Historical, Botanical and Medicinal Perspectives on Ginger (Zingiber officinale)

Adetutu Adewale*, Adegbola Peter Ifeoluwa, Owoade Abiodun Olusoji
Aborisade Abiodun Bukunmi and Oyekunle Olubunmi Simeon

1Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, PMB 4000, Ogbomoso, Nigeria.
2Department of Physiology, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, PMB 4000, Ogbomoso, Nigeria.

Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/JOCAMR/2021/v15i430274
(1) Dr. Aditi Singh, Amity University, India.
(2) Betül Gürünlü, Istanbul Technical University, Turkey.
(2) Kalpana, Dr. Ambedkar Institute of Technology for Handicapped, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/72871

Received 17 June 2021
Accepted 24 August 2021
Published 02 September 2021

ABSTRACT

Ginger is one of the most valuable culinary medicinal spice with inestimable economic uses. Because it is, a well acknowledged plant both in folkloric and advanced medicine, there are no paucity of information on the many important uses of ginger in the literature. In this review, we conveyed important details on the chemistry, pharmacology, toxicity and clinical uses of ginger. Our review of over 171 articles showed that ginger use has a worldwide coverage. Randomized clinical trial studies on ginger are most prominent on the alleviation of pregnancy-induced nausea and vomiting with fascinating outcome. In addition, the prospective use as anti-inflammatory, thrombolytic, and anti-diabetic agent were well noticed. Although the dependent on plant as source of drug in the search for disease remedy is premised on their acclaimed effectiveness and safety, available data have showed plants may possess some toxic potential, overall, our review showed that ginger might be safe with no adverse effects when investigated in normal rodent and human.

*Corresponding author: E-mail: aadetutu@lautech.edu.ng;
Keywords: Ginger; pharmacology; clinical trial; toxicity; medicinal uses.

1. INTRODUCTION

Ginger (Zingiber officinale) Roscows is a popular rhizome among the Asians and Africans [1]. It is a food spice often called ginger. This plant belongs to the Zingiberaceae family [2,3]. The Zingiberaceae plant family consists of 49 genera and 130 species. The Zingiber are about 80-90. Zinger is a Greek word derived from zingiberis that originate from the Sanskrit name of a spice called singibera. The latin name Zingiber means horn like shape and refers to roots that appears like deer’s antlers [4]. It is the plant’s underground stem or rhizome that is popularly known as ginger (Fig. 1) [5]. Ginger plant is herbaceous having a fibrous root and annual aerial parts of approximately 1.5 m. Rather than a real stem, ginger plant has a pseudo stem from which the leaves with short petioles egress [5]. The iconic ornamental features of Z. officinale are derived from the overlapping sheaths of its areal shoot especially at the base [5]. The rhizomes (ginger) are used for vegetative propagation and as food and medicine.

![Fig. 1. Picture showing the rhizome of ginger](image)

2. PROXIMATE AND PHYTOCHEMISTRY

2.1 Proximate Composition

The presence of important nutritional constituent in Z. officinale attests to its many nutritional benefits. According to [6], ginger is abundant in calcium (46.6±1.16%/g), sodium (31.2±0.15%/g), copper (25.5±0.3%/g), iron (25.5±0.6%/g), zinc (21.0±0.11%/g) and manganese (15.0±0.5%/g). The moisture content in ginger as reported by [7] was 68.71±0.86% while the ash, fat, fiber, protein and sugar content was 122.13±4.72, 157.91±2.62, 154.82±4.42, 150.06±9.24 and 69.85±1.74 mg/g respectively. Calcium was (68.28±0.75 mg/100g), iron (8.42±0.50 mg/100g), potassium (128.58±0.52 mg/100g), phosphorus (5.18±0.26), magnesium (102.67±0.69 mg/100g), and manganese (2.15±0.10 mg/100g) in a study reported by (Mushtaq et al., 2019). In another study, the mineral composition was higher than reported by [6]. The extracts was said to contain 25.70±1.27 mg/100g phosphorus, 40.96±1.95 mg/100g sodium, 37.34±1.18 mg/100g potassium, 35.66±1.09 mg/100g calcium, 19.60±0.62 mg/100g manganese, 4.06±1.99 mg/100g zinc and 1.44±0.07 mg/100g iron [8].

Furthermore, Onimawo et al. [9] reported sodium to be 7.32±0.02 mg/100g, zinc 4.99±0.04 mg/100g, iron 9.68±0.02 mg/100g and calcium 182.67±0.04 mg/100g in ginger powder. Taoheed et al. [10] reported 76.02±0.04% as the moisture content and 1.83±0.04%, 0.80±0.02%, 1.95±0.01%, 3.04±0.02% and 16.37±0.01% to be the crude protein, fat, fibre, ash and carbohydrate content respectively.

Similar to Taoheed et al., [10], the moisture content reported by Onimawo et al. [9] in ginger powder was 75.20±0.53%, however, the report on the ash (0.81±0.01%), crude protein (8.91±0.04%), crude fat (11.71±0.19%), crude fibre (1.38±0.50%) and CHO (2.01±0.23%) content showed disparity. The moisture content in the ethanol extract of ginger was 30.21±0.25%, crude protein 0.56±0.06%, crude fat 5.01±0.48%, crude fibre 0.96±0.05%, ash 5.03±0.10% and higher carbohydrate 84.24±0.85% content [11]. In a similar study, the methanol extract reportedly contain 6.45% moisture, 6.65% ash, 8.83% crude protein, 5.71% crude fat, 0.92% crude fibre and 71.46% carbohydrate [12].

According to Ogbuewu et al. [13], ginger powder contains 6.35±0.35% moisture, 5.45±0.46% crude protein, 6.57±0.98% ash and 10.36±0.67% crude fibre. (Wang et al. [14] reported the moisture content to be 68.71±0.80 mg/g, ash content to be 122.13±4.72 mg/g, fat content 57.91±2.62 mg/g, dietary fiber 154.82±4.42 mg/g, protein 150.06±9.24 mg/g and total sugar as 69.85±1.74 mg/g. Furthermore, amino acids constituents such as valine, arginine, lysine, leucine, isoleucine, histidine, phenylalanine, threonine, methionine, aspartate, serine, glutamate, proline, glycine, alanine, cysteine and tyrosine [8,15,13] have also been identified.

2.2 Phytochemistry

The phytochemical studies on the extract and powder showed different class of compounds...
with biological functions. Taoheed et al. [10] reported the presence of alkaloids, phenolics, flavonoids, terpenoids, tannins, saponins, cardiac glycosides. Quantitative assessment of the phenolic, saponin, tannin, oxalate, and phytin constituents revealed high saponin (4.01±0.07 mg/100g) low tannin (0.02±0.00 mg/100g), oxalate (0.26±0.0.02 mg/100g), phytin (0.28±0.01 mg/100g), content [12]. Adanlawo and Dairo, [8] conversely, reported 14.55 mg/100g as oxalate content, 28.83±0.73 mg/100g as phytin content and 0.26±0.06% as tannin content. Total phenolic was 14.27±0.28 mgGAE/g.d.w and flavonoid was 15.49±0.26 mg rutin/g.d.w. In all these studies, differences were observed in the location, period, and season of ginger collection. Therefore, the chemical and biological constituent of ginger is both season, region and temperature dependent.

