

Therapeutic Role of Ginger

Irum Naureen¹, Aisha Saleem^{2*}, Obaida Zahid², Gulshan Umar Din², Anam Sadiq², Khadija Tul-Kubra², Azka Rauf², Tahmeena Naqeeb²

¹Assistant Professor, School of Zoology, Minhaj University Lahore, Pakistan

²M. Phil Researcher, School of Zoology, Minhaj University Lahore, Pakistan

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*Corresponding author: Aisha Saleem

M. Phil Researcher, School of Zoology, Minhaj University Lahore, Pakistan

Abstract

Different plants are used by human to treat different diseases. Ginger is an herb that belongs to Zingiberaceae family. Due to its high chemistry with above 60 compounds, it is used to treat many diseases and is beneficial for health. It is used as antioxidant, antiulcer, anti-cancer, anti-diabetic, anti-inflammatory and used for nausea and vomiting and also improves immune system. Some compounds of ginger are shogaols, gingerols and zingerone. The aim of article is to show the study of different scientists about the effect of ginger in different disease. Gingerol, shogaol suppress the production of pro inflammatory cytokines such as IL-1, TNF- α , and IL-8. Ginger is productive in glycemic control for people with type 2 diabetes. The active ingredients of ginger include gingerols, which exhibit antioxidant activity. Ginger plays an important role in improving the activity of gastrointestinal track. Due to ginger effect, the level of cardiovascular disorders, digestive problems and diabetes mellitus can decrease.

Keywords: Ginger, medicinal plant, antioxidant, anti-inflammatory.

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INTRODUCTION

Humans' reliance on medicinal plants to treat a variety of diseases has been reported since the beginning of time. People used to rely on plants for nourishment because they shielded them from physiological risks [2]. Ginger (*Zingiberofficinale*) is a perennial herb with slender, bright green grass-like leaves and purple-marked yellowish green blooms [1]. Ginger rhizome (*Zingiberofficinale*) of the family Zingiberaceae is widely used as an important cooking spice for many foods and beverages around the world, especially in Southeast Asia, Central Africa, and South Africa, Africa and the United States [4].

In conventional medicines like Chinese medicine, Ayurveda, and Unani-Tibb, It is one of the most frequently used up herbs with many applications [3]. It is mostly used in the form of dried powder and fresh paste. It was used for the cure of many ailments in conventional medicine, for example inflammatory

problems, and proven several pharmacological doings like antiemetic activities, antiulcer effect, anti-inflammatory, antioxidant, anti-platelet, glucose and lipid lowering, cardiovascular effects, anti-microbial activities, digestive problems, respiratory disorders, neuro-protection effects and anti-cancer activities [5, 7].

Several volatile (unstable) oils and pungent phenol compounds present in rhizome, for example shogaols, gingerols and zingerone play a role to the taste and aroma of ginger [8]. Volatiles and non-volatiles compounds are two large types for fresh ginger. In volatiles compounds mono terpenoid and Sesquiterpene hydrocarbons are include that give ginger odour and taste. In non-volatile pungent compounds Shogaols, parasols, Gingerol and zingerone are including [8]. Ginger has extraordinary healthful effects; therefore, numerous pharmacological researches have been conducted in current years.



Fig-1: Ginger [4]

Botanical Classification[11]**Kingdom:** Plantae**Subkingdom:** Tracheobionta – Vascular plants**Super-division:** Spermatophyta**Class:** Monocotyledons**Subclass:** Zingiberidae**Order:** Zingiberales**Family:** Zingiberaceae**Genus:** Zingiber**Species:** Officinale**Phytochemistry of *Zingiberofficinale***

According to the structure and place of origin of rhizomes, the components of ginger are many and also can vary for example dry or fresh. *Zingiberofficinale* consist of numerous elements that are minerals, phytochemicals, carbohydrates, etc. Proximate constituents also present in it for example moisture, proteins, fats, fibre and ash. Ginger also holds significant quantities of vitamins, minerals and some enzymes, like, an effective proteolytic enzyme called zingibain. Moreover, oleoresins and waxes are the elements that can be extracting are its important ingredients or functional elements [11]. The vital oil of *Zingiberofficinale* with the help of gas chromatography

and gas chromatography-mass spectrometry methodologies. The consequences disclosed that it has 2.4% of crucial oil made up of 6.6% carbonyl compounds, 64.4% sesquiterpene, 6.6%, 5.6% alcohols, and 2.4% monoterpene hydrocarbons [12]. The recognized constituents are listed in Table 1.1. They can recognize more than 60 compounds in ginger gathered into two categories, which are volatiles and non-volatiles. Volatiles contain sesquiterpene and monoterpenoid hydrocarbons giving the unique odour and sense of taste of ginger. On the other hand, non-volatile compounds comprise gingerols, shogaols, paradols, and zingerone [9].

