Journal of Complementary and Alternative Medical Research

15(4): 44-67, 2021; Article no.JOCAMR.72871
ISSN: 2456-6276

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

Adetutu Adewale[1*], Adegbola Peter Ifeoluwa [1], Owoade Abiodun Olusoji[1], Aborisade Abiodun Bukunmi [1] and Oyekunle Olubunmi Simeon [2]

[1]Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, PMB 4000, Ogbomoso, Nigeria.
[2]Department 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
Editor(s):
(1) Dr. Aditi Singh, Amity Univesity, India.
Reviewers:
(1) 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

Review Article

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}* Roscoes 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 Zingiberacea plant family consists of 49 general and 130 specie. The Zingibers are about 80-90. Zingiber 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

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 0.98±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, caffenic 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-Shagaol, caffeine, Garllic Acid, chloragenic, 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-terpeneol, citronellol, β-neral, δ-elemene and nery acetate whereas neral and trans-farnesal 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 Fig. 2.

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

Phenolic Acids in Ginger		**Gingerol related compounds in Ginger**	
Compound name	Molecular formula	Compound name	Molecular formula
5-Acetoxy1,7-bis(4hydroxy-3-methoxyphenyl) heptan-3-one	C23H28O7	[8]-Gingerol	C19H30O4
6-Gingerdiol	C17H28O4	[10]-Gingerol	C21H34O4
6-Gingerol	C17H26O4	[8]-Shogaol	C19H28O3
Methyl-6-gingerol	C18H28O4	[10]-Shogaol	C21H32O3
3-Acetoxy6-gingerdiol/5-acetoxy-6-gingerdiol	C19H30O5	(3*S*,5*S*)-[6]-Gingerdiol	C17H28O4
Diacetoxy-4-gingerdiol	C19H28O6	(3*R*,5*S*)-[6]-Gingerdiol	C17H28O4
8-Gingerol	C19H30O4	(3*S*,5*S*)-[8]-Gingerdiol	C19H32O4

Phenolic Acids in Ginger		Gingerol related compounds in Ginger	
Acetoxy-6-gingerol	C19H28O5	(3*R*,5*S*)-[8]-Gingerdiol	C19H32O4
Methyl-3-acetoxy6-gingerdiol/ methyl-5-acetoxy-6-gingerdiol	C20H32O5	(3*S*,5*S*)-[10]-Gingerdiol	C21H36O4
6-Shogaol	C17H24O3	(3*R*,5*S*)-[10]- Gingerdiol	C21H36O4
Diacetoxy-6-gingerdiol	C21H32O6	[10]-Gingerdiol 3,5-diacetate	C25H40O6
1-Dehydro-6-gingerdione	C17H22O4		
10-Gingerol	C21H34O4		
Methyl diacetoxy6-gingerdiol	C22H34O6		
Diacetoxy-8-gingerdiol	C23H36O6		
1-Dehydro-8-gingerdione	C19H26O4		
Acetoxy-10-gingerol	C23H36O5		
1-Dehydro-10-gingerdione	C21H30O4		

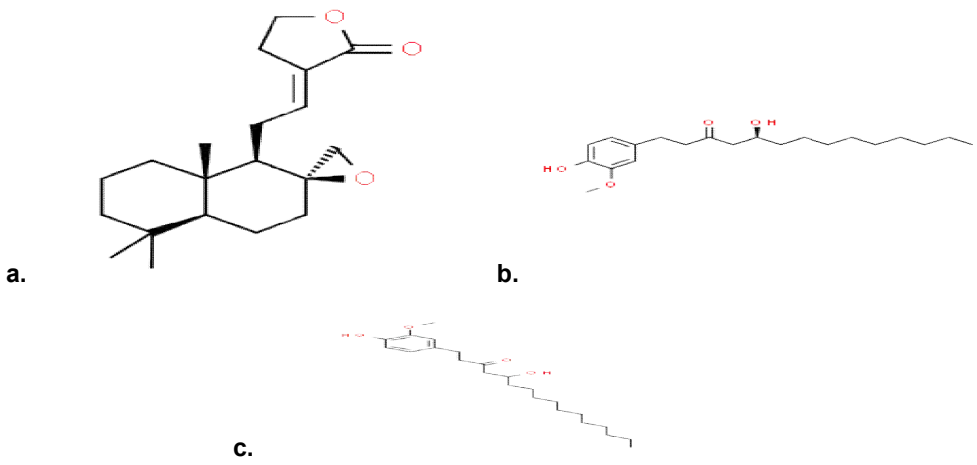

Fig. 2. Compounds characterized in ginger using NMR (a: Galanolactone, b: 10-gingerol, c: 12-gingerol)

3. ETHNO-MEDICINAL USES

Ginger has found divers uses in folklorie 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 spice and condiments. In the Chinese Ayuvedic 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 *Saliva 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, hepato-protecive, anti-obesity,

anti-platelet aggregation, neuro-protective and renal-protective. Therefore, there are no literature shortfalls on the importance of *Z. officinale* and these would be discussed elaborately below.

4.2 Antioxidant Activity of *Z. officinale*

Many human degenerative diseases develop and progresses from prolong 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 (IC_{50}) 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 possess 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 quercetine inhibit hydroxyl radicals at lower temperature (37^oC) than when the temperature was raised (80^oC). 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 IC_{50} value around 20 µM. Dehydrogingerdiones showed IC_{50} 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 O_2^- 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*. (2016) 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 perfringes, Staphylococcus aureus, Campylobacter jejuni, Baceillus cereus, Saccharomyces cerevisae, 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 Penicillum 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 ethanol 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 E_2 (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, lipooxidase and hyalucronidase inhibition assay, the ginger ethylacetate 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 Ninjurin-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-lipooxygenase, 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 potential. 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 nitrides [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. Summarily, 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 hyperglycacmia but to also ameliorate complications associated with diabetics. 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 streptozotoocin 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-shogaol 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), pucket depth, plague 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 (SIRTI 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 it 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-kB 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 shogoal 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 (HcLa). 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 myocardiac 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]. Dyslipidemicc 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 Ca^{2+} 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-serotonins-3-receptor and blockade of Ca^{2+} 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 nitoprusside 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 rotarod 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 neuroproteective 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)-mammalial 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-kB 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 856 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. Vutyavanich *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 prepitant 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 relive 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-shogoal 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 hepatobilliary 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