As reported by Ghafoor et al. [16], total phenolic content of ginger varied with the drying method. The content was 919.44±0.02 using oven drying method, 732.64±0.03, 931.94±0.02 and 664.58±0.04 using microwave oven, freeze-drying and air drying method respectively whereas the content in fresh ginger was 43.75±0.01. In another study, Gabr et al. [17] reported 26.30 mg/100g and 9.13 mg/100g as the phenolic and flavonoid content for ginger extract.

Sequisterpenes and phenolic compounds are the major constituents in ginger. Phenolic compounds identified in ginger included gallic acid, 3,4-dihydroxybenzoic acid, catechin, 1,2-dihydroxybenzene, syringic acid, caffeic acid, rutin trihydrate, β-coumaric acid, trans-ferulic acid, apigenin 7-glucoside, resveratrol, quercetin, trans-cinnamic acid, naringenin, kaemferol and isorhamnetin. These compounds were more when ginger was oven dried than the fresh ginger and when the other drying methods were used for drying [16].

As reported by Gabr et al. [17], identified compounds using HPLC included; pyrrogallol, 4-amino-benzoic, 3-OH-Tyrosol, 6-gingerol Ellagic, 6-Shagoal, caffeine, Garlic Acid, chlorogenic, catechol, catechin and other phenolics in the ethanol extract of ginger.

More than 50 constituents mainly monoterpenoids have been characterized from ginger oil [18,19]. Gingerols are primarily responsible for the pungent odour of fresh ginger [20]. The gingerols are homologous series of phenols whereas in dry ginger, shogaols formed from gingerol during thermal processing constitute the pungent odour [21,20]. Generally, there are differences in the composition of dry and fresh gingers. The active constituents could be grouped as volatile essential oils and harsh phenol compounds (fragrant). Using gas chromatography, the volatile oils could easily be measured. In a study by Zhao and Xu. [22], seven additional compounds absent in fresh ginger were identified in dry ginger i.e linalool, terpinen-4-ol, 4-terpenol, citronellol, β-neral, δ-elemene and nery acetate whereas neral and trans-farnesial present in fresh ginger were absent in the dry ginger. It is believed that the unstable compounds in fresh ginger changes to more stable alcohols and phenols during drying process [23]. Some already identified compounds are showed in Table 1 [24,25].

Park et al. [26], reported isolated antimicrobial compounds characterized using Nuclear Magnetic Resonance (NMR) and ESI-MS in ginger rhizome. The compounds included 10-gingerol, 12-gingerol, galanolactone, 3,5-Diacetoxy-6-gingerdiol and 5-acetoxy-6-gingerol.

Table 1. Some identified compounds in the rhizome of Zingiber officinale

<table>
<thead>
<tr>
<th>Phenolic Acids in Ginger</th>
<th>Gingerol related compounds in Ginger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound name</td>
<td>Molecular formula</td>
</tr>
<tr>
<td>5-Acetoxy1,7-bis(4hydroxy-3-methoxyphenyl) heptan-3-one</td>
<td>C23H28O7</td>
</tr>
<tr>
<td>6-Gingerdiol</td>
<td>C17H28O4</td>
</tr>
<tr>
<td>6-Gingerol</td>
<td>C17H26O4</td>
</tr>
<tr>
<td>Methyl-6-gingerol</td>
<td>C18H28O4</td>
</tr>
<tr>
<td>3-Acetoxy6-gingerdiol/5-acetoxy-6-gingerdiol</td>
<td>C19H30O5</td>
</tr>
<tr>
<td>Diacetoxy-4-gingerdiol</td>
<td>C19H28O6</td>
</tr>
<tr>
<td>8-Gingerol</td>
<td>C19H30O4</td>
</tr>
</tbody>
</table>
Phenolic Acids in Ginger

<table>
<thead>
<tr>
<th>Phenolic Acids in Ginger</th>
<th>Ginger related compounds in Ginger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetoxy-6-gingerol</td>
<td>C19H28O5</td>
</tr>
<tr>
<td>Methyl-3-acetoxy-6-gingerdiol</td>
<td>C20H32O5</td>
</tr>
<tr>
<td>methyl-5-acetoxy-6-gingerdiol</td>
<td>C20H32O5</td>
</tr>
<tr>
<td>6-Shogaol</td>
<td>C17H24O3</td>
</tr>
<tr>
<td>Diacetoxy-6-gingerdiol</td>
<td>C21H32O6</td>
</tr>
<tr>
<td>1-Dehydro-6-gingerdione</td>
<td>C17H22O4</td>
</tr>
<tr>
<td>10-Gingerol</td>
<td>C21H34O4</td>
</tr>
<tr>
<td>Methyl diacetoxy-6-gingerdiol</td>
<td>C22H34O6</td>
</tr>
<tr>
<td>Diacetoxy-8-gingerdiol</td>
<td>C23H36O6</td>
</tr>
<tr>
<td>1-Dehydro-8-gingerdione</td>
<td>C19H26O4</td>
</tr>
<tr>
<td>Acetoxy-10-gingerol</td>
<td>C23H36O5</td>
</tr>
<tr>
<td>1-Dehydro-10-gingerdione</td>
<td>C21H30O4</td>
</tr>
</tbody>
</table>

![Chemical structures](image)

**Fig. 2.** Compounds characterized in ginger using NMR (a: Galanolactone, b: 10-gingerol, c: 12-gingerol)

### 3. ETHNO-MEDICINAL USES

Ginger has found diverse uses in folklore medicine. Throughout the world, ginger is historic in its use as cooking spice and medicine [27]. In Brazil, Australia, China, Africa, India, United States and the Middle East, the rhizome of ginger is cultivated for medicinal purposes [28,29,30]. According to El-Sayed and Mustafa, [31] ginger rhizome is widely used as a spice and condiments. In the Chinese Ayurvedic medicine, ginger is employed in treating conditions like stomachache, nausea, diarrhea, toothaches, rheumatism, cholera, and hemorrhage [4]. In a survey of culinary species in traditional medicinal system of Nkonkobe Municipality Eastern Cape, South Africa, the infusion and decoction of ginger rhizomes was reported for the treatment of respiratory disorder [31]. In Morocco, the infusion is also used in the management of respiratory infection [33]. The fresh root of ginger in Oyo State Nigeria is popularly used for the treatment of cough [34]. In a Southern State in Nigeria, the juice is used for the management of hypertension, as laxative, anti-cough, and anti-catarrh. In combination with *Salvia officinalis*, it is used for treating stomachache and cough [35].