Table-1: Phytochemicals of Ginger [11]

Sr.	Category	Components
1	Non-volatile pungent components	Gingerols, shogaols, paradols, zingerone [10]
2	Miscellaneous	Zingibain[10]
3	Sesquiterpenoids	Zerumbone, α -zingiberene, β -sesquiphellandrene, β -bisabolene, (E-E)- α -farnesene, arcurcumene, zingiberol.[10]
4	Monoterpenoids	Geraniol, curcumene β -phellandrene, (+)-camphene, 1,8-cineole, citral, terpineol, borneol, linalool, neral [10]

Therapeutic Effects of *Zingiberofficinale***Anti-Inflammatory Effects**

In ginger gingerol, shogaol and other structurally related substances are usually present. These substances inhibit the production of prostaglandin and leukotriene by suppressing lipoxygenase or prostaglandin synthetic activity. Furthermore these molecules suppress the production of proinflammatory cytokines such as IL-1, TNF- α , and IL-8 [24, 25]. Ginger can inhibit the activity of cyclo-

oxygenase 2(COX 2), an enzyme whose products increase the symptoms of inflammation [26]. Shogaol also involve in down regulation of inflammatory iNOS and COX-2 gene expression [25]. Rhizome hexane fraction extracted from ginger inhibited the excessive production of NO, PGE, TNF-alpha, and IL-1beta. Ginger inhibit allergic reactions that is why it is used in treatment of allergic diseases.[28,29] Ginger extract can reduce activation of NF- κ B that is linked to a variety of inflammatory diseases such as cancer, atherosclerosis, myocardial infarction, diabetes, allergy,

asthma, arthritis, crohn's disease, multiple sclerosis, alzheimer's disease, osteoporosis, psoriasis, septic shock, and AIDS [30, 31].

Antioxidant role of Ginger

Free radicals are the molecules that are produced during food metabolism and energy production in body has natural system for scavenging of these extra free radicals. Increased production of free radicals leads oxidative stress that can damage the DNA [32, 33]. In the imbalance condition antioxidants are usually provided as dietary supplements [34]. Ginger is one of the richest sources of antioxidants. The active ingredients of ginger include gingerols, which exhibit antioxidant activity [35]. Enzymes such as xanthine oxidase are involved in the generation of reactive species. Gingerol molecule of ginger has potent inhibitory effect on enzyme activity [36]. Dietary feeding of ginger significantly attenuate lindane-induced lipid peroxidation that is accompanied by the modulation of OFR-scavenging enzymes as well as reduced glutathione (GSH) and the GSH-dependent enzymes, glutathione peroxidase (Gpx), glutathione reductase (GR) and glutathione S-transferase (GST) [37].

Ginger for nausea and vomiting treatment

Ginger is commonly utilized for relieving nausea and vomiting. It is also an antiemetic. It has carminative effect that helps to break and expel intestinal gas [38, 23]. Ginger is effective in ameliorating nausea and vomiting in pregnancy (NVP). Nausea and vomiting during pregnancy also known as morning sickness affects about 80% of pregnant women [40]. One of the study shows that dose of ginger taken by pregnant women's suffering from mild to moderate nausea and vomiting reduce nausea and vomiting [41]. Ginger is more powerful in relieving mild to moderate

nausea and vomiting in less than 16 weeks of gestational age. [42]. Ginger is expected to enhance antiemetic effects and counteract oxidative damage to tissues by binding to 5-HT₃ receptors and increasing detoxification enzymes [43].

Anti-diabetic effects

In the past few years, the health encouraging power of ginger has been greatly discovered and it is measured to be extraordinary in herbal medications. Diabetes mellitus and its concerns are one of the foremost reasons of mortality in the world. According to an estimate, at the end of the year 2030, this disease will affect approximately 376 million people worldwide [43, 44]. Some examination studies have verified the efficiency of ginger against diabetes and its problems. Ginger composition with a great content of gingerols and shogaols did not make major changes in blood glucose, blood coagulation, blood pressure, and heart rate in rat samples [44].

Though, ginger mainly dropped blood glucose, serum total cholesterol, LDL, VLDL, and triglycerides, and raised HDL in hyperglycemic rats, in models that are diabetic, lacking in the apolipoprotein in diabetic rats [45]. The ethanol extract of ginger condensed body weights and levels of glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, free fatty acids, and phospholipids in high-fat nutrition [46]. They reinforced from this hypoglycaemic potential, too [47]. Furthermore, In Australia, the University of Sydney found ginger was productive in glycemic control for people with type 2 diabetes. It may benefit to control high blood sugar levels. Additional scientific experiment in diabetes patients that ingested three grams of dry ginger for 30 days displays that blood glucose, triglyceride, and total and LDL cholesterol levels notably decreased [15, 45].

