

# Medicinal Biospecificity of Ginger and Its Efficacious Bioactive Compounds in the Context of Its Biological Activities Against Predominant Health Issues: Current Study and New Avenues

Haseeba Shahzad<sup>1,4,\*</sup>, Shaifa Saleem<sup>1</sup>, Waqas Hanif<sup>2</sup>, Zareena Ali<sup>3</sup>, Muhammad Zeeshan Ahmed<sup>4</sup>, Haq Nawaz<sup>4</sup>, Zelle Humma<sup>3,5</sup>, Laraib Rana<sup>6</sup>, Muhammad Qamar Farid<sup>7</sup>, Hajira Kalsoom<sup>1</sup>, Samavia Jaan<sup>1</sup>

<sup>1</sup>School of Biochemistry and Biotechnology, University of the Punjab, Quaid-i-Azam Campus, Lahore 54590, Pakistan.

<sup>2</sup>Department of Pathology, Combined Military Hospital, Bannu, Pakistan.

<sup>3</sup>Department of Biochemistry and Biotechnology, The Women University Multan, Pakistan.

<sup>4</sup>Department of Biochemistry, Bahauddin Zakariya University, Multan 60800, Pakistan.

<sup>5</sup>Department of Experimental Medicine, University of Genoa, Italy.

<sup>6</sup>Department of Biochemistry, Faculty of Biological sciences Quaid-i-Azam University, Islamabad 45320, Pakistan.

<sup>7</sup>Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand.

## Corresponding author\*

haseebashahzad388@gmail.com

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## Abstract

There is a multitude of life-threatening and widespread health issues worldwide, regarding weak immunity, severe inflammation, viral infections, bacterial infections as well as antimicrobial resistance (AMR), high free radicals generation, and cancer. Ginger, a perennial plant of the Zingiberaceae family with several authentic nutritional and medicinal values used in many countries as traditional medicine. That is why, the study was designed to highlight recent studies about medicinally most efficacious bio-active compounds of ginger along their biological significance related to immuno-stimulatory, anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, and anti-cancer effects. Our study also recognized future gaps in research. The study included professional research data under duration from 2001-2022 appearing in books and scholarly journals, collected from scientific database platforms via PubMed, Web of Science, Google Scholar, Springer Nature, Science Direct and Scopus. The present study includes the medicinal effects of almost 44 most influential ginger compounds like phenolics, terpenoids, flavonoids, and vinyllyl ketonic compounds etc. Our results revealed the strong alleviating effects of gingerols, shogaols, paradols, and polyphenols. Moreover, the ginger essential oil has proven to be very effective both for antiviral and antibacterial activity. However, no data is available in previous literature for components of ginger involved in immuno-stimulatory, effects. There is also a need to explore components for antibacterial activity. However, research has been conducted on ginger for only a few viruses despite its strong alleviating effects. Besides this, more study is needed to comprehend the comprehensive mechanism of action (especially at the molecular level) regarding the anti-bacterial and anti-viral activity of ginger and its constituents.

**Keywords:** Anti-bacterial; Anti-cancer; antioxidant; antiviral; Immunostimulatory; Anti-inflammatory; Ginger bioactive compounds; new avenues; mechanism of action.

## INTRODUCTION

Herbal medicines' use is increasing as compared to the use of chemicals day by day, therefore, more research has been performed on phytochemicals to make them more effective for the intervention of various ailments (Ishiguro et al., 2007). But it is very troublesome to explore the effectiveness of herbal treatment because of the presence of many compounds in various forms (Raynor et al., 2011). Ginger (*Zingiber officinale*) is an Angiospermae and belongs to the family Zingiberaceae. Its rhizomes are widely used as a spice and traditional medicine in many countries like the subcontinent and the United States (Shahrajabian et al., 2019). Due to the diverse phytochemistry of ginger, the components of

ginger are classified as volatiles and non-volatiles. Volatile components of ginger include sesquiterpene and monoterpenoid hydrocarbons which provide a distinct taste and aroma to ginger while the non-volatile pungent components include shogaols, paradols and zingerone (Jolad et al., 2005). Ginger has diversified nutritional and medicinal importance. The general nutritional and non-nutritional components of ginger and their quantities have been represented in table 1. Ginger contains more than 400 different compounds. The major compounds present in ginger are terpenes, phenolic compounds, carbohydrates, proteins, lipids, gingerols, and shogaols. There are many phytochemicals present in ginger that play an effective medicinal role. The major classification of phytochemicals has been represented in figure 1 and

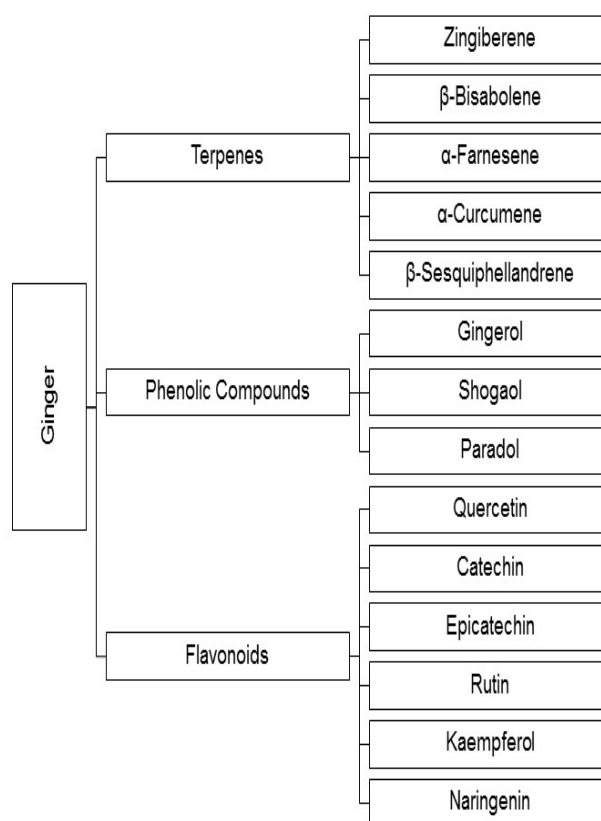
the structures of major bioactive compounds of ginger have been depicted in figure 2. Moreover, the oil extract of ginger has been observed to contain e-citral, z-citral, ocimene, and camphene (Munda et al., 2018).

Ginger shows a wide range of prophylactic and curative functions. It suppresses the level of cholesterol in the blood, prevents excessive clotting, is used to treat dyspepsia, and improves appetite (Palatty et al., 2013). Other properties of ginger include fat loss, prevention of cardiovascular diseases, anti-cancer, and anti-inflammatory action (Elshater et al., 2009). Gingerols play an important role in the alleviation of arthritis and pain. Ginger also possesses antioxidant, antimicrobial, and anti-allergic properties because of the presence of gingerols and shogaols (Semwal et al., 2015). Ginger is consumed as a painkiller for chest pain, menstrual pain, and back pain. It is utilized to cure cough, bronchitis, and upper respiratory tract infections (Shukla & Singh, 2007). Besides this, in China and many other countries, ginger is used for the treatment of rheumatism, nervous disorders, toothache, stroke, asthma, constipation, catarrh, gingivitis, diabetes, and migraine. Due to its antiviral properties and warming effect, it is also used for relieving flu and colds (Qidwai et al., 2003). Moreover, it is also used as a stimulant, diuretic, and carminative in Asian medicines (Shadmani et al., 2004). Ginger essential oil has proved to be very effective, particularly concerning antibacterial and antiviral activity (Koch et al., 2008; Mostafa et al., 2018). The constituents present in ginger essential oil and their percentage have been represented in table 2. Besides this, the strong effects of ginger oleoresin, particularly, regarding antioxidant activity have been observed (Ji et al., 2017).