### 4. BIOLOGICAL ACTIVITIES

#### 4.1 Pharmacological Activity of Ginger

Employing standard *in-vitro* and animal models, many pre-clinical studies have extensively reported arrays of biological, nutritional, medicinal, and pharmacological potential of different extracts, fractions, and bioactive principles from species of *Z. officinale* worldwide. Notable among these documented activities includes but not limited to anti-oxidants, anti-microbial, anti-cancer, anti-diabetic, anti-inflammatory, hepatoprotective, anti-obesity,
4.2 Antioxidant Activity of *Z. officinale*

Many human degenerative diseases develop and progress from prolonged oxidative stress. Reactive oxygen species characterized by the presence of unpaired electron are very reactive and therefore could interact with the cellular biomolecules such as protein, DNA and lipids and as a such rendering them unstable. These events are particularly reported in several human disease such as cancer, Alzheimer disease, atherosclerosis, diabetes, Parkinson’s disease and many more. [36,37]. In oxidative stress, the cellular anti-oxidative mechanism is over-whelmed which therefore result in the oxidative state [38]. To subvert the activity of reactive species in oxidative state, plant antioxidant compounds are being exploited for their potential as antioxidants. The antioxidant activity of ginger has been mainly credited to some of its secondary metabolites including zingerone, gingerols, shogaols and paradols.

The methanol extract of ginger was reported by Murugesan et al. [37] to prevent Reactive Oxygen Specie (ROS) induced damage and suppresses inflammatory response. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity and the lipid peroxidation inhibition by ginger was reported to occur in a concentration dependent manner. Significant values were reported for both the DPPH and lipid peroxidation inhibition by ginger. Both the aqueous and methanol extracts exhibited 50% inhibitory concentration (IC₅₀) of 128±9.85 µg/ml and 71.55±2.17 µg/ml respectively whereas the reducing antioxidant power assay compare favourably with ascorbic acid [39]. According to the study, the antioxidant efficacy correlates with polyphenols and flavonoid contents of ginger. In tandem with Bekkouch et al. [39], 20 µg/ml of ginger extracts showed DPPH inhibition reaching 90.1% [40]. Explorative study conducted on ginger and tumeric showed that although the two plants in isolation are rich in Phenolic and Flavonoids and possess significant DPPH inhibitory and FRAP antioxidants activity, the ginger-tumeric in combination possesses higher content of phenolics (103.39±6.58 mg of GAE/g) and flavonoids (4.27±0.05 mgCE/100g) and demonstrated improved FRAP (947.69±0.19 mg/100g) activity. [11].

In linoleic acid model, good antioxidant efficacy comparable to Buthylated Hydroxyl Toluene (BHT) was reported for ginger. Both ginger and quercetin inhibit hydroxyl radicals at lower temperature (37°C) than when the temperature was raised (80°C). The metal chelating properties of ginger was associated to its inhibitory activity against degradation of deoxyribose. Ginger extract inhibits metal-ion dependent OH radical generation and as a result is a powerful OH⁺ scavenger in competition with 2-deoxy-D-ribose [40]. Kinetic behaviour of 6-gingerol isolated from ginger on DPPH scavenging reaction reached steady state at 180 min with IC₅₀ value around 20 µM. Dehydrogingerdiones showed IC₅₀ value of 30 µM. Among the treated compounds, 4-shogaol showed the least inhibitory effect on oxidation of liposome. According to the study, the activity of the gingerols (6-gingerol. 8 and 10-gingerol) correlated with alkyl chain length of the gingerols whereas; the alkyl chain substituents had no influence on the activity. The author concluded that the scavenging effects and inhibitory effect on auto-oxidation of oils might have been contributed by the alkyl chain substituents, while the inhibitory effects against liposome peroxidation was somewhat contributed exclusively by the alkyl chain length. [41]. Comparative in-vitro antioxidant study of different solvents extracts of ginger reported by Shirin and Jamuna, [42], indicates that the antioxidant component and activity of ginger was solvent dependent. Higher antioxidant activity was observed in the alcoholic extracting media.

Hot water, ultrasonic assisted, alkaline solution, and enzyme assisted extraction of polysaccharide components of ginger yielded components with no difference in the quality but variation in the proportion. All the polysaccharides exhibited concentration dependent 2, 2’-azino-bis 3-ethylbenzthiazoline-6- sulfonic acid (ABTS) and DPPH radical scavenging activity at 5 mg/ml, scavenging abilities above 99% was reported for all the extracts obtained by different extraction methods indicating notable ABTS radicals scavenging ability. The alkaline solution extracted polysaccharide showed the strongest DPPH and O₂⁻ inhibition while the hot water extracted polysaccharide demonstrated the weakest activity. Similarly, the alkaline solution extract demonstrated the strongest hydroxyl radical
scavenging potential. Although all the extracts had the potential to act as hydroxyl radical scavenger, the extraction method had great impact on the degree of activity. According to the study, the activity difference was attributable to polysaccharides structure viz varied monosaccharide composition. Contrary to the order of potency against DPPH and superoxide radical, ferrous chelating activities was strongest in the enzyme assisted and ultrasonic assisted polysaccharides. This activity was associated with the high contents of COOH and C=O groups in the polysaccharide structures (Chen et al., 2020).

The submission of Oboh et al. [43], indicates that anti-oxidant property of ginger may contribute to its potency when used for the management of Alzheimer’s disease. According to the study, ginger extracts inhibits sodium nitroprusside and quinolinic acid induced lipid peroxidation in rat brain by decreasing the brain MDA contents.

Banji et al. [44] also submitted that zingerone regulated oxidative perturbations in irritable bowel disordered rats by inducing a marginal increase in the levels of glutathione peroxidase, superoxide dismutase, and glutathione, decreased the levels of malondialdehyde (MDA) and plasma corticosterone.

Banji et al. [44] concluded that zingerone could be regarded as a potential antioxidant agent by protecting colonic cells from lipid peroxidation via reduction in the formation of MDA. Elevation in the levels of superoxide dismutase (SOD) with zingerone indicates its ability to rapidly dismutate superoxide anion to less dangerous hydrogen peroxide.

Stoilova et al. [40] reported that alcohol extract of Z. officinale showed higher antioxidant activity than quercetin and butylated hydroxytoluene (BHT). In the same study, the extract’s ability to scavenge DPPH, inhibit peroxidation of linoleic acid at different temperature, and prevent formation of conjugated dienes was observed. Tohma et al. [49] reported the LCMS analysis and antioxidant activity of water and ethanol extracts of ginger. The availability of compounds such as pyrogallol, p-hydroxybenzoic acid, ferulic acid, vanillin, p-coumaric, gallic, ascorbic acid, caffeic and syringic acid might be credited for the observed radical quenching and reducing activity.

4.3 Antimicrobial Activity of Z. officinale

The use of compounds and substances of natural origin against microbial activity by mankind is an age long practice. Presently, there is increased attention on the utilization and development of natural products with antimicrobial potential due to increase in cases of microbial resistance and cost of allopathic drugs [45].