Table-2: Result from different author study about anti-cancer effect of ginger

Research	Aim of study	Conclusion/ findings	References
Anti-cancer	Evaluate anti-inflammatory and anti-cancer effects of gingerols	Indicate a crucial role of LTA H in cancer and also support the anticancer efficacy of gingerols	[4,53]
Anti-cancer	Investigate the effect of gingerol on the proliferation and invasion of cells in culture	Anti-oxidative property of gingerol may be involved in its anti-invasive activity of hepatoma cells.	[58]
Anti-cancer	Investigate if zerumbone will produce the anticancer effects on pancreatic carcinoma cell lines	Zerumbone was able to induce apoptosis of pancreatic carcinoma cell lines.	[57]
Anti-cancer	Investigate zerumbone, can enhance the anticancer effects of TRAIL	Zerumbone can potentiate trail-induces apoptosis and resulting in enhancement of the anticancer effects of TRAIL.	[50]
Anti-diabetic effects	Investigate the ex vivo effect ginger extract on the development of atherosclerosis	Ginger extract significantly attenuates the development of atherosclerotic lesions.	[70]
Anti-oxidative stress effects	Evaluate two Zingiber varieties to compare the medicinal potential	Ginger has potential medicinal properties in leaves and young rhizomes.	[71]
Anti-inflammatory effects	Evaluate the effect of ginger extract on the expression of NFκB and TNF-α in liver cancer-induced rats	Ginger extract significantly reduced the elevated expression of NFκB and TNF-α in rats with liver cancer	[72]

Anti-cancer effect

Ginger performs as a chemo-free spice, several investigators concentrated on the ginger and its numerous bioactive compounds that are cancer preventive and potential cancer beneficial usages [55, 56]. Components like 6-gingerol, 6-shogaol, 6-paradol, and zerumbone in ginger reveal anti-inflammatory and anti-tumorigenic actions. The ginger result in averting or beating cancer development has been considered in a selection of cancer types, including lymphoma, hepatoma, colorectal cancer, breast cancer, skin cancer, liver cancer, and bladder cancer [53]. Colorectal cancer is more widespread in vegetarians and ginger could be operational in minimizing the degree of this disease.

The efficacy of ginger against 1, 2 dimethylhydrazine (DMH)-brought colon cancer. They detected that ginger supplementation can stimulate several enzymes such as glutathione peroxidase, glutathione-S-transferase, and glutathione reductase and overwhelm colon's cancerous agents [49]. Zerumbone orally in mouse models and witnessed inhibition in diversity of colonic adenocarcinomas through overpowering of colonic infection in a dose dependent way [54]. Cataracts of caspase proteins trigger by ginger and its useful constituents [50].

Gingerol inhibits TRAIL-induced NF- κ B stimulation by damaging the nuclear translocation of NF- κ B, overwhelms cIAP1 expression, and raises TRAIL-induced caspase-3/7 stimulation [51]. Ginger's useful stems from its ability to cover prostaglandin and leukotriene biosynthesis by hindering the enzyme arachidonate 5-lipoxygenase's biosynthesis [58]. Gingerol usefully was found in the experiment to stop the tumor growth, which was done in vivo in nude mice, an effect that was arbitrated by the hindrance of LTA4H movement. Avoidance of colorectal cancer are the first consequences that identify a direct target of 6-gingerol by inhibiting LTA4H to clarify its anticancer action [53].

Role in immunonutrition

Dietary patterns are main significant factor occupied in the appropriate functionality of the protected method. Among some newer concept in the domain of diet, immunonutrition is connected with the position of sure nutrients in bringing equilibrium in the individual protected organism. Immunonutrition, a lot based on the attitude to have a diet that can get better the immune system, maintain homeostasis, and helps to fight against unknown and mean cells. Many studies have indicated that diet influence the different essential and factors of the immune system [59]. Chronic (or acute) inflammation is a multi-step process mediate by activate inflammatory or protected cells [60].

In antique times the medicinal practitioners alert on herbs and spices for humanizing the body systems [2]. In many cultures carrot and its yield when

extreme boost the resistant system. In totaling, it has many other proclaimed helpful belongings [34]. The anti-inflammatory possible of ginger has been established in a quantity of technical investigations. In this situation, carrot also holds the capacity to restrain combination of IL-1, TNF- α , and IL-8, measured as pro-inflammatory cytokines [24].

Ginger tuber contains powerful compounds able of inhibiting sensitive to reactions and may be useful for the behavior and hindrance of sensitive to diseases [29] Inflammatory diseases, as well as cancer, atherosclerosis, myocardial infarction, diabetes, allergic reaction, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, septic shock, and AIDS [31]. Its inactivation or objective look is vital for the good performance of the immune system. Its physically powerful anti-inflammatory and antioxidant things can be used as medicinal agents [66].