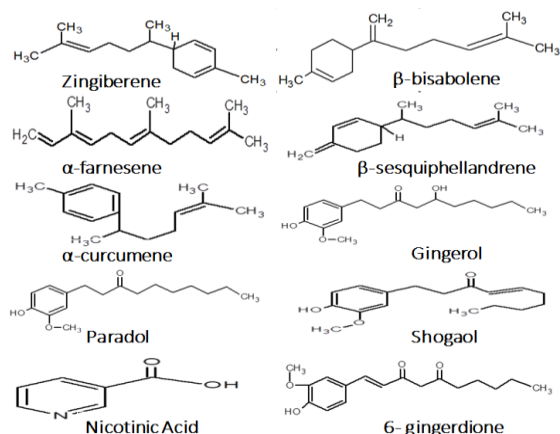
In previous literature, there is abundant data available regarding various effective and authentic medicinal approaches of ginger for various ailments but there is no such review available, in which data has been analyzed with a special focus on recent studies (2001-2022) regarding specificity of ginger bioactive compounds with respect to its biological activities to demonstrate the immuno-stimulatory, anti-inflammatory, anti-viral, anti-bacterial, antioxidant and anticancer effects. Besides this, no data is available in past in which after the most recent study (up to 2022), a future research gap got identified. This review has been planned to keep in view the most common and serious health problems and their intervention issues of the day. Our review will provide valuable data for drug manufacturers to isolate the bioactive components of ginger for manufacturing herbal drugs against particular disorders. Besides this, it will also provide new pathways for the researchers to fulfill the future gap to remove the hot issues of the day easily.

**Table 1.** General composition of Ginger (Agriculture, 2018; Nawaz et al., 2018).

Components	Value per 100g
Water	78.89g
Carbohydrates	17.77g
Total Lipids	0.75g
Proteins	1.82g
Ash	0.77g
Total Dietary Fiber	2.0g
Total Phenolic acids	0.63g
Total Tannins Content	0.28g
Total Flavonoid Content	3.93g
Ca	16mg
Fe	0.60mg
Mg	43mg
P	34mg
K	415mg
Na	13mg
Zn	0.34mg
Vitamin C	5.0mg
Choline	28.8mg



**Figure 1.** Classification of major phytochemicals present in Ginger (Ghasemzadeh et al., 2010; Shukla & Singh, 2007).



**Figure 2.** Structures of major phytochemicals present in Ginger (drawn by chem draw).

**Table 2.** Representation of percentage composition of constituents of ginger essential oil.

Compounds	%	Reference
$\beta$ -Bisobolene	12.5	
$\alpha$ -Zingiberene	25	(Varoni et al., 2018)
$\beta$ -Sesquiphellandrene	18	
$\beta$ -Phellandrene	8	
$\alpha$ -Zingiber	24	(Ferreira et al., 2018)
Geranial	15	
Farnesene	7.6	
Geranial	26	(Singh et al., 2008)
$\alpha$ -Zingiberene	9.5	
Neral	7.4	
1,8-cinrol	10	
Camphene	12	(Snuossi et al., 2016)
$\alpha$ -Zingiberene	7	
$\beta$ -Phellandrene	11	
Camphene	5	
ar-Curcumene	11.3	(Mesomo et al., 2013)
Eucalypto	3	
Geranial	11	
$\beta$ -Cedrene	8.6	
Geranial	16	(Moreira da Silva et al., 2018)
Geranyl acetate	8.4	
z-Citral	9.2	
Zingiberene	14	
$\beta$ -Sesquiphellandrene	27	(Borah et al., 2017)
$\alpha$ -Farnesene	10.5	
Caryophyllene	15.3	
$\beta$ -Bisabalene	11	
$\alpha$ -Zingiberene	20	(Wang et al., 2006)
$\beta$ -Sesquiphellandrene	13	
ar-Curcumene	15	
Citral	7.5	
ar-Curamene	59	(Nogueira de Melo et al., 2011)
$\alpha$ -Zingiberene	7.5	
1,8-Cinrol	8	
Farnesene	7.6	
Geranial	26	(Chmit et al., 2014)
Neral	7.4	
$\alpha$ -Zingiberene	9.5	

**Table 3.** Representing the percentage composition of constituents of ginger oleoresin by different methods (Supardan et al., 2012).

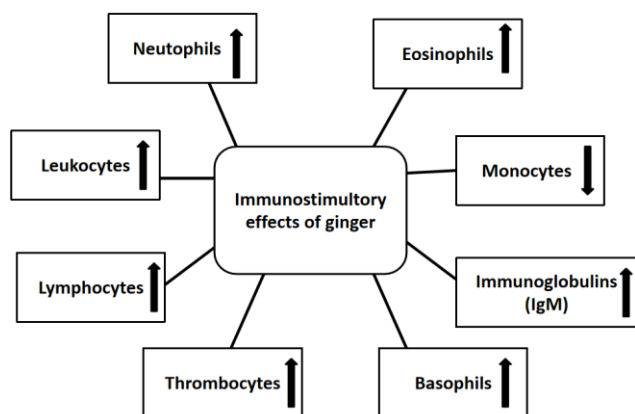
Components	Composition (%)	Method
Nortrachelogenin	6.74	
Ar-curcumene	8.9	Ultrasonic-assisted extraction
$\beta$ -sesquiphellandrene	5.02	
Zingerone	13.85	
Shogaol	7.92	
Farnesene	6.29	
Zingiberene	5.13	
Zingerone	14.47	Soxhlet
$\beta$ -sesquiphellandrene	5.44	
Shogaol	7.14	
$\beta$ -sesquiphellandrene	6.54	
Zingiberene	16.77	
Geraniol	9.01	CO <sub>2</sub> Supercritical
Gingerol + shogaol	3.48	
$\beta$ -phellandrene	12.86	

## GINGER AS AN IMMUNO-STIMULANT

Immunostimulant is an agent that aids in increasing the body's immune-response. Immunity is defined as the body's ability to resist infection or toxins by the action of sensitized white blood cells and specific antibodies (Divangahi et al., 2021). Immune-deficiency leads to various abnormalities and disorders including DiGeorge syndrome, chronic mucocutaneous candidiasis, interleukin-12 receptor deficiency, hyper-immunoglobulin M syndrome, severe combined immunodeficiency disease, leukocyte adhesion deficiency syndrome, chronic granulomatous disease, and Wiskott-Aldrich syndrome, etc (Vaillant & Qurie, 2021).

Ginger exhibits immuno-stimulatory and anti-infection properties against pathogenic bacteria, worms, and viruses (Sanderson et al., 2002). It also shows its immunomodulatory effects in animals, like fish (Nya & Austin, 2009). White blood cells (WBC) are considered to be primary defenders of the body. In an experiment, when the rainbow trout were fed with ginger, an increased number of WBC, neutrophils, and other blood cells was observed (Nya & Austin, 2009). It has been noticed that herbal plants boost immunity by elevating the number of blood cells (Sahu et al., 2007). Like humans, fishes also have specific and nonspecific defense systems to protect themselves against microbes. In fishes, mucus and skin are the primary non-specific defenses. When any pathogen enters the body both humoral and cellular defenses are activated and phagocytosis is part of non-specific immunity. The increased phagocytotic activity of WBCs was observed in fishes fed with ginger (Haghighi & Rohani, 2013). The phagocytotic activity was compared in two groups of fish. In a group of fishes, with a 0.1% ginger diet, the mean phagocytosis index was  $2.21 \pm 0.082$  while it was greater,  $2.37 \pm 0.263$  in fishes fed with a 1% ginger diet

(Dugenci et al., 2003). Besides this, plasma proteins that play a role in humoral defense were also found to increase. It was concluded that both humoral and cellular immunity were enhanced by using ginger extract in the case when any pathogen entered the body through injury (Dugenci et al., 2003). When plasma protein level was compared between two groups of fishes, it was observed that in a group with a 0.1% ginger diet the level of protein in fishes was  $2.26 \pm 0.2541$  (g/dl) while it was significantly greater,  $3.84 \pm 0.13$  (g/dl) in fishes fed with 1% ginger diet (Dugenci et al., 2003). Ginger shows immunomodulatory effects due to the presence of gingerols, shogaols, zingerone, and paradols (Rasmussen, 2011). It has been observed that 6-gingerol suppressed the expression of TNF- $\alpha$  and iNOS by blocking PKC and NF- $\kappa$ B signaling pathways in macrophages of lipopolysaccharide-stimulated mice (Lee et al., 2009). It has been reported that PKC stimulates NF- $\kappa$ B which in turn regulates the iNOS expression at the transcriptional level (Simon et al., 2015). Similarly in another study, 6-gingerol was observed inhibiting the iNOS expression and NO production in activated macrophages of J774.1 mice (Ippoushi et al., 2003). In another study, 6-gingerol inhibited the formation of IL-12, TNF- $\alpha$ , and IL-1 $\beta$  in macrophages as well (Tripathi et al., 2007). The other mechanistic actions of ginger as an immunostimulant are represented in figure 3.