Ginger essential oil has been well reported with antimicrobial efficacy [46,47,170]. The antimicrobial study on essential oil and fractions obtained by hydro distillation method using resazurin micro-titer assay plate and micro dilution method revealed potent activity against drug resistant mycobacterium spp. The minimum inhibitory concentration for the oil and fractions was ranged between 31.35 to >250 µg/ml against non-tuberculosis mycobacterium. The fraction with y-cudesmol as the major components was most active against mycobacterium tuberculosis and non-tuberculosis mycobacteria [48]. Similar study on the essential oil of ginger from Adamawa region (Cameroon) obtained by steam distillation showed that only the ethylacetate fraction and the crude essential oil extract showed activity against tested microbial strain [49].

Susceptibility study on Helicobacter pylori showed that extracts of ginger have 14 mm inhibition zone while when combined with cinnamon, the inhibition zone was 20 mm. In addition, CagA gene expression profile of Helicobacter pylori, was used as indication for the inhibitory effect of the extracts. Combination of cinnamon and ginger caused expression inhibition of CagA gene to approximately 1.94 times than pre-exposure relative to the urec gene (a house keeping gene). The implication is that ginger in combination with cinnamon is useful as anti-ulcer agent [50].

Polyvinyl alcohol/gum arabic/chitosan (PM/GN/CS) composite films incorporated with ginger essential oil significantly inhibited the growth of Bacillus cereus, Escherichia, Salmonella typhimurium and Staphylococcus aureus demonstrating ginger essential oil PVA/GA/CS composite film as promising alternative wound dressing and food pack aging materials [51]. Ginger oils are well reported with antimicrobial activity. Sunilson et al. [52] documented the food preservative potential of various ginger extracts in inhibiting some food
borne pathogens such as *Escherichia coli*, *Salmonella enteriditis*, *Clostridium perfringens*, *Staphylococcus aureus*, *Campylobacter jejuni*, *Bacillus cereus*, *Saccharomyces cerevisiae*, *Hansenula anomala*, *Mucor mucedo* and *Candida albicans*. Zinger officinale root extract gold and zinc oxide (ZNO) nanoparticles were effective against bacteria strains (*Staphylococcus aureus*, *Klebsiella pneumonia*, *Staphylococcus spp.*, and *Listeria sp.*) [53]. Dietary supplementation and administration of zingerone has also been demonstrated to augment immunity and resistance against *Vibrio alginolyticus* [54]. Janaki et al. [55] also submitted that fungi species *Candida albicans* and *Penicillium notatum* were susceptible to ginger ZnO nanoparticles with increasing concentration. Biofilm formation of many species of gram positive and negative bacteria was inhibited by ethanol extract of ginger rhizome (Nikolic et al., 2014). Furthermore, antimicrobial evaluation of methanol extract of Nigerian Zinger officinale species against *Pseudomonas aeruginosa*, *Salmonella typhi*, *Klebsiella pneumonia*, *Staphylococcus aureus* and *Escherichia coli* revealed a significant zone of inhibition of the isolates in a dose dependent manner [56]. Synergistic activity of ginger ethanolic extract and clarithromycin inhibited 72% of 24 different strains of *Helicobacter pylori* (HP). It was concluded that the plant have potential to attenuate HP related gastroduodenal diseases (Nostrol et al., 2006). Fungicidal activity of methanol extract on some species (*Aspergillus niger*, *Penicillium digitatum*, *Helminthosporium solani* and *Mucor piriformis*) isolated from tomato has hitherto been documented. The extract significantly reduced radial growth and completely inhibited all pathogens at 25% concentration [57].

### 4.4 Anti-inflammatory Activity of Z. officinale

The use of ginger as an anti-inflammatory agent opened up researches; taking advantage of the knowledge for the management of inflammatory related diseases. Studies and reviews have given insight into the possibilities of anti-inflammatory compounds in the management of inflammatory related diseases [38,58].

Several in-vitro and in-vivo anti-inflammatory studies have established the pharmacological efficacy of the extracts and constituents of ginger targeting the signal pathways involved in inflammatory processes and inhibiting production of inflammatory molecules.

For instance, Lantz et al. [59] reported that ginger extracted with 1:1 dichloromethane and methanol inhibits prostaglandin E2 (PGE$_2$) production with an IC$_{50}$ value of 0.1 μg/ml similar to indomethacin. According to the report, synergy was observed in the activity of the extracts than when 6-, 8-, or 10-gingerol was tested individually. In addition, the gingerols subfraction significantly inhibits LPS (lipopolysacharrides) induced COX-2 gene expression. The authors concluded the extracts appeared to not only inhibit COX-2 enzyme activity but also alter its mRNA level suggesting two sites of action.

In an in-vitro study, using diene-conjugate, β-glucosidase, lipoxidase and hylaconidase inhibition assay, the ginger ethyl acetate and water extracts inhibited the enzymes more strongly than the ethanol, diethyl ether, and n-butanol extract. Active constituents of ginger viz 6-gingerol demonstrated stronger activity than 6-shogoal and 6-paradol [60].

Molecular mechanistic studies on ginger extract as an anti-inflammatory was assessed using Ninjirin-1, TRINFRI NADPH oxidase suppression and as soluble RAGE expression as indices. Ninj-1 was recently identified as a key player in inflammatory stimulation, it inhibition is associated with decreased expression of pro-inflammatory ICAM-1, VCAM-1 and MCP-1 [61,62]. Ginger extract induces decrease Ninj-1 expression and consequently lower VCAM-1 and MCP-1 expression.

The anti-inflammatory effect of ginger extract according to the study was established by decreasing TNFRI-gene expression. These potentials of ginger to suppress TNRI-gene expression is an important mechanism since TNF-TNFRI interaction result in the activation of NF-KB which further induces the expression of VCAM-1 and MCP-1 [62].

Ezzat et al., [63] assessed both the in-vitro and in-vivo anti-inflammatory activity of water, and ethanol extracts and compounds of ginger. Membrane stabilization, anti-lipoxygenase, protease inhibition, and protein denaturation assays were used in the in-vitro study while carrageenan induced rat paw oedema was used in the in-vivo study. Water extracts of ginger exhibited the strongest anti-lipoxygenase activity, which prompted the author to isolate 6-paradol,
6-shogoal, 6-gingerol, 8-gingerol, 5-gingerol, and 10-gingerol. Of all the isolated compounds 6-paradol, 6-shogoal, and 1-dehydro-6-gingerol exhibited potent activity in all the assays. In the in-vivo study, water extract of ginger ameliorated rat paw oedema in a dose dependent manner.

The extracts at 200 mg/kg also reduced PGE$_2$, TNF-α, IL-6 and monocyte chemo attractant protein-1 (MCP-1) production. The author concluded ginger extract demonstrated anti-inflammatory activity and this activity was mediated by inhibiting macrophage and neutrophils activation as well as negatively affecting monocyte and leukocyte migration which was evidenced by decline pro-inflammatory cytokines and chemokine levels. Contrary to the wide spread believe implicating phenolics compounds of ginger to its pharmacological activity, [64], was able to establish the role and contribution of the pungent-tasting gingerols and the aromatic essential oils to the anti-inflammatory potentials. According to the study, anti-inflammatory activity in arthritis female Lewis rats was suggested to be mediated by mimicking phytoestrogens, although the ginger essential oil only offered protection during the late stage of arthritis.