Similarly, intraperitoneal injections of ginger take out decreased the number of eosinophils along with diminished levels of IL-4, IL-5, and eotaxin levels in the lungs [67] However, higher doses of [6]-gingerol (50 mg/kg-100 mg/kg) inhibited foot edema induced by carrageen in [68]. Ginger necessary oil improved the humoral immune answer in immunosuppressed mice [69]. The proposition that ginger and its efficient ingredient are helpful in overcome the toxicity arises due to chemicals via accent of enzymes [68]. In this perspective, unwarranted burning up of alcohol is also a hazard factor causal to many disorders like liver necrosis. The results are of significant importance in treat disorder like asthma, gout, arthritis, etc. However, cohort studies and controlled trails need to be conduct as these would be helpful for dieticians to necessitate the pharmacological application of carrot [64].

Ginger for digestive health

Ginger also has an ability to help in transport of phytochemicals and nutrients in blood stream to cells of body. Crohn's disease, diverticular disease, gastro-esophageal reflux disease (GERD) is gastrointestinal disorders caused due to dietary factors. Pancreatic amylase and lipase activity are enhanced by ginger. Ginger plays an important role in improving the activity of gastrointestinal track [63]. Ulcerative colitis is one gastrointestinal disease characterize with provocative responses. Cancer necrosis factor- α (TNF- α) amplify the seditious reply by activate a flow of unaffected response [62]. Ginger also helps in attractive the development of germs resides in the gastrointestinal territory. In recent times, the outcome is rather final that ginger help in civilizing the strength of gastrointestinal tract.

Effect on cardiovascular

Ginger's antiarrhythmic activity is one of its most significant effects. The studies show the outcome

of ginger on blood lipids in both animals and humans. In animals the results show that ginger significantly decreases plasma cholesterol, but not in patients who are suffering from any heart disease such as coronary artery disease. Ginger is used as antiplatelet treatment, and it stops coronary heart disease. In this approach, ginger has less potent than aspirin, but in contrast, it has lesser side effects than aspirin. The function of aspirin is inhibiting arachidonic acid-induced platelet release and aggregation and COX activity; ginger also works as same as the mechanism of action [18].

Obesity is a chronic metabolic disease that leads to multiple complications, such as diabetes, hypertension, hyperlipidemia, and cardiovascular diseases. One study, ginger supplementation has valuable effects on insulin resistance, lipid profile, and promoting weight loss, which illustrates its significant potential in the treatment of type 2 diabetes. On the feature of anti-diabetic cardiomyopathy, gingerol also showed its protective effect on cardiovascular diseases [34]. Daily dietary intake of ginger is regarded as an eco-friendly option, which can be beneficial for weight loss/ maintenance, enhance glycemic control, lipid profile and vascular health, reduce blood pressure, and

inflammation, and ultimately, all of these can improve cardiovascular health [35].

Cardiovascular disorders (CVD) are a major cause of morbidity and mortality in the world. The changing lifestyles and dietary patterns are major contributory factors in the prevalence and pathogenesis of CVD [48]. Ginger and its functional ingredients play many roles in improving the cardiovascular health of individuals. At a molecular level, it reduces retinoid binding protein (RBP) mRNA expression levels in the liver and visceral fat resulting in improved lipid metabolism [64]. Apart from ginger itself, some of the pure compounds of ginger, gingerol and -shogaol, has been studied for their effects on BP in laboratory animals and both produced a depressant effect [6]. Later reports revealed that the peripheral pressor effect of [6]-shogaol in rats is caused by the release of a peptide like substance from the sympathetic nerve endings [34]. That treatment with an ethanol extract of ginger in isoproterenol-treated rats increased the levels of endogenous myocardial antioxidants decreased the levels of serum marker enzymes (LDH, creatinine kinase, aspartate aminotransferase, and alanine aminotransferase), and increased myocardial lipid peroxides [27].

Benefits of Ginger	References
Helpful in weight loss.	[13]
Helpful in the improvement of breast milk volume	[14]
Effective in knee osteoarthritis patients	[21]
Ability to treat rheumatoid arthritis	[17]
Minimize menstrual blood loss.	[16]
Reduced the frequency of vomiting and nausea during chemotherapy.	[19]
Recover the muscle strength after exercise	[20]
Cardiovascular effect and Anti-diabetic effect.	[18]
Effective to maintain blood glucose level.	[15]
Potential to reduce migraine attacks	[22]
Relieve moderate to mild nausea and vomiting during pregnancy.	[23]

CONCLUSION

Ginger is used as a spice in kitchen. Ginger get more attention due to high photochemistry and used as medicinal purpose. Its unique compounds such as shogaols, gingerols and zingerone reduce health problems. It is used as antioxidant, antiulcer, anti-cancer, anti-diabetic, anti-inflammatory and used to improve cardiovascular disorder and the activity of gastrointestinal track. Different research shows ginger have wide range of good effects on human health.