**Figure 3.** Mechanistic action of immune-stimulatory effects of ginger (Shokr & Mohamed, 2019). (Upward arrow-indicating the enhancing activity, Downward arrow-indicating the reducing activity)

### GINGER AS AN ANTI-INFLAMMATORY

When inflammation happens, certain chemicals from the white blood cells of the body enter tissues to protect them from invaders. This increases the blood flow to the site of damage or infection and thus causes redness. Besides this, the leakage of fluid in tissues by certain chemicals results in swelling as well (Varela et al., 2018). Sometimes, acute inflammation (uncontrolled) may become chronic and leads to a variety of inflammatory disorders including bowel and

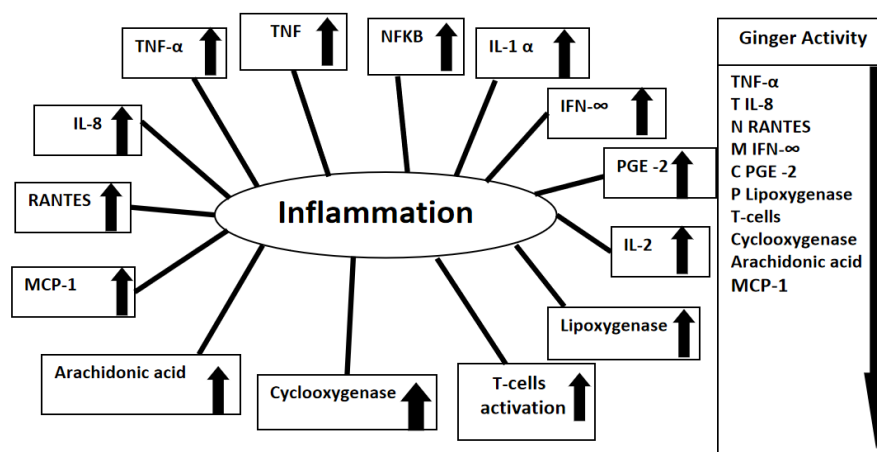
cardiovascular diseases, cancer, and arthritis (Zhou et al., 2016).

Ginger has proved to be very beneficial for the intervention of inflammatory disorders. Ginger shows strong anti-inflammatory activity due to the presence of vinyllyl ketonic compounds. Besides this, 6-paradol, 6-shogaol, and 1-dehydro-6-gingerol are the constituents of ginger that have been observed to cause an anti-inflammatory effect (Ezzat et al., 2018). The anti-inflammatory mechanism of the actions of ginger connecting its constituents has been illustrated in table 4. Many enzymes are involved in causing inflammation like lipoxygenase shows its action by forming inflammatory lipid mediators such as hepxilins, hydroxy fatty acid derivatives, lipoxins, and leukotrienes (Kuhn et al., 2007). Cyclooxygenase is involved in the formation of prostaglandins and thromboxane. Ginger shows its action by decreasing the effect of cyclooxygenase, lipoxygenase, and arachidonic acid (Lantz et al., 2007). In the experimental model of rheumatoid arthritis, more anti-inflammatory action has been noticed by combining both gingerols and ginger extract oil as compared to gingerols alone (Funk et al., 2009). In inflammatory bowel diseases (IBD) which include ulcerative colitis and Crohn's disease, an elevated level of TNF and PGE2 has been observed (Nakamura et al., 2006) because both diseases are responsible for inflammation (Kawahara et al., 2015). Ginger shows a protective effect against IBD by decreasing the level of both TNF and PGE2 (El-Abhar et al., 2008). In one study, TNF- $\alpha$  expression was compared in two groups of rats. In one group, liver cancer was induced by a choline-deficient diet and in the other group, a choline-deficient diet was given along with ginger extract. It was observed that the expression of TNF- $\alpha$  in rats with only a choline-deficient diet was  $83.3 \pm 4.52\%$  while it was reduced in the group, that was also given the ginger diet along with choline-deficient diet where it was  $7.94 \pm 1.32\%$  ( $P < 0.05$ ). Similarly the expression of NF $\kappa$ B was also observed in both these groups and it was observed that it was  $88.3 \pm 1.83\%$  in group with only choline-deficient diet and it was significantly reduced in group that was also given ginger diet along with choline-deficient diet where it was  $32.35 \pm 1.34\%$  ( $p < 0.05$ ) (Habib et al., 2008). Besides this, ginger has been observed to reduce the symptoms of gout (Grzanna et al., 2005) and also relieve osteoarthritis of the knee (Altman & Marcussen, 2001).

Monocyte chemoattractant protein-1 (MCP-1) is a protein that is involved in inflammation. Inflammation is also associated with the increased level of RANTES production which activates the T cells (Appay & Rowland-Jones, 2001) due to which the formation of IL-2 and IFN- $\gamma$  also increases. In an experiment, when ginger was given to rats with high RANTES levels, it was observed that ginger not only reduced inflammation and restricted T-cell activation but also suppressed the level of RANTES and MCP-1 (macrophage

inflammatory protein) (Ezzat et al., 2018). Besides this, the anti-inflammatory role of ginger oil has been noted by inhibition of IL-1 $\alpha$  (Zhou et al., 2006). 6-gingerol decreases NO production by inhibiting cytokines (IFN- $\gamma$  and TNF- $\alpha$ ) that stimulate the production of NO (Amri & Touil-Boukoffa, 2016). Gingerol and shogaol inhibit the activity of prostaglandin synthetase enzymes and thus

suppress the formation of prostaglandin. They also inhibit the action of cytokines i.e IL-1 and IL-8 that are involved in inflammation (Verma et al., 2004). The comparison of factors involved in inflammation and counter effects of ginger has been shown in figure 4 in a nutshell.



**Figure 4.** Comparison of factors involved in causing inflammation and therapeutic effects of ginger in a nutshell (Ezzat et al., 2018; Verma et al., 2004; Zhou et al., 2006). Abbreviations: TNF: Tumor necrosis factor; NFKB: nuclear factor kappa-light-chain-enhancer of activated B cells; IL: Interleukin; IFN: Interferon; PGE-2: Prostaglandin E-2; MCP-1: Monocyte chemo-attractant protein-1; RANTES: regulated on activation, normal T cell expressed and secreted. (Upward arrow-indicating increasing activity, Downward arrow-indicating decreasing activity)

**Table 4.** Representing the anti-inflammatory mechanisms of ginger connecting its constituents. Abbreviations: NO, nitric oxide; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; PGE2, prostaglandin E2; GDNPs, ginger-derived nanoparticles.