1. El-Sharaky AS, Newairy AA, Kamel MA, Eweda SM. Protective effect of ginger extract against bromobenzene-induced hepatotoxicity in male rats. Food Chem. Toxicol. 2009;47(7):1584–1590.
2. Baldin VP, Regiane Bertin de Lima Scodro, Carla Maria Mariano Fernandez, Andressa Lorena Ieque, Katiany Rizzieri Caleffi-Ferracioli, Vera Lucia Dias Siqueira, Aryadne Larissa de Almeida, José Eduardo Gonçalves, Diógenes Aparício Garcia Cortez, Rosilene Fressatti Cardoso. Ginger essential oil and fractions againstMycobacteriumspp. Journal of Ethnopharmacology. 2019;244:112095.
3. AlAskar A, Shaheen NA, Khan AH, AlGhasham N, Mendoza MA, Matar DB, Gmati G, AlJeraisy M, AlSuhaibani A, Effect of Daily Ginger Consumption on Platelet Aggregation, Journal of Herbal Medicine; 2019.
4. Shahrajabian MH, Sun W, Cheng Q. Pharmacological Uses and Health Benefits of Ginger (Zingiber officinale) in Traditional Asian and Ancient Chinese Medicine, and Modern Practice. Not Sci Biol. 2019;11(3):309-319.
5. Habtemariam S. The chemical and pharmacological basis of ginger (Zingiber officinale Roscoe) as potential therapy for diabetes and metabolic syndrome; In: Habtemariam, S. Medicinal Foods as Potential Therapies for Type-2 Diabetes and Associated Diseases. 1st Ed. Elsevier. Academic Press 2020; 2019.
6. Yasodai R, Kavimani M, Prabhu K. Phytochemical analysis and quantitative nutritional evaluation of *Zingiber oficinale* roscae (Ginger). International Journal of Research In Pharmaceutical Sciences. 2020;11(2):2090-2094.
7. Wang J, Li D, Wang P, Hu X, Chen F. Ginger prevents obesity through regulation of energy metabolism and activation of browning in high-fat diet-induced obese mice. Journal of Nutritional Biochemistry. 2019;70:105–115.

8. Adanlawo TG, Dairo FAS. Nutrient and Anti-nutrient Constituents of Ginger (*Zingiber officinale,* Roscoe) and the Influence of its Ethanolic Extract on Some Serum Enzymes in Albino Rats. International Journal of Biological Chemistry. 2007;1(11):38-46.
9. Onimawo IA, Esekheigbe A, Okoh JE. Determination of Proximate and Mineral Composition of Three Traditional Spices". Acta Scientific Nutritional Health. 2019;3.7 :111-114.
10. Taoheed A, Tolulope AA, Saidu AB, Odewumi OG, Sunday RM, Usman M. Phytochemical Properties, Proximate, and Mineral Composition of Curcuma longa Linn. and Zingiber officinale Rosc.: A Comparative Study. Journal of Scientific Research & Reports. 2017;13(4):1-7.
11. Mushtaq Z, Nadeem MT, Arshad MU, Saeed F, Ahmed MH, Ul-Ain HB, Javed A, Anjum FM, Hussain S. Exploring the biochemical and antioxidant potential of ginger (Adric) and turmeric (Haldi), International Journal of Food Properties. 2019;22(1):642-1651.
12. Ugwoke CEC, Nzekwe U. Phytochemistry and Proximate Composition Of Ginger (Zingiber officinale). Journal of Pharmaceutical and Allied Sciences. 2010;7(5):118 –1187.
13. Ogbuewu, IP, Jiwuba PD, Ezeokeke, CT, Uchegbu, M.C.. Okoli IC, Iloeje MU.. Evaluation of Phytochemical and Nutritional Composition of Ginger Rhizome Powder. Int'l Journal Of Agric. And Rural Dev. 2014;17(1):1663-1670 .
14. Wang J, Li D, Wang P, Hu X, Chen F. Ginger prevents obesity through regulation of energy metabolism and activation of browning in high-fat diet-induced obese mice. Journal of Nutritional Biochemistry. 2019;70:105–115.
15. Olubunmi BA, Seun FA, Funmilayo TA. Food Value of Two Varieties of Ginger (Zingiber officinale) Commonly Consumed in Nigeria. Nutrition. 2013:1-5.
16. Ghafoor K, Juhaimi FA, Özcan MM, Uslu N, Babiker EE, Ahmed IAM. Total phenolics, total carotenoids, individual phenolics and antioxidant activity of ginger (Zingiber officinale) rhizome as affected by drying methods. LWT - Food Science and Technology. 2020;126:1-7.
17. Gabr SA, Alghadir AH, Ghoniem GA.. Biological activities of ginger against cadmium-induced renal toxicity. Saudi Journal of Biological Sciences. 2019;26: 382–389.
18. Langner E, Greifenberg S, Gruenwald J. Ginger: history and use. Advances in Therapy. 1998;15(1):25-44.
19. Evans WC. Ginger. Trease and Evans Pharmacognosy, 15th ed. WB Saunders, Edinburgh. 2002;277–280.
20. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): A review of recent research. Food and Chemical Toxicology. 2008;46:409–420
21. Wohlmuth H, Leach DN, Smith MK, Myers SP. Gingerol content of diploid and tetraploid clones of ginger (*Zingiber officinale* Roscoe). J. Agric. Food Chem. 2005;53:5772–5778.
22. Zhao AH, Xu HI. Differences in volatile oils and the phenol compounds in the fresh and dried gingers. In: 27th International Horticultural Congress and Eshibition, 13-19 August, 2006, Seoul, Korea. 2006;62 (Abstract)
23. Qin F, Xu H. Active compounds in gingers and their therapeutic use in complimentary medication. Medicinal and Aromatic Plant Science and Biotechnology. 2008;2(2):72-78.
24. Nishidono Y, Saifudin A, Nishizawa M, Fujita T, Nakamoto M, Tanaka M. Identification of the Chemical Constituents in Ginger (Zingiber officinale) Responsible for Thermogenesis. Natural Product Communications. 2018;13(7): 869-873.
25. Asamenew G, Kim H, Lee M, Lee S, Kim YJ, Cha Y, Yoo SM, Kim JB. Characterization of phenolic compounds from normal ginger (Zingiber officinaleRosc.) and black ginger (Kaempferia parvifloraWall.) using UPLC–DAD–QToF–MS. European Food Research and Technology. 2019;245: 653–665.
26. Park M, Bae J, Lee D. Antibacterial Activity of [10]-Gingerol and [12]-Gingerol isolated from Ginger Rhizome against Periodontal Bacteria. Phytother. Res. 2008;22: 1446–1449.
27. Nour, AH, Yap SS, Nour AH. Extraction and chemical compositions of Ginger (Zingiber officinal Roscoe) essential oils as cockroaches repellent. Australian Journal of Basic and Applied Sciences. 2017;11(3):1-8.