REFERENCES

- Grant, K. I. (2000). Ginger. *Am J Heath System Pharm* 57, 945 – 947.
- Butt, M. S., & Sultan, M. T. (2009). Green tea: nature's defense against malignancies. *Critical reviews in food science and nutrition*, 49(5), 463-473.
- Rong, X., Peng, G., Suzuki, T., Yang, Q., Yamahara, J., & Li, Y. (2009). A 35-day gavage safety assessment of ginger in rats. *Regulatory Toxicology and Pharmacology*, 54(2), 118-123.
- Sabulal, B., Dan, M., Kurup, R., Pradeep, N. S., Valsamma, R. K., & George, V. (2006). Caryophyllene-rich rhizome oil of *Zingibernimmonii* from South India: Chemical characterization and antimicrobial activity. *Phytochemistry*, 67(22), 2469-2473.
- Jafarzadeh, A., & Nemat, M. (2018). Therapeutic potentials of ginger for treatment of Multiple sclerosis: A review with emphasis on its immunomodulatory, anti-inflammatory and anti-oxidative properties. *Journal of neuroimmunology*, 324, 54-75.
- Ali, B. H., Blunden, G., Tanira, M. O., & Nemmar, A. (2008). Some phytochemical, pharmacological and toxicological properties of ginger

- (Zingiberofficinale Roscoe): a review of recent research. *Food and chemical Toxicology*, 46(2), 409-420.
7. Sharma, P. K., Singh, V., & Ali, M. (2016). Chemical composition and antimicrobial activity of fresh rhizome essential oil of Zingiberofficinale Roscoe. *Pharmacognosy Journal*, 8(3).
 8. Semwal, R. B., Semwal, D. K., Combrinck, S., & Viljoen, A. M. (2015). Gingerols and shogaols: Important nutraceutical principles from ginger. *Phytochemistry*, 117, 554-568.
 9. Jolad, S. D., Lantz, R. C., Solyom, A. M., Chen, G. J., Bates, R. B., & Timmermann, B. N. (2004). Fresh organically grown ginger (Zingiberofficinale): composition and effects on LPS-induced PGE2 production. *Phytochemistry*, 65(13), 1937-1954.
 10. Langner, E., Greifenberg, S., & Gruenwald, J. (1998). Ginger: history and use. *Advances in therapy*, 15(1), 25-44.
 11. Butt, M. S., & Sultan, M. T. (2011). Ginger and its health claims: molecular aspects. *Critical reviews in food science and nutrition*, 51(5), 383-393.
 12. Onyenekwe, P. C., & Hashimoto, S. (1999). The composition of the essential oil of dried Nigerian ginger (Zingiberofficinale Roscoe). *European food research and technology*, 209(6), 407-410.
 13. Attari, V. E., Ostadrahimi, A., Jafarabadi, M. A., Mehralizadeh, S., & Mahluji, S. (2016). Changes of serum adipocytokines and body weight following Zingiberofficinale supplementation in obese women: a RCT. *European Journal of nutrition*, 55(6), 2129-2136.
 14. Paritakul, P., Ruangrongmorakot, K., Laosooksathit, W., Suksamarnwong, M., & Puapornpong, P. (2016). The effect of ginger on breast milk volume in the early postpartum period: A randomized, double-blind controlled trial. *Breastfeeding Medicine*, 11(7), 361-365.
 15. Khandouzi, N., Shidfar, F., Rajab, A., Rahideh, T., Hosseini, P., Taheri, M. M. (2015). The effects of ginger on fasting blood sugar, hemoglobin A1c, apolipoprotein B, apolipoprotein AI and malondialdehyde in type 2 diabetic patients. *Iranian Journal of Pharmaceutical Research: IJPR*, 14(1); 131.