Sr. No.	Ginger/Constituents	Dose	Research Subjects	Mechanism of action	Reference
1	6-gingerol-rich fraction	50 & 100 mg/kg	Female specie Wistar rats	Levels of NO, TNF- $\alpha$ and myeloperoxidase enzyme, enhance	(Abolaji et al., 2017)
2	Extract of Ginger and zinger-one	0.1,1, 10&100 mg/kg	Female specie (BALB/c mice)	Reduces the level of IL-1 $\beta$ and inhibits the stimulation of Necrotic factor- $\kappa$ B	(Hsiang et al., 2013)
3	6-shogaol	100 $\mu$ M	Human intestinal epithelial cells (HT29/B6, Caco-2)	Ceased the PI3K/Akt, NF- $\kappa$ B signaling pathways	(Luettig et al., 2016)
4	GDNPs	0.3 mg	Female mice (C57BL/6 FVB/NJ)	By using GDNPs 2, levels of IL-10 and IL-22 and level of TNF- $\alpha$ , IL-6, and IL-1 $\beta$ decrease.	(Zhang et al., 2016)
5	Extract of Ginger	50 mg/mL	Mice (C57BL/6J)	Ginger extract prevents the production of TNF- $\alpha$ and Activates the Akt & NF- $\kappa$ B.	(Ueno et al., 2014)
6	6-gingerol, 6-dehydroshogaol, 6-shogaol	2.5 and 5,10 $\mu$ M	Macrophage cells of the mouse (RAW 264.7)	NO, PGE <sub>2</sub> production is stopped.	(Zhang et al., 2013)

## GINGER AS AN ANTIVIRAL

The World health Organization (WHO) and other public health agencies have warned about the emergence of infectious diseases at alarming rates that have not been previously noted (Organization, 2021). The centers for disease control and prevention (CDC) elaborates on

emerging infectious diseases. Among all categories of infectious diseases, viral agents are the most serious threat to global populations (Prevention., 2021). The 21<sup>st</sup> century is marked by major pandemics and epidemics due to novel viral agents that have been the source of mortality and morbidity around the world such as Ebola virus, Zika virus, Middle-Eastern Respiratory Syndrome

(MERS), influenza A (H1N1) pdm/09, Human Immunodeficiency Virus (HIV), Middle-Eastern Respiratory Syndrome (MERS), West Nile virus, chikungunya virus and currently severe acute respiratory syndrome virus 2 (SARS-CoV-2) (Ong et al., 2020). Besides this, the hepatitis C virus (HCV) is a critical illness. HCV may lead to acute or chronic hepatitis and principally causes liver cancer. Universally, approximately 58 million human beings have chronic HCV infection. According to an approximation of WHO, almost 290 000 human beings expired from hepatitis C in 2019. At present, no efficient vaccine exists against hepatitis C (WHO, 2022) and Pakistan is ranked second after China which is suffering from hepatitis at an alarming rate. In 2018, a very alarming prevalence rate of hepatitis C virus was observed in small towns in Pakistan (Ahmed et al., 2020).

In China, fresh ginger is used as a folk medicine for the treatment of airway infections. Ginger shows antiviral activity against various types of viruses like human respiratory syncytial virus (HRSV) and it has been observed that the effects of dried ginger are different from fresh ginger against HRSV because both dried and fresh ginger contain different constituents. Fresh ginger shows better results against the virus as compared to dried ginger (Jolad et al., 2005). HRSV causes lethality and death by inducing bronchiolitis and pneumonia (San Chang et al., 2013). Ginger reduces viral invasion by preventing the attachment and internalization of the virus into the cells. At high concentrations, fresh ginger stimulates the low respiratory tract mucosal cells to secrete IFN- $\beta$ , the cytokine which inhibits the replication of viruses (Ali et al., 2008). Experimental studies have shown that an aqueous extract of ginger also reduces the infectivity of feline calicivirus (FCV). Antiviral activity occurs due to a chemical interaction between phytochemicals like proanthocyanins, polysaccharides, polyphenols, and some other compounds present in natural extracts and the virus (Aboubakr et al., 2016). The aqueous extract of ginger contains 1,2-propanediol, 1,2-benzene dicarboxylic acid, and 2,3-butanediol which does not affect the receptors of the cell for FCV but inhibits the attachment of viruses with cells by causing alterations in viral capsid. FCV is used as a surrogate for norovirus in experiments because it is very difficult to grow noroviruses in cell culture (Aboubakr et al., 2016). Norovirus is an enteric virus and is considered to be a major contributor to foodborne illnesses. Aqueous extract of ginger has proved to be very beneficial in the prevention of foodborne diseases. We can also use its extract to wash vegetables and fruits in combination with water to prevent them from viral contamination (Aboubakr et al., 2016). Several terpenes in the alcoholic extract of ginger have been observed with anti-rhinoviral activity (Adom et al., 2019). Besides this, gingerone has been observed in causing the inhibition of many types of influenza A viruses including

H9N2, H1N1, and H5N1 (Onyiba, 2022). Propanediol in an aqueous extract of ginger has revealed strong anti-chikungunya activity (Kaushik et al., 2020; Wang et al., 2020). Ginger essential oil (composition shown in table 2) has depicted antiviral activity with high accuracy. The inactivation of caprine alphaherpesvirus-1 (up to 100%) by disruption of the virus envelope and other structures needed for virus attachment to host cells has been observed by ginger essential oil (Camero et al., 2019). More than 90.0% reduced activity of HSV-2 by preincubation with ginger oil also indicated its effective antiviral influence (Koch et al., 2008). Moreover, in invitro experimentation, direct inactivation of Tulane and hepatitis A viruses have been observed by gingerol (Patwardhan et al., 2020) while zerumbone has been observed with reduced activity of Epstein-Barr virus (Onyiba, 2022). In Hepatitis C-infected patients, ginger administration revealed the reduction in viral load by suppression of aspartate aminotransferase,  $\alpha$ -fetoprotein and alanine aminotransferase (Abdel-Moneim et al., 2013). However therapeutic effects of ginger have also been observed against SARS-CoV-2. In coronavirus disease, the cleavage of polyprotein a/b (PP a/b) takes place via papain-like protease (PLpro) at different sites, producing several proteins necessary for viral replication and survival (Goswami et al., 2020). Molecular docking has disclosed the potential inhibition of PLpro by 10-gingerol, 6-gingerol and 8-gingerol (Shin et al., 2020). The binding potential of shogaol, gingerol, zingiberene, zingerone, zingiberenol and geraniol with catalytic domain of MPro has also been observed in docking studies. Meanwhile, interference with S protein-ACE2 binding has also been remarked by shogaol, zingiberenol, geraniol, zingiberene, gingerol and zingiberene (Ahkam et al., 2020). S protein inhibition of corona virus has been examined by 10-shogaol, 10-paradol, 10-gingerol, 8-paradol, 8-gingerol, 10-gingerol and sesquiphellandrene (terpene) (Joshi et al., 2020).

In a study carried out in Saudi Arabia, a decrease in hospitalization (28.0%) has been observed in COVID-19 patients using the ginger diet as compared to nonusers (38.0%) (Aldwihi et al., 2021). Similarly in another study, in COVID patients treated with ginger extract, low serum level of TNF- $\alpha$ , IL-1, and IL-6 was observed along with short-time mechanical ventilation as compared to the control (Shariatpanahi et al., 2013)

## GINGER AS AN ANTIBACTERIAL

Bacterial infections are the most common infections everywhere. Not only this but with time antibiotic stewardship issue has become the most serious health threat worldwide. The problem can be resolved by replacing allopathic medicines with herbal drugs. Antimicrobial resistance (AMR) is a threat worldwide to development and health. It necessitates quick and crucial multisectoral action to attain sustainable development

goals. WHO has stated that worldwide, antimicrobial resistance is among the 10 topmost health threats for human beings (WHO, 2021). Globally, one of the most common reasons for mortality is antimicrobial resistance (AMR), especially in settings where health care organizations do not get the least possible standards set by the World Health Organization (WHO) or some other quasi-governmental organization. According to analytical statistical models, in 2019, the bacterial AMR led to approximately 4.95 million demises. Owing to AMR, 6 main pathogens caused 929 000 (660 000–1 270 000) demises, these pathogens include *Escherichia coli*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* (Murray et al., 2022).