6-gingerol successfully suppressed inflammation in Balb/Mice by decreasing myeloperoxidase activity, TNF-α, IL-1β, COX-2, inducible nitric oxide synthase and nitrates [65].

In both in-vitro and in-vivo studies, ginger extracts have proven effective in improving the inflammatory disease; rheumatoid arthritis [37]. In rheumatoid arthritis patient, ginger supplementation improved the condition by decreasing disease manifestation through increase in FOxP3 gene expression and by decreasing RORyt and T-bet genes expression.

6-gingerol ameliorated allergic condition by suppressing infiltration of mast cells in mucosal and serum OVA specific IgE. The ginger compounds also inhibited the expression of Th1 and Th2 cytokines in ovalbumin sensitized spleen as well as suppressed anti-CD3-induced T-cell proliferation. The compound also inhibited the phosphorylation of MAP kinases, nuclear localization of c-fos and NF-kB and calcium release. Summily, 6-gingerol according to the study alleviate allergy by inhibiting T-cell activation and proliferation through decrease cytokine production viz-a-viz B-cell and mast cell activation arrest.

### 4.5 Anti-Diabetics and Anti-Obesity Activity of Z. officinale

Scientific studies on the efficacy of ginger have not only proven the potential to remediate hyperglycaemia but to also ameliorate complications associated with diabetes. With respect to this, studies are additionally focused on the anti-inflammatory, antioxidant and organ protective potentials of plant extracts in pharmacological investigation against diabetes.

In animal model, ginger extract have shown beneficial effects against hyperglycaemia in alloxan and streptozotooocin induced diabetes [66,67,68,69,70,71,72,73] via diverse mechanism including improved glucose utilization, glycolytic enzymes regulation and improvement of insulin sensitivity [69, 74].

In addition, ginger extracts and its compound; 6-shogoal attenuates painful diabetic neuropathy in mice by reducing Transient receptor potential vanilloid-1 (TRPV1) and N-methyl-D-aspartate receptor (NMDARZB) expression in the spinal cord [75]. Review study has laid down evidence on increased NF-kB; cytokine, oxidative stress level in diabetes whereas ginger and some of its phenolics suppress NF-kB pathway and related genes such as COX-2 viz-a-viz abrogating inflammation [75].

In human with type 2 diabetes, oral ginger supplementation improved the anthropogenic parameters but showed no difference in the NF-kB suppression compared with the placebo [77]. The glycemic status and lipid profile of obese patients with type 2-diabetes and supplemented with ginger powder improved significantly when the body mass index, fasting blood glucose, glycated hemoglobin, cholesterol, triglycerides, low density lipoprotein cholesterol, fasting insulin and insulin resistance index was observed to decrease in the patients. Additionally, high-density lipoprotein cholesterol beta cell functions, and insulin sensitivity index increased significantly compared to the placebo [78]. In a similar trial study, where 2 g ginger was given twice daily for 8 weeks to type-2-diabetes patient, in addition to the lipid profile level, clinical attachment loss (CAL), pocket depth, plaque index and bleeding on probing (BOP) showed no significant difference in the intervention group, whereas the HDL cholesterol and total antioxidant capacity increased significantly. Glycated hemoglobin, MDA, and fasting blood glucose decreased significantly [78]. The author
concluded supplementation using ginger may improve glycemic control, lipid profile and antioxidant status in type-2-diabetes. Ginger is also well established to have shown beneficial effects against obesity [80,81,82]. To understand the anti-obesity effect in tandem with ginger on energy metabolism, Wang et al. [7] assessed the glucose, lipid profile, heat production and respiratory exchange ratio in high fat diet fed mice. According to the study, ginger corrected the dysregulation observed in the levels of glycolytic and TCA cycle intermediates. The extract additionally prevent body weight gain by inducing browning of white adipose tissue through alteration in protein levels of some brown and beige adipocyte selective markers (SIRT1 and AMPK) [7]. Ginger also increased energy expenditure, type 1 muscle fiber and up regulated peroxisome proliferator activated receptor (PPARS) in skeletal muscle and liver.

The extract when used to pretreat cultured skeletal muscle myotubes, increased palmitate induced oxygen consumption, which is suggestive of increased cellular fatty acid catabolism. Overall ginger sustained the activity of PPARS pathway and improved exercise endurance capacity through increase in fat catabolism [83].

4.6 Anticancer Activity of Z. officinale

Ginger and its compounds have been studied for their ability to inhibit cancer in several cell type. 6-gingerol slightly affected viability whereas in synergy with TRAIL, it enhances viability and induces apoptosis, by increasing caspase 3/7 activation and inhibit NF-κB activation in gastric cancer cells. 6-shogaol unlike 6-gingerol reduces viability and showed no significant synergy with TRAIL in a caspase 3/7 independent manner. 6-shogaol also damaged the microtubules indicating that it induces mitotic arrest in gastric cancer cells [84].

In human breast cancer cell line, 6-gingerol decreases cell migration and motility and at 10 uM, reduces cell adhesion up to 16%. The matrix metalloproteinase (MMP-2) protein and mRNA expression level were also decreased with 6-gingerol treatment. Only the mRNA expression of MMP-9 was decreased in MDA-MB-231 human breast cancer cells lines [85]. On phorbol ester induced inflammation and skin tumor promotion in mice, 6-gingerol inhibited skin papillomagenesis and suppressed TPA-induced epidermal ornithine decarboxylase activity and inflammation [86]. According to Farombi et al. [87], 6-gingerol also delays tumorigenesis in benzo(a)pyrene and dextran sulphate sodium induced colorectal cancer in mice. Both methyl shogaol and 4-o-prenyl-[6]-gingerol retained highest inhibition for amino peptidase epoxide hydrolase activities in human colon cancer cells. Methyl shogaol was most potent against the cancer cells and demonstrated selective toxicity against the cells. 6-gingerol was also potent as inhibitor of leukotriene A4 hydrolase whereas 10-gingerol exhibited the highest LTA4H amino peptidase and epoxide hydrolase inhibitory activities. The compounds provided a lead as potential therapeutic agents for colorectal cancer [88]. Zhang et al., 2017 showed that 6-gingerol possesses some cytotoxic potentials against human cervical adenocarcinomas cells (HeLa). According to the study, 6-gingerol could stimulate cell cycle arrest, delay angiogenesis, and improve apoptosis. In a similar study, it also induces cell death, autophagy and caspase mediated apoptosis in Hela cells [89]. 10-gingerol on the other hand induces cell cycle arrest, and apoptosis in human and mouse mammary carcinoma cells.