 16. Kashefi, F., Khajehei, M., Alavinia, M., Golmakani, E., & Asili, J. (2015). Effect of Ginger (Zingiberofficinale) on heavy menstrual bleeding: A placebo-controlled, randomized clinical trial. *Phytotherapy research*, 29(1), 114-119.
 17. Aryaeian, N., Shahram, F., Mahmoudi, M., Tavakoli, H., Yousefi, B., Arablou, T., & Karegar, S. J. (2019). The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis. *Gene*, 698, 179-185.
 18. Arzati, M. M., Honarvar, N. M., Saedisomeolia, A., Anvari, S., Effatpanah, M., Arzati, R. M., & Djajali, M. (2017). The effects of ginger on fasting blood sugar, hemoglobinA1c, and lipid profiles in patients with type 2 diabetes. *International journal of endocrinology and metabolism*, 15(4).
 19. Sanaati, F., Najafi, S., Kashaninia, Z., & Sadeghi, M. (2016). Effect of ginger and chamomile on nausea and vomiting caused by chemotherapy in Iranian women with breast cancer. *Asian Pacific Journal of Cancer Prevention*, 17(8), 4125-4129.
 20. Matsumura, M. D., Zavorsky, G. S., & Smoliga, J. M. (2015). The effects of pre-exercise ginger supplementation on muscle damage and delayed onset muscle soreness. *Phytotherapy Research*, 29(6), 887-893.
 21. Mozaffari-Khosravi, H., Naderi, Z., Dehghan, A., Nadjarzadeh, A., & FallahHuseini, H. (2016). Effect of ginger supplementation on proinflammatory cytokines in older patients with osteoarthritis: outcomes of a randomized controlled clinical trial. *Journal of nutrition in gerontology and geriatrics*, 35(3), 209-218.
 22. Martins, L. B., Rodrigues, A. M. D. S., Rodrigues, D. F., Dos Santos, L. C., Teixeira, A. L., & Ferreira, A. V. M. (2019). Double-blind placebo-controlled randomized clinical trial of ginger (ZingiberofficinaleRosc.) addition in migraine acute treatment. *Cephalalgia*, 39(1), 68-76.
 23. Sharifzadeh, F., Kashanian, M., Koochpayehzadeh, J., Rezaian, F., Sheikhsari, N., & Eshraghi, N. (2018). A comparison between the effects of ginger, pyridoxine (vitamin B6) and placebo for the treatment of the first trimester nausea and vomiting of pregnancy (NVP). *The Journal of Maternal-Fetal & Neonatal Medicine*, 31(19), 2509-2514.
 24. Tjendraputra, E., Tran, V. H., Liu-Brennan, D., Roufogalis, B. D., & Duke, C. C. (2001). Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. *Bioorganic chemistry*, 29(3), 156-163.
 25. Verma, S. K., Singh, M., Jain, P., & Bordia, A. (2004). Protective effect of ginger, ZingiberofficinaleRosc on experimental atherosclerosis in rabbits.
 26. Vickers, N. J. (2017). Animal communication: when i'm calling you, will you answer too?. *Current biology*, 27(14), R713-R715.
 27. Ansari, M. N., Bhandari, U., and Pillai, K. K. (2006). EthanolicZingiberofficinale R. extract pretreatment alleviates isoproterenol-induced oxidative myocardial necrosis in rats. *Indian J. Exp. Biol*, 44(11), 892-897.
 28. Jung, H. W., Yoon, C. H., Park, K. M., Han, H. S., & Park, Y. K. (2009). Hexane fraction of ZingiberisRhizomaCrudus extract inhibits the production of nitric oxide and proinflammatory cytokines in LPS-stimulated BV2 microglial cells via the NF-kappaB pathway. *Food and Chemical Toxicology*, 47(6), 1190-1197.
 29. Chen, B. H., Wu, P. Y., Chen, K. M., Fu, T. F., Wang, H. M., & Chen, C. Y. (2009). Antiallergic potential on RBL-2H3 cells of some phenolic

