cholesterol, and decrease aminotransferases, hepatic malondialdehyde and nitric oxide. Combination regimens containing ginger extract and low dose of statins could be advantageous in treating hypercholesterolemic patients who are susceptible to liver function abnormalities (Heeba and Abd-Elghany, 2010). Histological examination of the pancreas demonstrates restoration of the structural derangements caused by streptozotocin in the ginger polyphenol extracts treated diabetic rats. Therefore, polyphenols from ginger could reduce diabetes induced pancreatic derangements in rats (Kazeem *et al*., 2015). Ginger also has a protective effect against bromobenzene induced hepatotoxicity in rats. Oral treatment of bromobenzene was found to elicit a significant decrease in the activities of the antioxidant enzymes; superoxide dismutase, glutathione peroxidase and the glutathion level, while the activities of glutathione reductase and drug metabolizing enzymes; glutathione S-transferase and cytochrome-P_{450} were enhanced. Bromobenzene treatment also enhanced production of nitric oxide products and activation of cyclooxygenase-2 and caspase-3. Pretreatment with different doses of ginger extract prior to bromobenzene treatment reduce its toxic effects (El-Sharaky *et al*., 2009). Carbon tetrachloride treatment elevates the activities of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyltransferase and the serum triglycerides and cholesterol concentration. It also increased RBCs counts and hemoglobin concentration, total or differential leucocytes counts. Methanol extract of ginger significantly ameliorate the carbon tetrachloride induced alterations in the biochemical and cellular constituents of blood (Attia *et al*., 2013). The hepatoprotective activity of extract of ginger was examined in-vitro and in-vivo. Extract slowed down liver fibrosis progression and prevents the generation of free radical induced by thioacetamide, which provide an insight into the mechanism of its biological action (Bardi *et al*., 2013). Study revealed the hepatoprotective effect of ginger aqueous infusion against paracetamol induced hepatotoxicity in rats. Examination of liver tissue for rat treated with paracetamol and extract and also with silymarin revealed normal hepatic architecture. In-vitro bioassay on primary culture of rat hepatocytes monolayer revealed that concentration at which extracts exhibit a hepatoprotective activity was of 15µg/ml (Yassin *et al*., 2010).

25. Renoprotective activity

Ginger has protective effect against ethanol induced damage and fibrosis in rats kidney. Ethanol induces kidney abnormality by oxidative DNA damage and oxidative stress. After a six weeks period of treatment with ginger extract, the results demonstrate proliferation of glomerular and peritubular and a significant rise in the level of 8-hydroxy 2-deoxyguanasin, cystatin-C plasma urea and creatinine. Ethanol treated rats showed a significant decrease in the urine creatinine and creatinine clearance. In addition, significant amelioration of changes in the structure of kidney, along with restoration of the biochemical alterations was found in the treated group (Shirpoor *et*

al., 2016). Ginger could serve as a preventive agent against gentamicin tubular toxicity. This study showed that, rats treated with gentamicin for seven days and then ginger for period of ten days demonstrated high intensity of nephrotoxicity, which was not significantly different form treated rats with gentamicin alone, it means that ginger possess a preventive, but not a curative property against gentamicin tubular toxicity (Nasri *et al*., 2013). Treatment with ginger extract had significant effect on plasma electrolyte profiles. Low plasma sodium level and increased plasma potassium levels were observed in ginger pretreated rats. The plasma creatinine, urea and uric acid levels were significantly reduced in ginger treated group compared to alcoholic control rats and ethanol withdrawal rats. It is concluded that the consumption of ginger produced a significant anti nephrotoxic effect in ethanol withdrawal rats (Maralla, 2013).

26. Anti-teratogenic activity

Ginger has antiteratogenic effect against the toxicity induced by fenitrothion and lead in female albino rats. Fenitrothion and lead increase the level of malondialdehyde, alanin amintransferase and aspartate aminotransferase and reduce the glutathione, activity of glutathione S-transferase, total plasma protein and albumin, also cause embryotoxicity and fetotoxicity. Supplementation with ginger in diet reduce the alteration in malondialdehyde, glutathione, glutathione S-transferase, alanin amintransferase and aspartate aminotransferase level, also decreased number of died fetus, growth retardation and fetal length, while, it increased fetal weight. The percentage of skeletal abnormalities and visceral irregularities were observed in all feti obtained from treated groups with different percentages. Supplementation with ginger reduces the developmental toxicity of fenitrothion and lead (Farag *et al*., 2010). Pregnant rats were administered with dry powder extracts of ginger orally. The daily food and water intake was significantly reduced during the exposure period. There was a significant embryonic loss in ginger fed rats. The results suggest that maternal administration of ginger during mid pregnancy results in reduced maternal weight gain and increased embryonic loss without affecting the postnatal growth and physical maturation of the surviving offspring (Dissubandara and Chandrasekara, 2007).

27. Proteoytic activity

Ginger proteases extracted from fresh ginger rhizome by using phosphate buffer exhibiting optimal proteolytic activity from 40 to 60°C and maximum milk clotting activity at 70°C. Ginger proteases capable of hydrolyzing isolated αS1-, β-, and κ-casein, of which αS1-casein was most susceptible to the enzyme; κ-casein was hydrolyzed with a higher specificity than αS1- and β-casein. Gel electrophoresis and mass spectra indicated that Ala90-Glu91 and His102-Leu103 of κ-casein were the preferred target bonds of ginger proteases. Its protease activity was strongly inhibited by iodoacetamide, p-chloromercuribenzoic acid, mercury and copper. The milk clotting activity, affinity, and specificity toward κ-casein showed that ginger protease is promising rennet like protease that could be used in manufacturing cheese and oriental-style dairy foods (Hashim *et al*., 2011; Huang, *et al*., 2011).

28. Other Activities

Study shows the effects of 6-gingerol on the biochemical parameters and ovarian histological improvements in estradiol valerate induced polycystic ovary syndrome rats. The administration of estradiol valerate led to increase body and ovarian weights, abnormality in serum sex steroid profile, decrease in antioxidant activity and increase in cyclooxygenase-2 gene expression. 6-gingerol treatments attenuated these alterations. 6-gingerol showed beneficial effects in the estradiol valerate induced Polycystic ovary syndrome rats via decreased expression of cyclooxygenase-2, restored biochemical parameters to normal and decreased of cysts in the ovaries (Pournaderi, *et al*., 2017). Gingerols and shogaols are the primary non-volatile actives within ginger. These compounds have demonstrated in-vitro to exert 5-HT3 receptor antagonism which could beneficial in chemotherapy induced nausea and vomiting. Research indicates they may bind to a currently unidentified allosteric binding site. Using in-silico techniques, such as molecular docking and GRID analysis, researcher characterized the recently available murine 5-HT3 receptor by identifying sites of strong interaction with particular functional groups at both the serotonin site and a proposed allosteric binding site situated at the interface between the transmembrane region and the extracellular domain. Results suggest that the ginger compounds and their structural analogues possess a high binding affinity to both sites and could act both competitively or non-competitively as has been shown for palonosetron and other modulators of Cys-loop receptors (Lohning, *et al*., 2016).

CONCLUSION

Ginger is an ancient herb used widely in history for its many natural medicinal properties. The health-promoting perspectives of ginger are well known. It can treat a wide range of diseases. Its functional ingredients like gingerols, shogaol, and paradols are the valuable ingredients which can prevent various cancers, cardiovascular disorders, diabetes mellitus, gastrointestinal disorders.

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