28. Langner E, Greifenberg S, Gruenwald J Ginger: history and use. Adv. Ther. 1998;15:25–44.
29. Blumenthal M, Goldberg A, Brinckmann J. Herbal medicine: expanded c ommission E monographs. Austin TX: American Botanical Council; Newton MA: Integrative Medicine Communications. 2000;153-159.
30. Yadav S, Sharma PK, Aftab AM. Ginger medicinal, uses, and benefits. European Journal of Pharmaceutical and Medical Research. 2016;3(7):127-135.
31. El Sayed SM, Moustafa RA. Effect of combined administration of ginger and cinnamon on high fat diet induced hyperl ipidemia in rats. Journal of Pharmaceutical, Chemical and Biological Sciences. 2016;3(4):561-572.
32. Asowata-Ayodele AM, Afolayan AJ, Otunola GA. Ethnobotanical survey of culinary herbs and spices used in the traditional medicinal system of Nkonkobe Municipality, Eastern Cape, South Africa. South African Journal of Botany. 2016;104(2016):69–75.
33. Fatima-Zahra E, Fouzia RF, Abdelilah R. Ethnobotanical Study of Medicinal Plants Used in Traditional Medicine in the Province of Sidi Kacem, Morocco. Asian J Pharm Clin Res. 2017;10(1):121-130
34. Ariyo OC, Usman MB, Olorukooba MM, Ariyo MO, Suleiman R, Aasa OS, Adetunji AJ, Oni OB. Ethnobotanical Survey of Medicinal Plants Used in the Treatment of Cough in Akinyele Local Government Area, Oyo State, Nigeria. European Journal of Medicinal Plants. 2020;31(8):101-113.
35. Ajibesin KK, Bala DN, Umoh UF. Ethno medicinal survey of plants used by the indigenes of Rivers State of Nigeria. Pharmaceutical Biology. 2012;50(9):1123-1143
36. Adegbola PI, Adetutu A, Olaniyi TD. Antioxidant activity of Amaranthus species from the Amaranthaceae family-A Review. South African Journal of Botany. 2020;133:111-117.
37. Murugesan S, Venkateswaran MR, Jayabal S, Periyasamy S. Evaluation of the antioxidant and anti-arthritic potential of Zingiber officinale Rosc. By in-vitro and in-silico analysis. South African Journal of Botany. 2020;130(2020):45-53.
38. Adegbola P, Aderibigbe I, Hammed W, Omotayo T. Antioxidant and anti-inflammatory medicinal plants have potential role in the treatment of cardiovascular disease: a review. (Am J Cardiovasc Dis. 2017;7(2):19-32.
39. Bekkouch Q, Harnafi M, Touiss I, Khatib S, Harnafi H, Alem C, Amrani S. In Vitro Antioxidant andIn Vivo Lipid-Lowering Properties of Zingiber officinaleCrude Aqueous Extract and Methanolic Fraction: A Follow-Up Study. Evidence-Based Complementary and Alternative Medicine. 2019:1-13.
40. Stoilova I, Krastanov A, Stoyanova A, Denev P, Gargova S. Antioxidant activity of a ginger extract (Zingiber officinale). Food Chemistry. 2007;102:764–770.
41. Masuda Y, Kikuzaki H, Hisamoto M, Nakatani N. Antioxidant properties of gingerol related compounds from ginger. Bio Factors. 2004;21: 293–296.
42. Shirin APR, Jamuna P. Chemical composition and antioxidant properties of ginger root (Zingiber officinale). Journal of Medicinal Plants Research. 2010;4(24):2674-2679.
43. Oboh G, Ademiluyi AO, Akinyemi AJ. Inhibition of acetylcholinesterase activities and some pro-oxidant induced lipid peroxidation in rat brain by two varieties of ginger (Zingiber officinale). Experimental and Toxicologic Pathology. 2012;64: 315– 319.
44. Banji D, Banji OJF, Pavani B, Kranthi Kumar C, Annamalai AR. Zingerone regulates intestinal transit, attenuates behavioral and oxidative perturbations in irritable bowel disorder in rats, Phytomedicine. 2014;21(4):423-429.
45. Emad MA. Plants: An alternative source for antimicrobials. Journal of Applied Pharmaceutical Science. 2011;01(06): 16-20.
46. Mesomo MC, Corazza ML, Ndiaye PM, Dalla Santa OR, Cardozo L, Scheer A de P. Supercritical CO2 extracts and essential oil of ginger (Zingiber officinaleR.): chemical composition and antibacterial activity. J. Supercrit. Fluids. 2013;80: 44–49.
47. Bellik Y. Total antioxidant activity and antimicrobial potency of the essential oil and oleoresin of *Zingiber officinale* Roscoe. Asian Pacific J. Trop. Dis. 2014;4:40–44.
48. Baldin VP, Scodro RBL, Fernandez CMM, Ieque AL, Caleffi-Ferracioli KR, Siqueira VLD, de Almeida AL, Gonçalves JE, Cortez DAG, Cardoso RF. Ginger essential