4.7 Cardio and Neuro-Protective Activity of Z. officinale

Both protective and ameliorative effects of ginger and its compounds were reported on the heart and brain. In rat model of doxorubicin-induced cardio toxicity, ethanol extract of ginger decreased the mortality rate, improved the electrocardiogram (ECG) tracing, and reduced oxidative myocardial changes [90]. Similarly, Hassanien, [91] suggested sufficient intake of ginger by individuals continually exposed to isoproterenol. The suggestion was premised on the improved outcome observed with ginger treatments of rats induced with acute myocardial infarction (MI). Obvious reduction in serum lipid profile except HDL level and cardiac biomarkers including lactate dehydrogenase (LDH), creatinine kinase, and improved heart histology prompted Subbaiah et al. [92] to conclude ginger is potent in minimizing alcohol-induced myocardial damage.

In diabetes induced heart abnormality, ethanol extract of ginger significantly reduced the level of androgenic lipoprotein particles that are likely to be deposited in the arterial wall through decrease in ApoB that mediates lipid transport to tissues and restoration of ApoB/Apo A ratio. Apo A is involved in reverse cholesterol transport. In
addition, treatment of diabetic rats with ginger extract decreased to significant level plasma C-reactive proteins, inflammatory cytokines, Hcy and cathepsin G. Cathepsin G is known to induce fibrosis, neurosis and myocyte hypertrophy through conversion of angiotensin I to angiotensin II [93] which is a pro-fibrotic and pro-inflammatory mediator. According to the study, higher levels of leptin and apo A and lower levels of apo B, cathepsin G, CRP, and Hcy were not only observed with ginger treatment but also, improved structural heart architecture [94]. Dyslipidemic effects induced by Triton WR-1339 was mitigated by ethanol ginger extracts when [95] administered ginger at various doses to experimental rats. The extract normalizes the serum lipid profile, serum cardiac function biomarkers, serum endocrine hormones and the oxidative stress parameters of the rats.

6-gingerol combined with higenamine promotes heart function in doxorubicin-induced cardiotoxicity by down regulating serum heart indices and promoting mitochondrial energy metabolism [96]. In H9c2 cells ginger in combination with higenamine also promotes mitochondrial energy metabolism signaling pathway as its mode of alleviating doxorubicin induced cardiomyocyte toxicity. [97] submitted that ginger extracts exhibits pleiotropic cardiac effect in cardiac hypertrophy via a mechanism that involves peroxisome proliferator activated receptor (PPAR) antagonism. In a monosodium glutamate induced heart toxicity rats model, aqueous extracts of ginger preserved the heart tissue speculative to be via anti-oxidative process [98]. In isoprotenol-induced myocardial fibroses, 6-gingerol reduced oxidative stress by augmenting SOD, CAT, GSH and GSH/GSSG ratio and reducing MDA level, suppressing inflammation and decreasing the expression of TNF-α and IL-6. The number of apoptotic cells were also reduced by 6-gingerol with accompanying reduction in protein expression of Bax, caspase-3 and Bax/Bcl-2 ratio. The authors validated the protective effects of 6-gingerol against myocardial fibrosis in mice [99]. Han et al. [100] further reported 6-gingerol as a protective compound to the cardiomyocytes when it decreases the intracellular Ca²⁺ via the inhibition of L-type calcium channel and contractibility in rats.

Evidence on the neuro-protective potentials of ginger and its compounds are available for animal models during various disease condition. For instance, in diabetic rats, histological observation of the brain showed that ginger repaired neuronal damage and prevented brain damage [101]. The extracts also relieve neuronal injury induced by hyperglycemia by augmenting antioxidant defense mechanism of the brain [102]. Ginger extracts protect ischemic brain damage in rat model of focal cerebral ischemia induced by the occlusion of right middle cerebral artery. The extracts reduced cognitive deficits induced by focal cerebral ischemia, it increases neurons ‘density in hippocampus and improved the spatial memory presumably via enhancement of blood flow [103]. In different brain areas viz cerebellum, brainstem, stratum, cerebral cortex, hippocampus of male rats, ginger alleviate brain toxicity induced by monosodium glutamate. According to the study, decreased epinephrine, norepinephrine, dopamine, and serotonin observed with monosodium glutamate toxicity was significantly increased. According to the authors, this activity of ginger might be due to the inhibition of 5-serotonin-3-receptor and blockade of Ca²⁺ channel [104].

Oboh et al. [105] stated that ginger extracts showed marginal inhibitory activity against acetylcholine esterase activities in-vitro. The extracts reduced MDA contents of brain exacerbated by sodium nitopruisside and quinolinic acid. The authors submitted that ginger extract might be exerting anti-Alzheimer’s properties through inhibition of acetyl cholinesterase activities and prevention of lipid peroxidation in brain. In a similar in-vivo study, observation of the authors showed that ginger extracts give as protective and therapeutic regimen improved the behavior and rotorod and as well decreased acetylcholine esterase activities consequently increasing acetylcholine level in rats. The extracts demonstrated some level of protection against neurodegeneration occasioned by Alzheimer’s disease in rats. The extract lowered the expression of NF-kB, IL-1β and MDA but increased the expression of SOD and catalase in the brain of rats [106].

Ginger in combination with Cyperus rotundus enhanced the cognitive behaviour and demonstrated neuroprotective effects in rats. It was obvious from the study that the combined extract enhanced memory, decreased acetylcholinesterase activity, increased neuronal density, and decreased oxidative stress and activated PERK1/2 in the hippocampus of rats. From the parameters, it was concluded that the memory improvement by the combined extract
might be elicited via enhanced cholinergic function [107].

The active components of ginger, 6-shogaol, 6-gingerol and 6-paradol were reported with neuroprotective functions. 6-shogaol for instance demonstrated anti-neuroinflammatory activity by suppressing TNF-α and nitric oxide levels. The compound also prevents dopaminergic cell loss in Parkinson’s disease model [108]. Neuritogenic effects of 6-shogaol was elicited by inducing nerve growth factor (NGF) biosynthesis and as well by mimicking NGF. This activity in PC-12 cells involved activation of MEK/ERK1/2 and PI3K/Akt signaling pathway [109]. 6-gingerol on another end attenuates microglia-mediated neuroinflammation and ischemic brain injury. The compound suppressed the levels of IL-1β, IL-6 and inducible nitric oxide synthase (iNOS) activity in the infarct penumbra, by suppressing phosphorylation of serine threonine kinase (Akt)-mammalian target of rapamycin (mTOR)-signal transducer and activator of transcription 3 (STAT3) in lipopolysaccharide stimulated microglia [110]. Sapkota et al. [111] stressed the role of 6-shogaol and 6-paradol in ameliorating autoimmune encephalomyelitis (EAE). The compounds relieved the clinical symptoms of EAE indicating they could serve as protecting agent against neurodegeneration. Paradol exhibited the most effective activity in preventing inflammation without cytotoxicity in BV2 microglia stimulated with lipopolysaccharide. In-vivo, 6-paradol reduced brain damage in middle cerebral artery occlusion mice by reducing the number of cells expressing iNOS, TNF-α and preventing neurological deficit and ensuring neural cell survival [112].