- constituents of *Zingiberofficinale* (ginger). *Journal of natural products*, 72(5), 950-953.
30. Habib, S. H. M., Makpol, S., Hamid, N. A. A., Das, S., Ngah, W. Z. W., & Yusof, Y. A. M. (2008). Ginger extract (*Zingiberofficinale*) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. *Clinics*, 63, 807-813.
 31. Aggarwal, B. B., & Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochemical pharmacology*, 71(10), 1397-1421.
 32. Hussein, M. R., Abu-Dief, E. E., Abd El-Reheem M. H., & Abd-Elrahman, A. (2005). Ultrastructural evaluation of the radioprotective effects of melatonin against X-ray induced skin damage in Albino rats. *Int. J. Exp. Pathol*, 86; 45–55.
 33. Ramaa, C. S., Shirode, A. R., Mundada, A. S., & Kadam, V. J. (2006). Nutraceuticals-an emerging era in the treatment and prevention of cardiovascular diseases. *Current pharmaceutical biotechnology*, 7(1), 15-23.
 34. B'arta, I., Smer'ak, P., Pol'ivkov'a, Z., Sest'akov'a, H., Langov'a, M., Turek, B. and B'artov'a, J. (2006). Current trends and perspectives in nutrition and cancer prevention. *Neoplasma*, 53; 19–25.
 35. Kikusaki, H. and Nakatani, N. (1993). Antioxidant effect of some ginger constituents. *J. Food Sci*, 58; 1407–1410.
 36. Chang, W. S., Chang, Y. H., Lu, F. J., & Chiang, H. C. (1994). Inhibitory effects of phenolics xanthine oxidase. *Anticancer Res*, 14; 501–506.
 37. Ahmed, R. S., Suke, S. G., Seth, V., Chakraborti, A., Tripathi, A. K., and Banerjee, B. D. (2008). Protective effects of dietary ginger (*Zingiberofficinale*Rosc.) on lindane-induced oxidative stress in rats. *Phytother. Res*, 22(7); 902–906.
 38. Viljoen, E., Visser, J., Koen, N., Musekiwa, A. (2014). A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutrition Journal*, 13(1).1-20.
 39. Suekawa, M., Ishige, A., Yuasa, K., Sudo, K., Aburada, M., & Hosoya, E. (1984). Pharmacological studies on ginger. I. Pharmacological actions of pungent constituents, (6)-gingerol and (6)-shogaol. *J. Pharmacobio-Dyn*, 7; 836–848.
 40. Quinla, J. D., & Hill, D. A. (2003). Nausea and vomiting of pregnancy. *American Academy of Family Physicians*, 68(1), 121–128.
 41. Hu, Y., Amoah, A. N., Zhang, H., Fu, R., Qiu, Y., Cao, Y., Sun, Y., Chen, H., Liu, Y., & Lyu, Q. (2020). Effect of ginger in the treatment of nausea and vomiting compared with vitamin B6 and placebo during pregnancy: A meta-analysis. *Journal of Maternal- Fetal and Neonatal Medicine*, 1712714.
 42. Saberi, F., Sadat, Z., Abedzadeh-Kalahroudi, M., & Taebi, M. (2013). Acupressure and ginger to relieve nausea and vomiting in pregnancy: A randomized study. *Iranian Red Crescent Medical Journal*, 15(9), 854–861.
 43. Geiger, J. L. (2005). The essential oil of ginger, *Zingiberofficinale*, and anaesthesia. *International Journal of Aromatherapy*, 15(1), 7–14.
 44. Weidner, M. S., & Sigwart, K. (2000). The safety of a ginger extract in the rat. *Journal of ethnopharmacology*, 73(3), 513-520.
 45. Bhandari, U., & Pillai, K. K. (2005). Effect of ethanolic extract of *Zingiberofficinale* on dyslipidaemia in diabetic rats. *Journal of ethnopharmacology*, 97(2), 227-230.
 46. Nammi, S., Sreemantula, S., & Roufogalis, B. D. (2009). Protective effects of ethanolic extract of *Zingiberofficinale* rhizome on the development of metabolic syndrome in high-fat diet-fed rats. *Basic & clinical pharmacology & toxicology*, 104(5), 366-373.
 47. Heimes, K., Feistel, B., & Verspohl, E. J. (2009). Impact of the 5-HT3 receptor channel system for insulin secretion and interaction of ginger extracts. *European journal of pharmacology*, 624(1-3), 58-65.
 48. Matsuura, E., Hughes, G. R., and Khamashta, M. A. (2008). Oxidation of LDL and its clinical implication. *Autoimmun. Rev*, 7; 558–566.
 49. Manju, V., & Nalini, N. (2005). Chemopreventive efficacy of ginger, a naturally occurring anticarcinogen during the initiation, post-initiation stages of 1, 2 dimethylhydrazine-induced colon cancer. *Clinica Chimica Acta*, 358(1-2), 60-67.
 50. Yodkeeree, S., Sung, B., Limtrakul, P., & Aggarwal, B. B. (2009). Zerumbone enhances TRAIL-induced apoptosis through the induction of death receptors in human colon cancer cells: Evidence for an essential role of reactive oxygen species. *Cancer research*, 69(16), 6581-6589.
 51. Ishiguro, K., Ando, T., Maeda, O., Ohmiya, N., Niwa, Y., Kadomatsu, K., & Goto, H. (2007). Ginger ingredients reduce viability of gastric cancer cells via distinct mechanisms. *Biochemical and biophysical research communications*, 362(1), 218-223.
 52. Mahomoodally, M. F., Aumeeruddy, M. Z., Rengasamy, K. R., Roshan, S., Hammad, S., Pandohee, J., ...& Zengin, G. (2021, February). Ginger and its active compounds in cancer therapy: From folk uses to nano-therapeutic applications. In *Seminars in cancer biology* (Vol. 69, pp. 140-149). Academic Press.
 53. Jeong, C. H., Bode, A. M., Pugliese, A., Cho, Y. Y., Kim, H. G., Shim, J. H., ... & Dong, Z. (2009). [6]-Gingerol suppresses colon cancer growth by targeting leukotriene A4 hydrolase. *Cancer research*, 69(13), 5584-5591.
 54. Kim, M., Miyamoto, S., Yasui, Y., Oyama, T., Murakami, A., & Tanaka, T. (2009). Zerumbone, a