oil and fractions against Mycobacterium spp. Journal of Ethnopharmacology. 2019;244:1-7.
49. Emmanuel T, Aristide B, Leopold T, Benoît NM, Joseph MT. Phytochemical screening, chemical composition and antimicrobial activity of Zingiber officinale essential oil of Adamaoua region (Cameroon). Journal of Chemical and Pharmaceutical Research. 2013;5(7):296-301.
50. Azadi M, Ebrahimi A, Khaledi A, Esmaeili D. Study of inhibitory effects of the mixture of cinnamon and ginger extracts on cagA gene expression of Helicobacter pylori by Real-Time RT-PCR technique. Gene Reports. 2019;17:1-7.
51. Amalraj A, Haponiuk JT, Thomas S, Gopi S. Preparation, characterization and antimicrobial activity of polyvinyl alcohol/gum arabic/chitosan compositefilms incorporated with black pepper essential oil and ginger essential oil. International Journal of Biological Macromolecules. 2020;151:366–375
52. Sunilson JAJ, Suraj R, Rejitha G, Anandarajagopal K, Anita AV, Kumari G, Promwichit P. In-vitro Antimicrobial Evaluation of *Zingiber officinale*, Curcuma longa and Alpinia galangal Extracts as Natural Food Preservatives. American Journal of Foof Technology. 2009;4(5):192-200.
53. Velmurugan P, Anbalagan K, Manosathyadevan M, Lee K, Cho M, Lee SM, Park JH, Oh S, Bang K, Oh B. Green synthesis of silver and gold nanoparticles using *Zingiber officinale* root extract and antibacterial activity of silver nanoparticles against food pathogens.Bioprocess Biosyst Eng. 2014;37(10):1935-43.
54. Chang Y, Liu C, Wu C, Chiang C, Lian J, Hsieh S. Dietary administration of zingerone to enhance growth, non-specific immune response, and resistance to Vibrio alginolyticus in Pacific white shrimp (Litopenaeus vannamei) juveniles. Fish and Shellfish Immunology. 2012;32: 284-290.
55. Janaki C, Sailatha E, Gunasekaran S. Synthesis, Characteristics and Antimicrobial activity of ZnO nanoparticles, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy; 2015.
56. Yusuf AA, Lawal B, Abubakar AN, Berinyuy EB. Omonije YO, Umar SI, Shebe MN, Alhaji YM. In-vitro antioxidants, antimicrobial and toxicological evaluation of Nigerian Zingiber officinale. Clinical Phytoscience. 2018;4(12):1-6.
57. Chiejina NV, Ukeh JA. Antimicrobial Properties and Phytochemical Analysis of Methanolic Extracts of Aframomum Melegueta and *Zingiber officinale* on Fungal Diseases of Tomato Fruit. Journal of Natural Sciences Researc. 2012;2(6).
58. Loung C, Rasmussen AN, Hoskin DW. The Phenolic Gingerols and Gingerol Derived Shogaols: Features and Properties Related to the Prevention and Treatment of Cancer and Chronic Inflammation. 2019;395-405.
59. Lantz RC, Chen GJ, Sarihan M, So´lyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytomedicine. 2007;14:123–128.
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.
61. Jennewein C, Sowa R, Faber AC, Dildey M, von Knethen A, Meybohm P, Zacharowski K. Contribution of Ninjurin1 to Toll-like receptor 4 signaling and systemic inflammation. American Journal of Respiratory Cell and Molecular Biology. 2015;53(5):656–663.
62. Toma L, Raileanu M, Deleanu M, Stancu CS, Sima AV. Novel molecular mechanisms by which ginger extract reduces the inflammatory stress in TNFα–activated human endothelial cells; decrease of Ninjurin-1, TNFR1 and NADPH oxidase subunits expression. Journal of Functional Foods. 2018;48: 654–664.
63. Ezzat SM, Ezzat MI, Okba MM, Menze ET, Abdel-Naim AB. The hidden mechanism beyond ginger (Zingiber officinale Rosc.) potent in vivo and in vitro anti-inflammatory activity. Journal of Ethnopharmacology. In press; 2017.
64. Funk JL, Frye JB, Oyarzo JN, Huaping JC, Timmermann ZBN. Anti-Inflammatory Effects of the Essential Oils of Ginger (Zingiber officinale Roscoe) in Experimental Rheumatoid Arthritis. PPharma Nutrition. In press.
65. Ajayi BO, Adedara IA, Farombi EO. 6-Gingerol abates benzo[a]pyrene-induced colonic injuryviasuppression of oxido-inflammatory stress responses in BALB/c

mice. Chemico-Biological Interactions. 2019;307:1–7.

66. Akhani SP, Vishwakarma SL, Goyal RK. Antidiabetic activity of *Zingiber officinale* in streptozotocin induced type I diabetic rats. J. Pharm. Pharmacol. 2004;56:101–105.
67. Bhandari U, Kanojia R, Pillai KK. Effect of ethanolic extract of *Zingiber officinale* on dyslipidaemia in diabetic rats. J. Ethnopharmacol. 2005;97:227–230.
68. Al-Amin ZM, Thomson M, Al-Qattan KK et al. Anti-diabetic and hypolipidaemic properties of ginger (Zingiber officinale) in streptozotocin-induced diabetic rats.Br. J. Nutr. 2006;96:660–666
69. Abdulrazaq NB, Cho MM, Ni NW. Beneficial effects of ginger (Zingiber officinale) on carbohydrate metabolism in streptozotocin-induced diabetic rats. Br. J. Nutr. 2011;108:1194–1201.
70. Jafri SA. Hypoglycemic effect of ginger (Zingiber officinale) in alloxan induced diabetic rats (Rattus norvagicus). Pak. Vet. J. 2011;31:160–162.
71. Kazeem MI, Akanji MA, Yakubu MT, et al. Protective effect of free and bound polyphenol extracts from ginger (Zingiber officinale Roscoe) on the hepatic antioxidant and some carbohydrate metabolizing enzymes of streptozotocin induced diabetic rats. Evid. Based Complement. Alternat. Med. 2013; 935486.
72. Kota N, Panpatil VV, Kaleb R, et al. Dose-dependent effect in the inhibition of oxidative stress and anticlastogenic potential of ginger in STZ induced diabetic rats. Food Chem. 2013;135:2954.
73. Sani NF, Belani LK, Sin CP, et al. Effect of the combination of gelam honey and ginger on oxidative stress and metabolic profile in streptozotocin-induced diabetic Sprague-Dawley rats. Biomed. Res. Int; 2014.
Available:https://doi.org/10.1155/2014/160695
74. Li Y, Tran VH, Kota BP, et al. Preventative effect ofZingiber officinaleon insulin resistance in a high-fat high-carbohydrate diet-fed rat model and its mechanism of action. Basic Clin. Pharmacol. Toxicol. 2014;115:209.
75. Fajrin FA, Nugroho AE, Nurrochmad A, Susilowati R. Ginger extract and its compound, 6-shogaol, attenuates painful diabetic neuropathy in mice via reducing TRPV1 and NMDAR2B expressions in the spinal cord. Journal of Ethnopharmacology; 2019.
Available:https://doi.org/10.1016/j.jep.2019.112396.
76. Saedisomeolia A, Arzati MM, Abdolahi M, Sedighiyan M, Rangel A, Muench G, Zarezadeh M, Jafarieh A, Honarvar NM. Mechanisms of Action of Ginger in Nuclear Factor-kappaB Signaling Pathways in Diabetes, Journal of Herbal Medicine; 2018.
Available:https://doi.org/10.1016/j.hermed.2018.10.004
77. Honarvar NM, Zarezadeh M, Khorshidi M, Arzati MM, Yekaninejad MS, Abdollahi M, Effatpanah M, Hashemi R, Saedisomeolia A. The effect of an oral ginger supplementation on NF-κB concentration in peripheral blood mononuclear cells and anthropomorphic data of patients with type 2 diabetes: A randomized double-blind, placebo-controlled clinical trial. Complementary Therapies in Medicine. 2019;42:7–11
78. El-Gayar MH, Maram MM, Ibrahim ANL, Hafiz MHA. Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus. Obesity Medicine. 2019;14 (2019):1-7.
79. Gholinezhad H, Bazyar H, Rashidi H, Salehi P, Haghighi-zadeh MH, Javid AZ. Using Ginger Supplement in Adjunct with Non-surgical Periodontal Therapy Improves Metabolic and Periodontal Parameters in Patients with Type 2 Diabetes Mellitus (DM) and Chronic Periodontitis. A Double-Blind, Placebo-Controlled Trial. Journal of Herbal Medicine; 2019.
Available:https://doi.org/10.1016/j.hermed.2019.100315. In press
80. Wang J, Gao H, Ke D, Zuo G, Yang Y, Yamahara J, et al. Improvement of liquid fructose-induced adipose tissue insulin resistance by ginger treatment in rats is associated with suppression of adipose macrophage-related proinflammatory cytokines. Evid Based Complement Alternat Med. 2013:e590376.
Available:https://doi.org/10.1155/2013/590376.
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