4.8 Hepato-Protective Activity of *Z. officinale*

Liver as a major organ with key functions for the survival of animal is well studied because of its predisposition to chemical challenge. Models involving chemical challenge of the liver inflict damage and injury, which can now be treated with potential agents for bioactivity study. Ginger extracts is well studied for it protective effects against liver damage using different models.

Motawi *et al.* [113] studied the efficacy of ginger against liver fibrosis induced with carbon tetrachloride in rats. The results showed reduction in liver markers (LDH, acid phosphate, 5’-nucleotidase, AST, ALT, ALP, GGT, total bilirubin, and glucose-6 phosphatase) and increase in antioxidant markers (GSH and SOD). The authors inferred ginger as attractive candidate for the treatment of liver fibrosis. Fahmi *et al.* [114] showed that ginger essential oil was able to reverse the cytotoxic effects of diethyl nitrosamine on liver function. As evidenced by decrease serum activities of liver enzymes (ALT, AST, ALP and LDH), the protective effects was connected with antioxidant potentials of ginger.

In hyperglycemia induced liver damage, ginger extract insignificantly reversed the increase observed in AST and ALT activity. The extract additionally caused a near normal restoration of the liver architecture [115].

In lead induced hepato-toxicity in rats, ginger extract improved the liver antioxidant status and reversed the histological alterations including focal necrosis, infiltration of inflammatory cells, centrilobular swelling, hepatocyte vacuolization, parenchyma disorganization and dilation of inter-hepatocyte space [116].

Abd-Elrhman *et al.* [117] synthesized ginger nanoparticles and examined the hepato-renal protective effects in carbon tetrachloride (CCL4) challenged rats. Treatment with ginger and the nanoparticles significantly suppressed the serum liver markers, lowered inflammation through decrease in TNF-α and IL-1β and as well improved antioxidant status of rats. On another note, ginger protected against liver cirrhosis induced by CCL4 [118]. Other report on the hepatoprotective effects of ginger include that of [119,120,121,122,123,124,125,126,127,128,129] where the liver was challenged with various xenobiotics. In all the studies, ginger significantly reduced the serum level of liver biomarkers and improved the antioxidant status of the experimental animals.

4.9 Renal-Protective Activity of *Z. officinale*

Ginger demonstrated protective effects on the kidney when it diminishes kidney injury inflicted by chronic fructose exposure in rats. The extract suppressed excessive renal interstitial collagen deposit, fructose-stimulated monocyte chemo-attractant protein-1, and receptor chemokine receptor-2. It also down regulates macrophage accumulation markers; CD68 and F4/80, TNF-α, IL-6, TGF-β1, Plasminogen activator inhibitor and restored the down regulated ratio of urokinase-type plasminogen activator. From the
study, the protective function of ginger was by suppression of renal over expression of macrophage-associated pro-inflammatory cytokines [130].

Cadmium induced lipid peroxidation in kidney was reversed through the antioxidant activity of ginger in experimental rats [131]. Uz et al. [132] revealed the effects of dietary ginger on renal ischemia/reperfusion injury in rats. Ischemia-reperfusion injury is a major cause of kidney failure. Ginger supplementation however caused marked reduction of the histological manifestation of renal injury and improved the antioxidant status of the kidney. In another study, improved antioxidant and decreased oxidant level was demonstrated by ginger against alcohol induced renal damage [133,134]. Diabetic nephropathy was extinguished upon administration of ginger to diabetic rats by reduction in NF-κB activation, which in effect improved the histological view of the kidney of diabetic rats, treated with the extract [135]. The increase in leptin, creatinine, and TNF-α in obese rat was significantly lowered by ginger extracts. The antioxidant status of the rats was also improved alongside the renal histology. The authors concluded ginger extract could ameliorate the renal damage induced by high-fat diet [136]. From the study of Rodrigues et al. [137], the increase mRNA expression of TNF-α, IL-1β, IL-2, IFN-γ and gentamicin inflicted inflammatory cell infiltration and tubular degeneration of the kidney were attenuated in rats suffering from gentamicin-induced nephrotoxicity. Improved antioxidant status was also observed in the study. In another study, similar reduction in inflammatory cells, renal histological damage, and decrease serum level of kidney markers were exhibited by the ethyl acetate and fresh juice extract of ginger [138]. Cadmium induced nephrotoxicity reported by Akinyemi et al. [139] was abrogated by ginger essential oil when it prevents the alterations of renal markers and levels of cytokines (IL-6, IL-10, TNF-α, urease and creatinine) and as well inhibited the activity of adenosine deaminase in rats. In another report, ginger restored the renal function and improved the antioxidant status of rats intoxicated with cadmium [17]. Lead induced histological renal damage as well as glomerular and tubular degeneration occasioned by basement thickening; pycnotic nuclei, medullary vascular congestion, and moderate to severe fibrosis were reversed in rats when administered with ginger extract [140]. Ferrous sulphate administered to rat caused fractional increase in sodium excretion and lower creatinine clearance which was evidently reversed with ginger, thus, further support the renal protective function in metal induced renal toxicity [141]. The renal injury induced by carbon tetrachloride in rats, which was consequently ameliorated by ginger treatments, was evidenced from improved kidney function, inhibition of inflammatory mediators and normalization of kidney histological architecture [142].

4.10 Clinical Trial Studies on Ginger

Perhaps the most clinical trial study on ginger is on the alleviation of pregnancy induced nausea and vomiting. Nausea is a common complaint among women in the first half of pregnancy. Up to 85% pregnant women experience nausea in early pregnancy [143]. The characteristics severity of pregnancy nausea is similar to that caused by cancer chemotherapy. Although recovery is inevitable, nausea could place a great stress on pregnant women [145]. Encouraging results have been obtained from using ginger for the treatments of nausea and vomiting in pregnancy [146].

In a trial study in the health centers of University of Medical sciences of Qazvin, efficacy of ginger was investigated in comparison with Vit. B6. Ginger at a dosage of 250 mg showed no difference in terms of efficacy in reducing symptoms of pregnancy-induced nausea [144]. Another randomized-double blind placebo-controlled trial study in 120 woman less than 20 weeks pregnancy with morning sickness at a tertiary metropolitan teaching hospital gave positive outcome on the use of ginger. Ginger extracts at 125 mg equivalent to 101.5 g dried ginger four times per day for four days significantly reduced nausea experience compared to the placebo group. Interestingly, retching was also reduced to a level with ginger extracts with no obvious risk of fetal abnormalities [146]. Similar double blind randomized controlled trials at Thammasat Hospital, although with increased population of 170 pregnant woman and twice daily dosage of ginger (0.5 g) and dimenhydrinate (50 mg) for 7 days showed improved efficacy comparable to the control in reducing pregnancy induced nausea and vomiting only after three days of treatment with significant difference in the side effect of dimenhydrinate (77.64%) relative to ginger (5.85%) [147].
Further randomized studies also support the efficacy of ginger. Vutyavanch et al. [148], at 1 g of ginger for 4 days, Smith et al. [149] at 1.05 g ginger and 75 mg of vitamin B6 both reported decrease nausea in pregnant subject. Zick et al., [150], at 1 g and 2 g of ginger for 3 days on the other hand investigated chemotherapy induced nausea and vomiting in cancer patients. Although supplementation of ginger with a prebiotic provided no additional benefits for reduction of chemotherapy-induced nausea retching and, vomiting it may have positive benefits in decreasing fatigue and non-gastrointestinal events.