Ginger shows its action against both gram-positive and gram-negative bacteria (Abdulzahra & Mohammed, 2014). The oil extract of dried ginger has proven to be very efficacious against various types of pathogens involved in food-borne diseases like *E.coli*, *Vibrio cholera*, *salmonella spp*, and *Klebsiella* (Islam et al., 2014). In an experiment when *V.harveyi* infected Lates calcarifer which is an Asian sea bass and was given a ginger diet, it was observed that ginger controlled the infection caused by *V.harveyi* (Talpur et al., 2013). *V.harveyi* is a gram-negative bacteria that causes death in Asian sea bass (Austin & Zhang, 2006). Ginger is found to increase the lysozyme activity (Talpur et al., 2013). Lysozymes are the enzymes that carry the hydrolysis of peptidoglycans present in the cell wall of bacteria. In this way, ginger inhibits the penetration of detrimental bacteria (Nile & Park, 2015). Besides this, the anti-bactericidal action of serum (which plays an important role in removing pathogens) also increases by ginger (Ellis, 2001). Ginger increases anti-protease activity and thus suppresses the attacking ability of bacteria. The increased respiratory burst action of neutrophils by ginger has also been reported (Talpur et al., 2013). A respiratory burst is a reaction in phagocytes that causes the degradation of bacteria. In fishes with a 0.1% ginger diet,  $1.05 \pm 0.050$  (nmol  $O_2$  / $10^5$  leucocyte) respiratory burst activity was observed while it was significantly greater,  $1.26 \pm 0.230$  ( $P < 0.001$ ) in fishes fed with a 1% ginger diet (Dugenci et al., 2003).

The ginger essential oil has been observed with strong anti-microbial properties against many bacteria. The percentage composition of ginger essential oil is represented in table 2. After the extraction of ginger essential oil by microwave-assisted hydrodistillation method and its chemical composition analysis by FTIR spectrometer, citral was found to be the most abundant (89.05%) chemical compound in oil (Kalhor et al., 2022). It was observed in the study that ginger oil obtained through hydrodistillation showed more sensitivity against *L.monocytogenes* as compared to other bacteria and depicted a big inhibition zone (37mm). It was also observed to be active against the strain *V.alginolyticus*, despite its high MIC value (minimum inhibitory concentration) (0.05-0.2mg/ml) (Mostafa et al., 2018). The moderate activity of ginger oil with MIC value 0.16-0.63 mg/ml against gram-positive bacteria demonstrated the high resistance of gram-negative bacteria against ginger oil as compared to Gram-positive bacteria (Snuossi et al., 2016). Ginger essential oil has been shown to inhibit activity against *E.coli* and *Shigella* due to the presence of bioactive constituents like gingerol, endo borneol, and zingiberene (Sivasothy et al., 2011). Similarly in another research conducted in Brazil, zerumbone isolation from ginger oil depicted its efficacy against *S.mutans* with 500  $\mu$ g/ml MBC (minimum bactericidal concentration) and 250  $\mu$ g/ml MIC. The efficacy of oil against biofilm formation and growth activity of *S.pyrogenes* resulted in 1mg/ml MBC and MIC (Wijesundara & Rupasinghe, 2018). The more sensitivity of gram-positive strains suggested that the thick peptidoglycan surrounding the membrane of the cytoplasm would be the bacterial target of essential oil (Cox & Markham, 2007). However, the possibility of another target cannot be proscribed. The better effect of oil against gram-negative bacteria suggested other microbial targets like plasma membranes as bioactive components of essential oil possess lipophilic properties which interact with membranes via influencing their permeability and fluidity (Rouseff & Perez-Cacho, 2007). The effective doses of ginger (Halo, MBC, and MIC) against different bacteria connecting different countries have been represented in table 5.

**Table 5.** Representing the effective doses of ginger against different bacteria connecting different countries. Abbreviations: MBC, Minimum bactericidal concentration; MIC, Minimum inhibitory concentration.

Bacteria	Halo (mm)	MBC ( $\mu\text{L/mL}$ )	MIC	Country	Reference
<i>E. coli O157:H7</i>		18.7	9.4 microliter/mL		
<i>P. aeruginosa</i>		4.7	2.3 microliter/mL		
<i>S. typhimurium</i>		18.7	9.4 microliter/mL	Brazil	(da Silva et al., 2018)
<i>S. aureus</i>		4.7	2.3 microliter/mL		
<i>L. monocitogenes</i>		9.4	4.7 microliter/mL		
<i>V. alginolyticus</i>		>25		Tunisia	(Snuossi et al., 2016)
<i>Shigella</i>			119.79%		
<i>E. coli</i>			106.02%	Saudi Arabia	(Ashraf et al., 2017)
<i>E. faecalis</i>			61.94%		
<i>P. aeruginosa</i>			21.65%		
<i>B. spizizenii</i>			0.24 milligram/mL		
<i>E. coli</i>			0.31 milligram/mL	Negeri Sembilan	(Sivasothy et al., 2011)
<i>P. stutzeri</i>			0.63 milligram/mL		
<i>B. licheniformis</i>			0.16 milligram/mL		
<i>K. pneumoniae</i>			0.47 milligram/mL		
<i>L. plantarum</i>	7.0			Brazil	(Ambrosio et al., 2017)
<i>S. enteritidis</i>	8.8				
<i>E. faecalis</i>			1.0 milligram/mL		
<i>S. aureus</i>			0.25 milligram/mL	Mexico	(López et al., 2017)
<i>S. epidemidis</i>			0.5 milligram/mL		
<i>S. mutans</i>		500 $\mu\text{g/mL}$	250 $\mu\text{g/mL}$	Brazil	(Moreira da Silva et al., 2018)
<i>S. aureus</i>	8.90				
<i>M. l nkluteus</i>	6.86				
<i>L. monocytogenes</i>	9.00			India	(Bag & Chattopadhyay, 2015)
<i>S. typhimurium</i>	6.61				
<i>B. cereus</i>	9.11				
<i>E. coli</i>	8.00				
<i>B. cereus</i>	8.3				
<i>S. typhi</i>	0.0				
<i>S. aureus</i>	15.8			Saudi Arabia	(Mostafa et al., 2018)
<i>P. aeruginosa</i>	11.2				
<i>E. coli</i>	0.0				
<i>K. pneumoniae</i>	20.5			India	(Singh et al., 2008)
<i>P. vulgaris</i>	18.4				
<i>S. pyogenes</i>		>1000 $\mu\text{g/mL}$	>1000 $\mu\text{g/mL}$	Canada	(Wijesundara & Rupasinghe, 2018)

## GINGER AS AN ANTIOXIDANT

The oxidative stress develops when in the organs and tissue, the development of extremely reactive species, for example, reactive nitrogen species (RNS), reactive sulfur species (RSS), and reactive oxygen species (ROS), prevail over the endogenous antioxidant defense system competence, brings about the dysfunctions and cellular damage, and ultimately gives rise to a broad range of diseases. Free radicals produce oxidative stress in the living system which is the major cause of many chronic diseases like cataracts, cancer, aging, rheumatoid arthritis, and autoimmune diseases (Pham-Huy et al., 2008). The inequality between vulnerable defense systems and too many reactive species causes harm to various cell structures as well as to many molecules like

DNA, lipids, and proteins, and finally leads to a broad range of diseases (Janssen-Heininger et al., 2008).