receptor δ pathway, The Journal of Nutritional Biochemistry; 2015. DOI:10.1016/j.jnutbio.2015.04.014. In press

82. Wang J, Ke W, Bao R, Hu X, Chen F. Beneficial effects of gingerZingiber officinale roscoe on obesity and metabolic syndrome: a review. Ann N Y Acad Sci. 2017;1398:83–98. Availavble:https://doi.org/10.1111/nyas.13375.
83. 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 proliferator-activated receptorδpathway. J Nutr Biochem. 2015;26:1058–67. Available:https://doi.org/10.1016/j.jnutbio.2015.04.014.
84. Ishiguro K, Ando T, Maeda O, Ohmiya N, Niwa Y, Kadomatsu K, Goto K. Ginger ingredients reduce viability of gastric cancer cells via distinct mechanisms. Biochemical and Biophysical Research Communications. 2007;362:218–223.
85. Lee HS, Seo EY, Kang NE, Kim WK. [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. Journal of Nutritional Biochemistry. 2008;19:313–319.
86. Parka K, Chun KS, Lee JM, Lee SS, Surh YJ. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. Cancer Letters. 1998;129:139–144.
87. Farombi EO, Ajayi BO, Adedara IA. 6-Gingerol delays tumorigenesis in benzo[a]pyrene and dextran sulphate sodium-induced colorectal cancer in mice, Food and Chemical Toxicology; 2020. Availabel:https://doi.org/10.1016/j.fct.2020.111483. In press
88. El-Naggar MH, Mira A, Abdel Bar FM, Shimizu K, Amer MM, Badria FA. Synthesis, Docking, Cytotoxicity, and LTA4H Inhibitory Activity of New Gingerol Derivatives as Potential Colorectal Cancer Therapy, Bioorganic & Medicinal Chemistry; 2016. Available:http://dx.doi.org/10.1016/j.bmc.2016.12.048
89. Chakraborty D, Bishayee K, Ghosh S, Biswas R, Mandal SK, Khuda-Bukhsh AR. [6]-Gingerol induces caspase 3 dependent apoptosis and autophagy in cancer cells: Drug–DNA interaction and expression of certain signal genes in HeLa cells. European Journal of Pharmacology. 2012;694(2012):20–29.
90. Azza AA, Galal Naglaa ZH, Eleiwa Kamel MA. Protective effect of Zingiber officinale (ginger) on doxorubicin induced oxidative cardiotoxicity in rats. Life Science Journal. 2013;10(2):2924-2934.
91. Hassanien MA. Ameliorating effects of ginger on isoproterenol-induced acute myocardial infarction in rats and its impact on cardiac nitric oxide. J Microsc Ultrastruct. 2020;8:96-103.
92. Subbaiah GV, Mallikarjuna K, Shanmugam B, Ravi S, Taj PU, Reddy KS. Ginger treatment ameliorates alcohol-induced myocardial damage by suppression of hyperlipidemia and cardiac biomarkers in rats. Phcog Mag. 2017;13:69-75.
93. Reilly CF, Tewksbury DA, Schechter NM, Travis J. Rapid conversion of angiotensin I to angiotensin II by neutrophil and mast cell proteinases. J Biol Chem. 1982;257:8619-22.
94. Ilkhanizadeh B, Shirpoor A, Ansari MH, Nemati S, Rasmi Y. Protective Effects of Ginger (Zingiber officinale) extract against Diabetes-Induced Heart Abnormality in Rats. Diabetes Metab J. 2016;40:46-53.
95. Taha NM, Mandour AA, Lebda MA. Antioxidative and Cardio-Protective Effects of Ethanolic Extract of Ginger on Triton WR-1339 Induced Hyperlipidemia in Rats. International Journal of Chemical Research. 2014;6(1):153-158.
96. Wen J, Zhang L, Wang J, Jiabo W Lifu W, Ruilin W, Ruisheng L, Honghong L, Shizhang W, Haotian L, Wenjun Z, Yanling Z. Therapeutic effects of higenamine combined with [6]-gingerol on chronic heart failure induced by doxorubicin via ameliorating mitochondrial function. J Cell Mol Med. 2020;24:4036–4050.
97. Rohini A, Neeraj A, Chandrasekar MJN, Sara UVS. Evaluation of Cardioprotective Effect of Zingiber Officinale in Experimental Animals. International Journal of Current Pharmaceutical Review and Research. 2013;4(1):1-9.
98. Ajibade AJ, Fakunle PB, Mene AA, Kehinde BD, Ajani RA. Some Cardioprotective Effects of Aqueous Extract of Ginger Against Monosodium Glutamate Induced Toxicity In The Heart Of Adult Wistar Rats. International Journal