In a systemic review study on the effect of ginger on platelet aggregation in human subject, out of eight clinical trials, four reported reduced platelet aggregation with ginger while four reported no effects. Notable reasons for the difference in observation were attributed to period of study, dose of ginger and the characteristics of the subjects [151]. The authors concluded further research is necessary to clearly define the safety in patients at increased risk of bleeding.

Ginger showed superior efficacy in relieving abdominal distention when it was compared with group that received platelet capsules. Ginger in addition, improved the ability of subjects to eat better than the placebo. In this randomized double blind placebo controlled trial study on the efficacy of ginger in preventing abdominal distention in post cesarean section patients, the authors concluded ginger could serve as alternative medicine to relieve abdominal distention, as it has no serious side effects [152]. Oral supplementation with ginger in patients with type 2 diabetes showed positive effects on patients anthropogenic parameters whereas the mean difference of NF-KB concentration in comparison with the placebo was marginal [153].

In rheumatoid arthritis patients who received 1.5 g ginger powder daily for 12 weeks or placebo, FoxP3 genes was significantly increased while RORyt and T-bet genes expressions were decreased significantly. Ginger also reduced the disease activity score in the patients [154]. Systemic review and meta-analysis of randomized controlled trials of the effects of ginger supplementation on inflammation and oxidative stress biomarkers in adults conducted by [155] shows the efficacy of ginger supplementation on attenuating C-reactive protein, IL-6 and TNF-α levels as well as improving oxidative status. The result supports the anti-oxidative and anti-inflammatory efficacy of ginger and its promising potential as adjuvant when used with conventional oral drug to mitigate inflammation and oxidative stress.

The pharmacokinetics of 6-, 8-, and 10-gingerols and 6-shogaol as well as their glucuronide and sulphate metabolites in human plasma showed that low level of 10-gingerol and 6-shogaol were detected in human plasma whereas majority of the 6-, 8-, and 10-gingerol and 6-shogaol existed in the glucuronide or sulphate conjugates after oral dosing of 2 g ginger extracts. The half-lives of all the compounds and their metabolites were between 1 and 3 hours in human plasma [156].

5. TOXICITY OF GINGER

Although the dependent on plant as source of drug in the search for disease remedy is premised on their acclaimed effectiveness and safety, available data have showed plants may possess some toxic potentials. Ginger as a Specie commonly used for culinary and medicinal purposes are considered safe [157, 158, 159, 160, 161, 162]. For the fact that ginger is commonly consumed, the safety when repeatedly consumed needs to be ascertained.

In an experimental study reported by Idang et al., [163] acute toxicity study on ginger showed that ginger fixed oil (hexane extract) at 0.2 ml/kg caused death of experimental rats as well as the essential oil. In the experiment, convulsion, paralysis, and decreased motor actively were observed in the experimental animals. Sub-chronic toxicity assessment of ginger showed that the fixed oil have potentials to induce array of toxicities; cellular and organ toxicities [163]. Although both the essential and fixed oil had no toxicological effects on hematological parameters of rats, the fixed oil have some liver toxicity effects as well as reversible toxicity on the spleen. Conversely, ethanol extracts of ginger showed no acute toxic effects on rats up to 5g/kg for 15 days [164]. In a 35 day safety assessment of ginger in rats, Rong et al. [165] reported that ginger powder up to 2000 mg/kg/day caused no acute toxic effects on both male and female rats, as well as all animals survived with no clinical sign observed over the duration of the experiment. On the hematological parameters, no significant difference was observed with the control. No changes were also observed in the liver, renal, and testicular functional parameters. In addition, lipid profile parameters of experimental rats were not affected, therefore
ginger has no interference with platelet, glucose and lipid metabolism under physiological condition.

Similarly, 13 weeks administration of ginger oil produced no mortality in male and female rats. No changes were observed in the locomotors activity and behavior all through the 13 weeks of study. No negative effect were observed in the weight, food and water intake of rats as well as in the liver, kidney, brain, lungs, stomach, and spleen weight of rats. The hematologic parameters were normal, no significant changes in hepatic function, both electrolytes and biochemical renal function markers of rats were within the normal range. The hepatobiliary function and lipid metabolism profile was intact. It was concluded that the ginger oil was nontoxic to both male and female rats up to 500 mg/kg [166].

According to Otunola and Afolayan, [167], blend of ginger with garlic and cayenne pepper as well produced no toxic effects in rats. It was reported that a single oral dose of the aqueous extract of spice mixture up to 500mg/kg produced no obvious adverse effects in rats. Subacute administration of the extracts to animals for 28 days showed no toxic effects on the hematological parameters. No alteration was observed in the renal, liver, and cardiac functions. The lipid profile of the experimental animals was also greatly improved indicating the combined spice extracts were safe.

6. CONCLUSION

We review over 171 articles on the toxicity, folkloric and medicinal uses of ginger. It was observed that ginger is a very useful spice with significant medicinal value. Our review showed that ginger contains phytochemical constituents, which have good anti-inflammatory, thrombolytic, and anti-diabetic properties. In addition, randomized clinical trial studies on ginger are most prominent on the alleviation of pregnancy-induced nausea and vomiting of which fascinating outcome were reported. Overall, our review showed that ginger might be safe with no adverse effects therefore, it use can be encouraged for the management of inflammatory and oxidative stress related diseases, it could as well serve as source of drug for the management of human diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


48. Baldin VP, Scodro RBL, Fernandez CMM, Ieque AL, Caleffi-Ferracioli KR, Siqueira VLD, de Almeida AL, Goncalves JE, Cortez DAG, Cardoso RF. Ginger essential...


60. Nile SH, Park SW. Chromatographic analysis, antioxidant, anti-inflammatory, and xanthine oxidase inhibitory activities of ginger extracts and its reference compounds. Industrial Crops and Products. 2015;70:238–244.


65. Ajayi BO, Adedara IA, Farombi EO. 6-Gingerol abates benzo[a]pyrene-induced colonic injury via suppression of oxido-inflammatory stress responses in BALB/c


81. Misawa K, Hashizume K, Yamamoto M, Minegishi Y, Hase T, Shimotoyodome A. Ginger extract prevents high-fat diet-induced obesity in mice via activation of the peroxisome proliferatoractivated


Neuroprotective and cognitive benefits of ginger in diverse rodent models and in human neuronal cells.


134. Ramudu MK, Kesireddy N, Chen C, Kuo CH, Kesireddy SR. Ginger Feeding Protects Against Renal Oxidative Damage