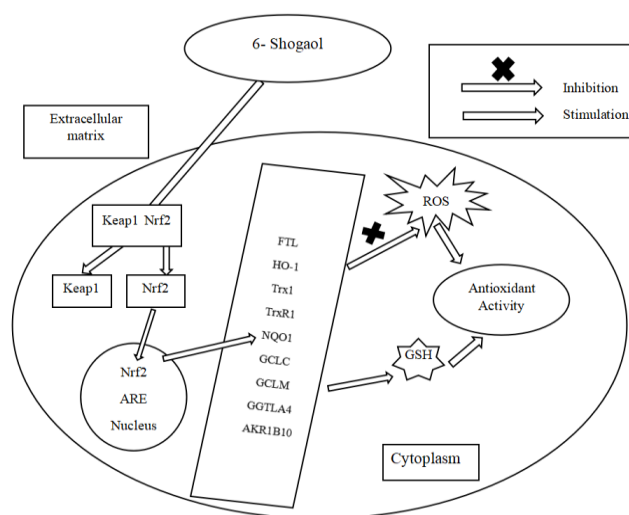
Medicinal plants contain many phytochemicals which are proved to be effective in alleviating the toxic effects of free radicals. Ginger also contains many phytochemicals like 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol which possess antioxidant properties due to their solubilizing side chains and hydroxyl groups which are further classified into two major groups diarylheptanoids and gingerol-related compounds (Si et al., 2018). Results on HPLC-MS/MS of both extracts confirmed that eight different types of phenolic acids are present in ginger that proved the effective antioxidant activity and cause a delay in the diseases which are caused by oxidative stress (Tohma et al., 2017).



Ginger is very useful for chemotherapeutic patients because patients produce many reactive oxygen species which are responsible for oxidative stress followed by more lipid peroxidation products like nitric oxide (Amin et al., 2012; Gupta et al., 2010; Srivastava et al., 2010). When the ginger extract was given to such patients, it showed its efficacy by enhancing the level of antioxidant enzymes and suppressing the level of lipid peroxidation products (Danwilai et al., 2017). 6-gingerol is the most abundant compound in ginger that shows antioxidant activity (Baliga et al., 2011). The comprehensive mechanism of action of 6-shogaol for anti-oxidant effects has been illustrated in figure 5. Newly identified cancer sufferers taking strong beneficial chemotherapy have been randomized to take 20 mg of 6-gingerol, a ginger extract per day which enhances the antioxidant enzymes (Danwilai et al., 2017). In one study, the level of antioxidant enzymes was compared between two groups of rats. In one group of rats, there were diabetic rats as control and in the other group, diabetic rats were fed with a ginger diet. A very low level of superoxide dismutase enzyme was observed in the control group which was  $90.40 \pm 3.10$  (U/mL) but it was significantly higher in ginger fed group where it was  $109.30 \pm 3.70$  (U/mL) ( $P < 0.05$ ). Similarly, the level of Glutathione peroxidase (U/mL) was  $22.90 \pm 0.89$  in the control group while it was significantly higher,  $26.31 \pm 2.10$  in the ginger-fed group. The overall antioxidant capacity (mM) of the control group was  $0.99 \pm 0.17$  mM while in the ginger treated group it was  $1.28 \pm 0.29$  ( $P < 0.05$ ) (Abdullah, 2012).

Ginger prevents the formation of hydroxyl radicals due to the presence of polyphenols because they form a chelate with  $Fe^{3+}$  (Stoilova et al., 2007). Polyphenol compounds show high antioxidant activity because they are reducing agents and free radical scavengers (Juntachote et al., 2006). Anthocyanins and ascorbic acid are two phenols that act as free radical scavengers (Pantelidis et al., 2007). Phenolics also improve the

quality of food by inhibiting the degradation of lipids which is why their use in the food industry is increasing day by day (Wojdyło et al., 2007). It has been observed that gingerol plays a dominant role in the inhibition of phospholipid peroxidation as well as inhibits the xanthine oxidase, the enzyme that is involved in the formation of reactive oxygen species (Nile & Park, 2015). The other mechanisms of different constituents of ginger for anti-oxidant effects have been shown in table 6.



**Figure 5.** The comprehensive mechanism of action of 6-shogaol for antioxidant activity (Chen et al., 2014): 6-shogaol causes the translocation of Nrf2 in the nucleus and enhances the expression of genes that target Nrf2 by modification of Keap1 and protects Nrf2 from proteasomal degradation. In this way the GSH level increases and the ROS level suppresses. Abbreviations: Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid related factor 2; ARE, antioxidant response element; FTL, ferritin light chain; HO-1, heme oxygenase-1; Trx1, thioredoxin 1; NQO1, nicotinamide adenine dinucleotide phosphate (NADPH) quinone dehydrogenase 1; TrxR1, thioredoxin reductase 1; GCLC, glutamate-cysteine ligase catalytic subunit; GGTLA4,  $\gamma$ -glutamyltransferase-like activity 4; GCLM, glutamate-cysteine ligase modifier subunit; AKR1B10, Aldo-keto reductase family 1 member B10; GSH, glutathione; ROS, reactive oxygen species.

**Table 6.** Representing the antioxidant mechanism of action of different components of ginger. Abbreviations: MDA, malondialdehyde; GSSG, glutathione disulfide; glutathione S-transferase P1; MT1, metallothionein.

Sr. No	Ginger/Constituents	Dose	Research Subjects	Mechanism of action	Reference
1	6-shogaol	20 $\mu$ M	Human colon carcinoma cells HCT-116	Enhancing the activation of MT1, FTL, AKR1B10, HO-1, GGTLA4, MT1, GCLM, and GCLC genes; decreasing the level of ROS; Enhancing the intracellular GSH/GSSG ratio; reducing the level of ROS	(Chen et al., 2014)
		100 mg/kg	Mice with wild-type and Nrf2/C57BL/6J mutations	Upregulation of HO-1, GCLC, and MT1 expression	
2	Ginger oleoresin (Composition shown in table 2)	100 $\mu$ g/mL	Mesenchymal, stem cells from humans	Stimulating HO-1, NQO1 gene expression; reducing ROS generation; stimulating Nrf2 translocation to the cell nucleus	(Ji et al., 2017)
3	Ginger phenylpropanoids	40 $\mu$ g/mL	BJ fibroblasts from the foreskin	Upregulation of Nrf2 activity and GSTP1 level	(Schadich et al., 2016)

Table 6. Cont.

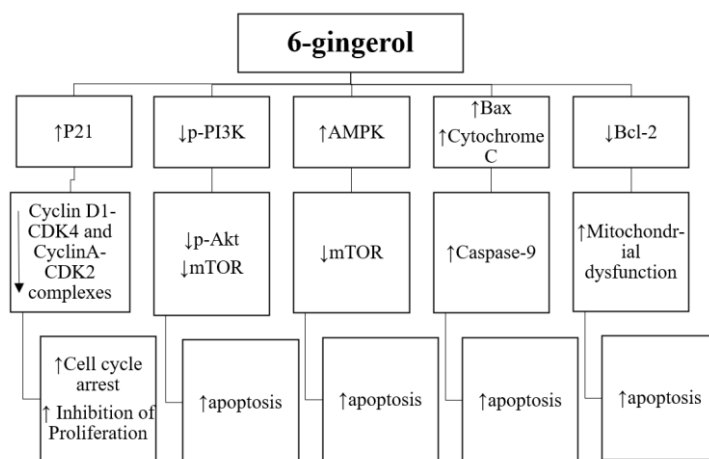
Sr. No	Ginger/Constituents	Dose	Research Subjects	Mechanism of action	Reference
4	6-gingerol rich fraction	50, 100 mg/kg	Wistar rats, females	H2O2 and MDA levels are being reduced, while antioxidant enzyme activity and GSH levels are being increased.	(Abolaji et al., 2017)
		100 mg/kg	Wistar albino rats, males	Lowering the MDA level; preventing catalase activity & GSH content from being depleted	(Saiah et al., 2018)
5	Ginger extract	200, 400 µg/mL	Human fibrosarcoma cells, strain HT1080	Reducing the production of reactive oxygen species (ROS)	(Romero et al., 2018)
		5, 25 µg/mL	Human chondrocyte cells C28I2	Increasing antioxidant enzyme gene expression and lowering ROS as well as lipid peroxidation levels	(Hosseinzadeh et al., 2017)
		78 to 313 µg/mL	Homogenates of rat hearts	MDA levels decreased	(Akinyemi et al., 2013)

## GINGER AS AN ANTICANCER

Cancer is a disease in which abnormal cells grow and spread uncontrollably throughout the body and damage normal body tissues (Fearon et al., 2011). Cancer is the second leading cause of death in the world. According to WHO's (2022) cancer report, 10 million deaths cases were observed in 2020 with nearly one in six deaths. However in lower-middle-income countries, 30% of cancer cases were observed (Organization, 2022). Globally, approximately 10.0 million cancer-related mortalities (9.9 million without non-melanoma skin cancer) and almost 19.3 million new patients of cancer (18.1 million without non-melanoma skin cancer) arose in the year 2020. Breast cancer in females has exceeded lung cancer as the most frequently detected cancer, with almost 2.3 million new patients (11.7%), after that lung, colorectal, prostate, and stomach cancers were 11.4%, 10.0 %, 7.3%, and 5.6% respectively. The highest cause of cancer-related death is lung cancer, with

approximately 1.8 million mortalities (18%), afterward here comes colorectal, liver, stomach, and female breast cancers in the range of 9.4%, 8.3%, 7.7%, and 6.9% respectively. On the whole, the frequency was 2 to 3 fold greater in transitioned countries when compared with transitioning countries (Sung et al., 2021).