of Recent Scientific Research. 2013;4(6):972 – 978

99. Han X, Liu P, Liu M, Wei Z, Fan S, Wang X, Sun S, Chu L. [6]-Gingerol ameliorates ISO-induced myocardial fibrosis by reducing oxidative stress, inflammation and apoptosis through inhibition of TLR4/MAPKs/NF-κB pathway. Molecular Nutrition & Food Research; 2020. DOI:10.1002/mnfr.202000003. In press
100. Han X, Zhang Y, Liang Y, Zhang J, Li M, Zhao Z, Zhang X, Xue Y, Zhang Y, Xiao J, Chu L.6-Gingerol, an active pungent component of ginger, inhibits L-type Ca2+ current, contractility, and Ca2+ transients in isolated rat ventricular myocytes. Food Science & Nutrition. 2019;7:1344–1352.
101. Ali-Sangi SM, Al-Jalaud NA. Prevention and treatment of brain damage in streptozo-tocin induced diabetic rats with Metformin, Nigella sativa, Zingiber officinale, and Punica granatum. Biomed. Res. Ther. 2019;7(6):3274-3285.
102. Shanmugam KR, Mallikarjuna K, Kesireddy N, Reddy KS. Neuroprotective effect of ginger on anti-oxidant enzymes in streptozotocin-induced diabetic rats Food and Chemical Toxicology. 2011;49: 893–897.
103. Wattanathorn J, Jittiwat J, Tongun T, Muchimapura S, Ingkaninan K. *Zingiber officinale Mitigates* Brain Damage and Improves Memory Impairment in Focal Cerebral Ischemic Rat. Evidence-Based Complementary and Alternative Medicine. 2011:1-8.
104. Waggas AM. Neuroprotective Evaluation of Extract of Ginger (*Zingiber officinale)* Root in Monosodium Glutamate=-Induced Toxicity in Different Brain Areas Male Albino Rats. Parkistan Journal of Biological Sciences. 2009;12(3):201-212.
105. Oboh G, Ademiluyi AO, Akinyemi AJ. Inhibition of acetylcholinesterase activities and some pro-oxidant induced lipid peroxidation in rat brain by two varieties of ginger (Zingiber officinale). Experimental and Toxicologic Pathology. 2012;64:315– 319.
106. Zeng G, Zhang Z, Lu L, Xiao D, Zong S, He J. Protective Effects of Ginger Root Extract on Alzheimer Disease-Induced Behavioral Dysfunction in Rats. Rejuvenation Research. 2013;16(2):124-133.
107. Sutalangka C, Wattanathorn J. Neuroprotective and cognitive-enhancing effects of the combined extract of Cyperus rotundus and Zingiber officinale. BMC Complementary and Alternative Medicine. 2017;17:135.
108. Park G, Kim HG, Ju MS, Ha SK, Park Y, Kim SY, Oh MS. 6-Shogaol, an active compound of ginger, protects dopaminergic neurons in Parkinson's disease models via anti-neuroinflammation. Acta Pharmacologica Sinica. 2013;34:1131–1139.
109. Seow SLS, Hong SL, Lee GS, Abd Malek SN, Sabaratnam V. 6-shogaol, a neuroactive compound of ginger (jahe gajah) induced neuritogenic activity via NGF responsive pathways in PC-12 cells. BMC Complementary and Alternative Medicine. 2017;17:334
110. Liu Y, Deng S, Zhang Z, Gu Y, Xia S, Bao X, Cao X, Xu Y. 6-Gingerol attenuates microglia-mediated neuroinflammation and ischemic brain injuries through Akt-mTOR-STAT3 signaling pathway, European Journal of Pharmacology; 2020. Available:https://doi.org/10.1016/j.ejphar.2020.173294
111. Sapkota A, Park SJ, Choi JW. Neuroprotective Effects of 6-Shogaol and Its Metabolite, 6-Paradol, in a Mouse Model of Multiple Sclerosis. Biomol Ther. 2019;27(2):152-159.
112. Gaire BP, Kwon OW, Park SH, Chun KH, Kim SY, Shin DY, Park SH, Chun KH, Kim SY, Shin DY, Cho JW. Neuroprotective Effect of 6-Paradol in Focal Cerebral Ischemia Involves the Attenuation of Neuroinflammatory Responses in Activated Microglia. PLoS One. 2015; 10(3): 1-17
113. Motawi TK, Hamed MA, Shabana MH, Hashem RM, Naser AFA. Zingiber officinale acts as a nutraceutical agent against liver fibrosis. Nutrition and Metabolism. 2011;8:40
114. Fahmi A, Hassanen N, Abdur-Rahman M, Shams-Eldin E. Phytochemicals, antioxidant activity and hepatoprotective effect of ginger (Zingiber officinale) on diethylnitrosamine toxicity in rats. Biomarkers. In press; 2019.
115. Alshathly MR. Efficacy of Ginger (Zingiber officinale) in ameliorating streptozotocin-induced diabetic liver injury in rats: Histological and biochemical studies. J Microsc Ultrastruct. 2019;7:91-101