- tropical ginger sesquiterpene, inhibits colon and lung carcinogenesis in mice. *International journal of cancer*, 124(2), 264-271.
55. Ryan, J. L., Heckler, C. E., Roscoe, J. A., Dakhil, S. R., Kirshner, J., Flynn, P. J., ... & Morrow, G. R. (2012). Ginger (*Zingiberofficinale*) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. *Supportive care in cancer*, 20(7), 1479-1489.
 56. Zick, S. M., Ruffin, M. T., Lee, J., Normolle, D. P., Siden, R., Alrawi, S., & Brenner, D. E. (2009). Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. *Supportive care in cancer*, 17(5), 563-572.
 57. Zhang, S., Liu, Q., Liu, Y., Qiao, H., & Liu, Y. (2012). Zerumbone, a Southeast Asian ginger sesquiterpene, induced apoptosis of pancreatic carcinoma cells through p53 signaling pathway. *Evidence-Based Complementary and Alternative Medicine*, 2012.
 58. Yagihashi, S., Miura, Y., & Yagasaki, K. (2008). Inhibitory effect of gingerol on the proliferation and invasion of hepatoma cells in culture. *Cytotechnology*, 57(2), 129-136.
 59. Lin, W. W., & Karin, M. (2007). A cytokine-mediated link between innate immunity, inflammation, and cancer. *J. Clin. Invest*, 117; 1175-1183.
 60. Grip, O., Janciauskiene, S., & Lindgren, S. (2003). Macrophages in inflammatory bowel disease, *Curr. Drug Targets Inflamm. Allergy*.
 61. Matsuda, A., Wang, Z., Takahashi, S., Tokuda, T., Miura, N., & Hasegawa, J. (2009). Upregulation of mRNA of retinoid binding protein and fatty acid binding protein by cholesterol enriched-diet and effect of ginger on lipid metabolism. *Life Sci*. 84; 903-907.
 62. Ardizzone, S., & Bianchi, P. G. (2005). Biologic therapy for inflammatory bowel disease. *Drugs*, 65; 2253-2286.
 63. Nanjundaiah, S.M., Annaiah, H. N., & M-Dharmesh, S. (2009). Gastroprotective Effect of Ginger Rhizome (*Zingiberofficinale*) Extract: Role of gallic acid and cinnamic acid in H⁺, K⁺-ATPase/H. pylori inhibition and anti-oxidative mechanism. *Evid. Based Complement. Alternat. Med.* [In press].
 64. Shati, A. A., & Elsaid, F. G. (2009). Effects of water extracts of thyme (*Thymus vulgaris*) and ginger (*Zingiberofficinale* Roscoe) on alcohol abuse. *Food Chem. Toxicol*, 47; 1945-1949.
 65. El-Sharakly, A. S., Newairy, A. A., Kamel, M. A., & Eweda, S. M. (2009). Protective effect of ginger extract against bromobenzene-induced hepatotoxicity in male rats. *Food Chem. Toxicol*, 47(7); 1584-1590.
 66. Grzanna, R., Lindmark, L., & Frondoza, C. G. (2005). Ginger—an herbal medicinal product with broad anti-inflammatory actions. *J. Med. Food*, 8(2); 125-132.
 67. Ahui, M. L., Champy, P., Ramadan, A., Pham Van, L., Araujo, L., Brou Andre, K., Diem, S., Damotte, D., Kati-Coulibaly, S., Offoumou, M. A., Dy, M., Thieblemont, N., & Herbelin, A. (2008). Ginger prevents Th2-mediated immune responses in a mouse model of airway inflammation. *Int. Immunopharmacol*, 8(12); 1626-1632.
 68. Young, H. Y., Luo, Y. L., Cheng, H. Y., Hsieh, W. C., Liao, J. C., & Peng, W. H. (2005). Analgesic and anti-inflammatory activities of [6]-gingerol. *J Ethnopharmacol*. 96: 207-210.
 69. Carrasco, F. R., Schmidt, G., Romero, A. L., Sartoretto, J. L., Caparroz-Assef, S. M., Bersani-Amado, C. A., & Cuman, R. K. (2009). Immunomodulatory activity of *Zingiberofficinale* Roscoe, *Salvia officinalis* L. and *Syzygiumaromaticum* L. essential oils: evidence for humor- and cell-mediated responses. *J. Pharm. Pharmacol*, 61(7); 961-967.
 70. Fuhrman, B., Rosenblat, M., Hayek, T., Coleman, R., & Aviram, M. (2000). Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice. *The Journal of nutrition*, 130(5), 1124-1131.
 71. Ghasemzadeh, A., Jaafar, H. Z., & Rahmat, A. (2010). Antioxidant activities, total phenolics and flavonoids content in two varieties of Malaysia young ginger (*Zingiberofficinale* Roscoe). *Molecules*, 15(6), 4324-4333.
 72. Habib, S. H. M., Makpol, S., Hamid, N. A. A., Das, S., Ngah, W. Z. W., & Yusof, Y. A. M. (2008). Ginger extract (*Zingiberofficinale*) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. *Clinics*, 63, 807-8133.