Studies suggest that ginger causes the cell death of various types of cancerous cells including ovarian, colon, brain, liver, cervical, skin, prostate, renal, pancreatic, gastric, and breast cancer (Srinivasan, 2014). Phytochemicals like gingerols, shogaols, paradols, and polyphenolics are the compounds that are part of ginger and are involved in the anticancer activity and reduce its risk by targeting at different stages (Cheng et al., 2011). The therapeutic mechanisms of different constituents of ginger against various types of cancer are mentioned in table 7. The potential mechanisms of 6-gingerol for suppressing proliferation and induction of apoptosis in cancer (figure 6) (Liu et al., 2017; Tahir et al., 2015).



**Figure 6.** Schematic diagram depicting the various signaling pathways of 6-gingerol for anti-cancer activity. Abbreviations: PI3K: Phosphoinositide 3-kinase; AMPK: 5 adenosine monophosphate-activated protein kinase; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; CDK: Cyclin-dependent kinase; mTOR: Mammalian target of rapamycin; Akt: Protein kinase B. (Upward arrow-indicating increasing activity, Downward arrow-indicating decreasing activity)

**Table 7.** Representing the therapeutic mechanism of action of different constituents of ginger against different types of cancer. Abbreviations: NF- $\kappa$ B, nuclear factor kappa light chain-enhancer of activated B cells; AMPK, 5 adenosine monophosphate-activated protein kinase; GDNP, Ginger derived nanoparticles; ERK, Extracellular signal-regulated kinase; Bcl-xL, B-cell lymphoma-xL protein; KRAS, Kirsten rat sarcoma viral oncogene; mTOR, mammalian target of rapamycin; STAT3, signal transducer and activator of transcription 3; c-Myc, cellular myelocytomatosis; Bcl-2, B-Cell Leukemia/Lymphoma 2; GST $\pi$ , glutathione-S-transferase; MRP1, multidrug resistance associated protein 1.

Sr. No.	Ginger/Constituents	Dose	Research Subjects	Mechanism of action	Reference
1	10-gingerol	50-100 and 200 $\mu$ M	Carcinoma cells from mouse breasts and human	Inhibit cell growth, reduce the cell division and responsible for S phase cell cycle apoptosis	(Bernard et al., 2017)
2	GDNPs -2	0.3 mg	Female, mice (C57BL/6)	By using GDNPs-2 the expression of cyclin D1 is restrained and intestinal epithelial cell multiplication is also restricted.	(Zhang et al., 2016)
3	Extract of ginger based on fluorescent carbon Nano-dots	1.11 mg/mL	Carcinoma cells (hepatocellular, HepG2 human)	Boost up the apoptosis, enhance the ROS level, and dominate the expression of <i>p53</i> .	(Li et al., 2014)
4	Ginger extract	100 mg/kg	Female mice (Swiss albino)	Ginger extract Activates the AMPK, and also by using it level of NF- $\kappa$ B is reduced, <i>p53</i> expression is enhanced and the level of NF- $\kappa$ B, D1 is reduced.	(El-Ashmawy et al., 2018)
		2–10 mg/mL	Human colorectal, adenocarcinoma (HT29)	Stimulate the cell apoptosis, and functions of the caspase-9 gene and downcast the level of <i>ERK</i> , <i>Bcl-xL</i> , <i>KRAS</i> , etc	(Tahir et al., 2015)
5	6-gingerol	60,100,140 $\mu$ M	HeLa human (cervical adenocarcinoma cells)	It is responsible for the cell cycle, arrest in the resting phase of the cell ( $G_0/G_1$ -phase), and also it is responsible for the down-regulation of cyclins levels (Cyclins A, D1, and E1) and it enhances the caspase gene expression and stops the mTOR signaling pathway	(Zhang et al., 2017)
6	Ginger extract with alginate beads	50 mg/kg	Male specie (Wistar rats)	Responsible for enzymatic activity i.e NADH dehydrogenase and succinate dehydrogenase activity	(Deol & Kaur, 2013)
7	6-shogaol	10, 20, 40 $\mu$ M	LNCaP, DU145,PC3, human prostate (cancer cells)	Responsible for the activation and deactivation of different mechanisms in signaling pathways i.e it stops STAT3, NF- $\kappa$ B signaling pathway, and it downregulates the expression of <i>D1</i> , <i>c-Myc</i> , <i>Bcl2</i> , surviving, and it is also responsible for cell apoptosis.	(Saha et al., 2014)
8	Gingerol-6, shogaol-6, Gingerol-10, shogaol-10.	10,100 $\mu$ M	PC-3, human prostate cancerous cells.	Stops the multiplication of prostate cancer cell and suppress MRP1, GST $\pi$ expression.	(Liu et al., 2017)

### Gastric Cancer (Stomach Cancer)

Another health-related problem is Gastric cancer which is also known as stomach cancer. This cancer is the 5th most prevalent cancer and the 3rd most popular basis for cancer-related mortality worldwide. The affliction of gastric cancer is incredibly more in Asia, central and eastern Europe, and Latin America while in most western European countries and North America, it is not a more widespread cancer (Ferro et al., 2014).

Studies have shown that 6-gingerol and 6-shogaol, the active components of ginger, are involved in an

anticancer activity that shows a different mode of action against gastrointestinal cancer (Ishiguro et al., 2007; Prasad & Tyagi, 2015). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a cytokine that plays a role in apoptosis and thus is involved in the suppression of metastasis in the host (Thorburn, 2007). 6-Gingerol upregulates the TRAIL-induced apoptosis by enhancing the TRAIL-induced caspase-3/7 activation. Caspase 3/7 are proteases that are involved in cell death machinery (Ishiguro et al., 2007). 6-gingerol suppresses the activity of inhibitors of caspase-3/7 like cIAP1 and

thus promotes cell death (Prasad & Tyagi, 2015). On the other hand, 6-shogaol disturbs the intracellular level of tubulin, a protein in microtubules that performs many cellular functions including mitosis. This disturbing level of tubulin induces mitotic arrest and thus causes apoptosis of cancerous cells (Mollinedo & Gajate, 2003).

### **Pancreatic Cancer**

Medically, the malignant tumor that develops in epithelial cells of glandular structures in the pancreatic ductal cells is called Pancreatic cancer (Aier et al., 2019). Now, the frequency and deaths related to pancreatic cancer are rising every year universally, no matter in Japan, Europe, the US, or China (Hu et al., 2021). It has been observed that 6-Shogaol and 6-gingerol are the components of ginger that induce apoptosis and anti-proliferative activity in tumor cells (Li et al., 2012; Lu et al., 2014). 6-Gingerol inhibits the growth of pancreatic cancer cells by hindering the cell cycle at the G1 phase. Retinoblastoma is a protein that regulates the cell cycle. The phosphorylated retinoblastoma is mainly involved in controlling the cell cycle at G1 to S phase. It has been observed that 6-gingerol inhibits the phosphorylation of retinoblastoma after suppressing the expression of cyclin A and cyclin-dependent kinase and thus blocks the cell cycle of cancerous cells by not allowing it to enter in S phase (Park et al., 2006; Stone et al., 2011). It has also been noticed after experiments that normal cells like Human umbilical vein endothelial cells (HUVEC) are unaffected by ginger as compared to Panic-1 cells. Features of apoptosis-like an increase in subG1 cells, fragmentation of nuclei, and caspase-3 activation have been noticed by the ginger extract in pancreatic cancer cells. However, treatment of cells with ginger for a long time increases the formation of reactive oxygen species which causes autaptic cell death (Akimoto et al., 2015).