116. Mannem P. Protective Effects of Ginger Extract against Lead Induced Hepatotoxicity in Male Albino Rats. IOSR Journal of Environmental Science, Toxicology and Food Technology (IOSR-JESTFT). 2014;8(5):53-59
117. Abd-Elrhman SY, Abd El- Fattah HM, Morsy GM, Elmasry S. Effect of Ginger Nanoparticles on Hepato-renal Toxicity Induced by Carbon Tetrachloride in Rats. Annual Research & Review in Biology. 2020;35(7):36-55.
118. Abd-Allah GA, El-Bakry KA, Bahnasawy MH, El-Khodary ER. Protective Effects of Curcumin and Ginger on Liver Cirrhosis Induced by Carbon Tetrachloride in Rats. International Journal of Pharmacology. 2016;12:361-369.
119. Yassin NAZ, ElRokh EM, El-Shenawy SMA, Ehasn NA. Sayed WH, Hassanein HMDE, Ibrahim BNM. Study of the hepatoprotective effect of ginger aqueous infusion in rats. J. Chemical. Pharm. Res. 2010;2(4):476-488.
120. El-Shemy MA, Abdalla AO, Fararh KM. Antioxidant and Hepatoprotective Effects of Ginger In Rats. Benha Veterinary Medical Journal. 2011;22(2):9-16.
121. Eman GE, Helal SM, Abd E, Atef M, Moussa S, Ghada AZ. Effect of Zingiber officinale on fatty liver induced by oxytetracycline in albino rats. The Egyptian Journal of Hospital Medicine (Jan. 2012). 2012;46:26–42
122. Abdel-Azeem AS, Hegazy AM, Ibrahim AS, Farrag AH, El-Sayed EM. Hepatoprotective, Antioxidant, and Ameliorative Effects of Ginger (Zingiber officinale Roscoe) and Vitamin E in Acetaminophen Treated Rats. Journal of Dietary Supplements. 2013;10(3):195–209.
123. Bardi DA, Halabi MF, Abdullah NA, Rouhollahi E, Hajrezaie M, Abdulla MA. In-Vivo Evaluation of Ethanolic Extract of Zingiber officinale Rhizomes for Its Protective Effect against Liver Cirrhosis. BioMed Research International. 2013:1-10.
124. Ezeasuka FJ, Ezejindu DN, Akudike CJ, Ndukwe GU. Hepatoprotective Effects of Ginger (Zingiber officinale) on Mercury-Induced Hepatotoxicity in Adult Female Wistar Rats. Advances in Life Science and Technology. 2015;39:7-12.
125. Hassan IH, El-desouky MA, Abd-Elaziz GM, Hozayen WG. Protective Effects of Zingiber officinale Against Carbon Tetrachloride Induced Liver Fibrosis. Int J Pharm Pharm Sci. 2016;8(3):377-381
126. Gholampour F, Behzadi GF, Owji SM, Vatanparast J. The protective effect of hydroalcoholic extract of Ginger (*Zingiber officinale* Rosc.) against iron-induced functional and histological damages in rat liver and kidney. Avicenna J Phytomed. 2017;7(6):542-553.
127. Ahd K, Dhibi S, Akermi S, Bouzenna H, Samout N, Elfeki A, Hfaiedh N. Protective effect of ginger (Zingiber officinale) against PCB-induced acute hepatotoxicity in male rats. RSC Advances. 2019;9:29120–29130
128. Ilyad EB, Mohammad RV, Mehrnaz M, Mahdi R, Amir H. The Antioxidant and Hepatoprotective Effect of Alcoholic Extract of Ginger Against the Cisplatin-induced Oxidative Stress in Rats. Biomed J Sci & Tech Res.| 2019;19(2):4240-14245.
129. Okda TM, Abd-Alhaseeb MM, Barka K, Ragab NM. Ginger potentiates the effects of silymarin on liver fibrosis induced by CCL4: the role of galectin-8. European Review for Medical and Pharmacological Sciences. 2019;23:885-891.
130. Yang M, Liu C, Jiang J, Zuo G, Lin X, Yamahara J, Wang J, Li, Y. Ginger extract diminishes chronic fructose consumption-induced kidney injury through suppression of renal overexpression of proinflammatory cytokines in rats. Complementary and Alternative Medicine. 2014;14(174):1-12.
131. Onwuka FC, Erhabor O, Eteng MU, Umoh IB. Protective Effects of Ginger Stoward Cadmium-Induced Testes and Kidney Lipid Peroxidation and Hematological Impairment in Albino Rats. Journal of Medicinal Food. 2011;14(7/8):817–821.
132. Uz E, Karatas OF, Mete E, Bayrak R, Bayrak O, Atmaca AF, Atıs O, Yıldırım ME, Akcay A. The Effect of Dietary Ginger (*Zingiber officinale* Rosc) on Renal Ischemia/Reperfusion Injury in Rat Kidneys, Renal Failure. 2009;31:4:251-260.
133. Shanmugam SK, Ramakrishna KR, Mallikarjuma CH, Sathyavelu RK. Protective effect of ginger against alcohol-induced renal damage and antioxidant enzymes in male albino rats. Indian Journal of Experimental Biology. 2009;48:143-149.
134. Ramudu MK, Kesireddy N, Chen C, Kuo CH, Kesireddy SR. Ginger Feeding Protects Against Renal Oxidative Damage

Caused by Alcohol Consumption in Rats. Journal of Renal Nutrition. 2011;21(3):263–270.
135. Payami S, Babaahmadi-Rezaei H, Ghaffari M, Mansouri E, Mohammadzadeh G. Hydroalcoholic Extract of Zingiber officinale Improves STZ-Induced Diabetic Nephropathy in Rats by Reduction of NF-kB Activation. J Nat Pharm Prod. 2019;14(2):1-6.
136. Bin-Meferij MM, El-Kott AF, Shati AA, Eid RA. Ginger Extract Ameliorates Renal Damage in High Fat DietInduced Obesity in Rats: Biochemical and Ultrastructural Study. Int. J. Morphol. 2019;37(2):438-447.
137. Rodrigues FAP, Prata MMG, Oliveira ICM, Alves MTQ, Freitas REM, Monteiro HSA, Silva JA, Vieira PC, Viana DA, Libório AB, Havt A. Gingerol Fraction from *Zingiber officinale* Protects against Gentamicin-Induced Nephrotoxicity. Antimicrobial Agents and Chemotherapy. 2020;58(4):1872–1878.
138. Lakshmi BVS, Sudhakar M. Protective Effect of *Zingiber offcinale* on Getamicin-Induced Nephrotoxicity in Rats. International Journal of Pharmacology. 2010;6(1):58-62.
139. Akinyemi AJ, Faboya OL, Paul AA, Olayide I, Faboya OA, Oluwasola TA. Nephroprotective Effect of Essential Oils from Ginger (Zingiber officinale) and Turmeric (Curcuma longa) Rhizomes against Cadmium-induced Nephrotoxicity in Rats. Journal of Oleo Science. 2018;67(10):1339-1345.
140. Pratap M, Jyothi M, Baburao G. Nephroprotective Effect of Ginger (Zingiber Officinale) Extract against Lead Induced Renal Toxicity In Male Albino Rats International Journal of Recent Scientific Research. 2017;8(12):22523-22528.
141. Gholampour F, Behzadi GF, Owji SM, Vatanparast J. The protective effect of hydroalcoholic extract of Ginger (Zingiber officinale Rosc.) against iron-induced functional and histological damages in rat liver and kidney. Avicenna J Phytomed. 2017;7(6):542-553.
142. Hamed MA, Ali SA, El-Rigal NS. Therapeutic Potential of Ginger against Renal Injury Induced by Carbon Tetrachloride in Rats. The Scientific World Journal. 2012:1-12
143. Maltepe C, Koren G. "The management of nausea and vomiting of pregnancy and hyperemesis gravidarum: a 2013 update,"Journal of Population Therapeutics and Clinical Pharmacology. 2013;20(2):184–192.
144. Javadi EHS, Salehi F, Mashrabi O. Comparing the Effectiveness of Vitamin B6 and Ginger in Treatment of Pregnancy-Induced Nausea and Vomiting. Obstetrics and Gynecology International. 2013:1-4.
145. Betz O, Kranke P, Geldner G, Wulf H, Eberhart LHJ. Is ginger a clinically relevant antiemetic? A systematic review of randomized controlled trials,"Forschende Komplementarmedizin und Klassische Naturheilkunde. 2005;12(1):14–23.
146. Willetts KE, Ekangaki A, Eden JA. Effect of a ginger extract on pregnancy-induced nausea: A randomised controlled trial. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2003;43:139–144
147. Pongrojpaw D, Somprasit C, Chanthasenanont A. A Randomized Comparison of Ginger and Dimenhydrinate in the Treatment of Nausea and Vomiting in Pregnancy. J Med Assoc Thai. 2007;90(9):1703-9.
148. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for Nausea and Vomiting in Pregnancy: Randomized, Double-Masked, Placebo-Controlled Trial. Obstetrics & Gynecology. 2001;97(4):577-582.
149. Smith CC, Franzcog K.W, Neil H, Vicki M. A Randomized Controlled Trial of Ginger to Treat Nausea and Vomiting in Pregnancy. OBSTETRICS & GYNECOLOGY. 2004;103(4):639-645.
150. Zick SM, Mack TR, Julia L, Daniel PN, Rivka S, Sara A, Dean EB. Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. Support Care Cancer. 2009:17:563–572.
151. Marx W, McKavanagh D, McCarthy AL, Bird R, Ried K, Chan A, Isenring L. The Effect of Ginger (Zingiber officinale) on Platelet Aggregation: A Systematic Literature Review. PLoS ONE. 2015;10(10):1-13.
152. Tianthong W, Phupong V. A randomized, double-blind, placebo-controlled trial on the efficacy of ginger in the prevention of abdominal distention in post cesarean section patients. SCien Tifi C Repo Rts. 2018;8:1-5.
153. Honarvar NM, Zarezadeh M, Khorshidi M, Arzati MM, Yekaninejad MS, Abdollahi M, Effatpanah M, Hashemi R, Saedisomeolia

A. The effect of an oral ginger supplementation on NF-κB concentration in peripheral blood mononuclear cells and anthropomorphic data of patients with type 2 diabetes: A randomized double blind, placebo-controlled clinical trial. Complementary Therapies in Medicine. 2019;42:7–11.

154. Aryaeian N, Shahram F, Mahmoudi M, Tavakoli H, Yousefi B, Arablou T, Karegar SJ. The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis. Gene. 2009;698:179–185
155. Askari G, Aghajani M, Salehi M, Najafgholizadeh A, Keshavarzpour Z, Fadel A, Venkatakrishnan K, Salei-Sahlabadi A, Hadi A, Pourmasoumi M. The effects of ginger supplementation on biomarkers of inflammation and oxidative stress in adults: A systematic review and meta-analysis of randomized controlled trials, Journal of Herbal Medicine: in press; 2020.
156. Yu Y, Zick S, Li X, Zou P, Wright B, Sun D. Examination of the Pharmacokinetics of Active Ingredients of Ginger in Humans. The AAPS Journal. 2011;13(3): 417-426
157. Teo S, Stirling D, Thomas S, Hoberman A, Kiorpes A, Khetani V. 2002. A 90-day oral gavage toxicity study of D-methylphenidate D, L-methylphenidate IN Sprague –Dawley rats. Toxicol. 2002;179:183-196.
158. Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. Effects of chili consumption on postprandial glucose, insulin, and energy metabolism. Am J Clin Nutr. 2006;84(1): 63-69
159. Rong X, Peng G, Suzuki T, Yang Q, Yamahara J, Li Y. A 35-day gavage safety assessment of ginger in rats. Regulat Toxicol Pharmacol. 2009:54(2):118-123.
160. Hamlaoui-Gasmi S, Limam N, Mokni M, Limam F, Aouani E, Amri M, Marzouki L. Garlic-mode treatment effects on rat brain redox status. J Med Plant Res. 2011;5(20):5094–5098.
161. Haniadka R, Rajeev AG, Palatty PL, Arora R, Baliga MS. Zingiber officinale (Ginger) as an anti-emetic in cancer chemotherapy: A Review. J Altern Complimen Med. 2012;18:440-444.
162. Ye BG, Feng Y, Wang S. Scientific evaluation of the acute toxicity and 13-week sub-chronic toxicity of Rheum emodi rhizome extracts in Sprague Dawley rats. Food Chem Toxicol. 2014;66:278-285.
163. Idang EO, Yemitan OK, Mbagwu HOC, Udom GJ, Ogbuagu EO, Udobang JA. Toxicological Assessment of Zingiber officinale Roscoe (Ginger) Root Oil Extracts in Albino rats. Toxicology Digest. 2019;4(1):108–119.
164. Bardi DA, Halabi MF, Abdullah NA, Rouhollahi E, Hajrezaie M, Mahmood AA. In Vivo Evaluation of Ethanolic Extract ofZingiber officinale Rhizomes for Its Protective Effect against Liver Cirrhosis. BioMed Research International. 2013:1-10.
165. Rong X, Peng G, Suzuki T, Yang Q, Yamahara J, Li Y. A 35-day gavage safety assessment of ginger in rats. Regulatory Toxicology and Pharmacology. 2009;54: 118–123.
166. Jeena K, Liju VB, Kuttan R. A Preliminary 13-Week Oral Toxicity Study of Ginger Oil in Male and Female Wistar Rats. International Journal of Toxicology. 2011;30(6):662-670.
167. Otunola GA, Afolayan AJ. Assessment of oral safety profile of aqueous extract blend of three medicinal spices in Wistar rats. Tropical Journal of Pharmaceutical Research. 2017;16(1):91-99.
168. Chen X, Chen G, Wang Z, Kan J. A comparison of a polysaccharide extracted from ginger (*Zingiber officinale*) stems and leaves using different methods: Preparation, structure characteristics, and biological activities. International Journal of Biological Macromolecules. In press; 2019.
169. Li Y, Tran VH, Kota BP, et al. Preventative effect ofZingiber officinaleon insulin resistance in a high-fat high-carbohydrate diet-fed rat model and its mechanism of action. Basic Clin. Pharmacol. Toxicol. 2014;115:209.
170. López EIC, Hernández MFB, Mendoza JMR, Ortiz ADR, Melo MTO, Parrales RS, Hernandez T. Antimicrobial activity of essential oil of *Zingiber officinale* Roscoe (Zingiberaceae). Am. J. Plant Sci. 2017;8:1511–1524.
171. Nikolić M, Vasić S, Đurđević J, Stefanović O, Čomić L. Antibacterial and Anti-Biofilm Activity of Ginger (*Zingiber officinale* (Roscoe)) Ethanolic Extract. Kragujevac J. Sci. 2014;36: 129-136.

172. Nostro1 A, Cellini L, Bartolomeo SD, Cannatelli1 MA, Campli ED, Procopio1 F, Grande R, Marzio L, Alonzo V. Effects of Combining Extracts (from Propolis or *Zingiber officinale*) with Clarithromycin on Helicobacter pylori. Phytother. Res. 2006;20:187–190.

173. Zhang F, Zhang JG, Qu J, Zhang Q, Prasad C, Wei ZJ. Assessment of anti-cancerous potential of 6-gingerol (Tongling White Ginger) and its synergy with drugs on human cervical adenocarcinoma cells. Food and Chemical Toxicology. 2017; xxx:1-13.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/72871