### **Prostate Cancer**

One of the most prevalent types of malignant cancer (after skin cancer) in males is prostate cancer, which is linked to the reproductive system. In 2012, world statistics stated that 15% of male cancers are prostate cancers as well as it is the 2<sup>nd</sup> major cause (after lung cancer) of deaths in males related to cancers (Khazaei et al., 2019).

The cell cycle is maintained by cyclin-dependent kinases (cdks). In prostate cancer cells, ginger exhibits its activity by decreasing the level of cyclin D1 and cdk4 levels. It also reduces the cyclin E levels which control the cell cycle through S-phase (Karna et al., 2012). Besides this, ginger stalls the cell cycle by increasing the level of p21 which is a cdks inhibitor (Besson et al., 2008). Ginger also activates caspase-3 which cleaves many cellular proteins such as PARP (Karna et al., 2012). PARP play role in many cellular activities including repairing of DNA. The inhibition of PARP

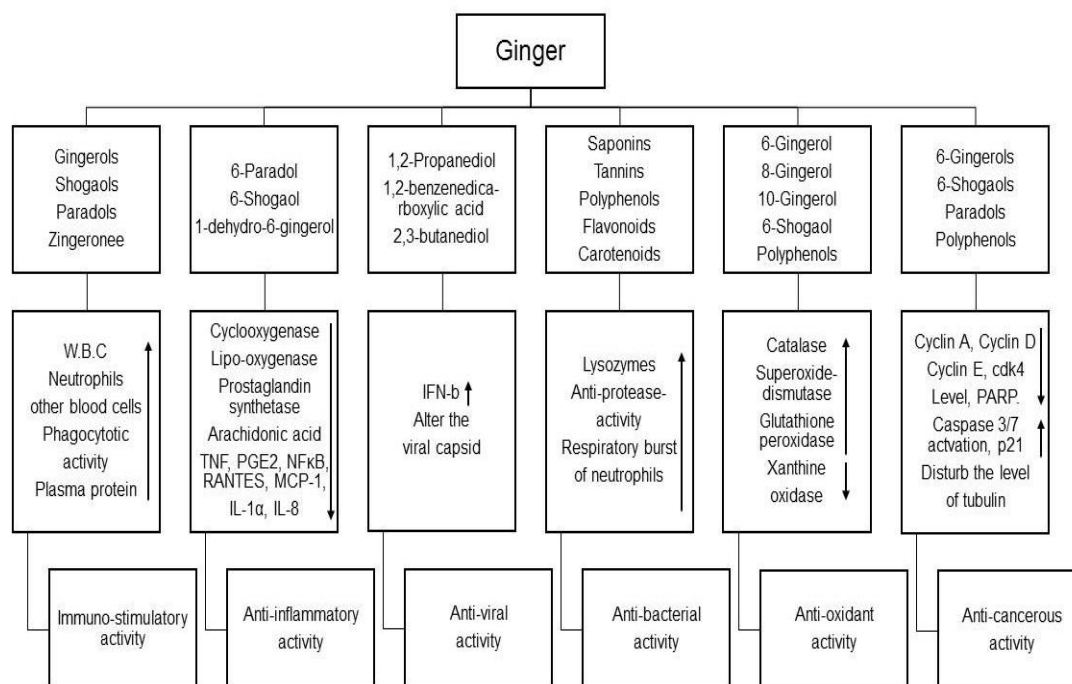
causes an increase in apoptosis due to a reduction in DNA repairing capacity (Morales et al., 2014). It concludes that ginger inhibits the growth of prostate cancer cells by apoptosis and by causing derangements in the cell cycle (Karna et al., 2012).

### **LIMITATIONS**

In addition to the medicinal effects of ginger, some side effects of ginger have also been observed. More bleeding has been observed during surgery in patients, who take regular doses of ginger (GHORBANIAN P., 2017). It means ginger is also unsafe for patients who have a bleeding disorder. Taking ginger more than 5 grams a day enhances the risk of side effects. Its high consumption causes skin rashes, mouth irritation, upset stomach, heartburn, and gas. In some cases, the consumption of ginger in combination with medicines also shows harmful effects (line, 2018; Mohan, 2017). It is even important to consult with a doctor before taking ginger while pregnant. Ginger is more treated as food rather than medicine therefore like drug manufacturers, the supplier of ginger does not show whether it is safe or not before selling in the market (Heitmann K1, 2013).

### **CONCLUSION**

Ginger is broadly used in ethnomedicines, having several bioactive compounds with apprehensible pharmacological actions. This review demonstrates the recent studies (under duration from 2001-2022) about the pharmacological actions of ginger and it's almost 44 bioactive compounds. In this study, ginger has unveiled immunostimulatory, anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, and anti-cancer effects by stimulating and inhibiting various mechanisms at the cellular, molecular and enzymatic levels. Our study provides a comprehensive overview of botanical authentication, experimental studies (in-vitro, in-vivo, and computational), pharmacological properties, and phytoconstituents profile of ginger along with their biological activities. Not only this, but this review has also recognized research deficiencies after analyzing the data (up to the year 2022) and has provided new pathways for future research. The present review is beneficial for the development of ginger-based ethnomedicines, for the treatment of the most common and serious health issues of the day with minimum cost and side effectiveness. The major components of ginger and their mechanism of action regarding immunostimulatory, anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, and anti-cancerous effects have been concluded in figure 7.



**Figure 7.** Showing the immunostimulatory, anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, and anti-cancerous effects of different components of ginger along their mechanism of action in a nutshell. (Upward arrow-indicating the increasing level, Downward arrow-indicating the decreasing level)

## Recommendations

We should consider any confounding factors when assessing the medicinal beneficial effects of ginger against chronic diseases. Increasing verification has depicted that different constituents of ginger have different molecular targets, metabolic pathways and bioactivities suggesting the significance of identifying the bioactive compounds and their biological mechanisms for a specific disease. Gingerols and shogaols have been observed to be very potent bioactive compounds of ginger regarding its biological significance. It has been noticed that a few rodent and in-vitro studies directly made comparisons between the bioactivities of shogaols and gingerols in limited disease models. It is suggested to compare the effectiveness of gingerols and shogaols in more models and thus develop unusual ginger formulations for particular diseases. To determine the optimum oral ginger composition will also enforce the study of the additive and synergistic effects of gingerols, shogaols and other bioactive compounds of ginger which will assist researchers to develop authentic standardization techniques to monitor the quality and composition of ginger formulations for specific disease. Once the unique ginger formulation is developed against a particular disease, the effective dose frequency and dose range should be established.

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**Authors Contribution:** **Haseeba Shahzad:** Conceptualization, design and directed the project, writing-review, editing, investigation, validation, data curation, data analysis, results interpretation, writing original draft and final approval. **Shaifa Saleem:** Writing-review, data analysis, critical revision and investigation. **Waqas Hanif:** Design, validation, critical revision, review editing, investigation, manuscript review and final approval. **Zareena Ali:** Writing-review, data analysis, and investigation. **Muhammad Zeeshan Ahmed:** Writing-review, validation, and critical revision. **Haq Nawaz:** Critical revision, validation and investigation. **Zelle Humma:** Review editing and critical revision. **Laraib Rana:** Writing-review and investigation. Laraib Rana contributed equally to this work with Muhammad Qamar Farid, Hajira Kalsoom, and Samavia Jaan.

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