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Review Article

PHYCHEMISTRY, PHYTOCHEMICAL, PHARMACOLOGICAL AND MOLECULAR STUDY OF *ZINGIBER OFFICINALE* ROSCOE: A REVIEW

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ABSTRACT

The rhizomes of *Zingiber officinale* Roscoe (Zingiberaceae), commonly known as ginger, is one of the most widely used spice and condiment. It is also an integral part of many traditional medicines and has been extensively used in Chinese, Ayurvedic, Tibb-Unani, Srilankan, Arabic, and African traditional medicines, since antiquity, for many unrelated human ailments including common colds, fever, sore throats, vomiting, motion sickness, gastrointestinal complications, indigestion, constipation, gastritis, epigastric discomfort, gastric ulcerations, indigestion, nausea vomiting etc, and scientific studies have validated the ethnomedicinal uses. The present review tries to summarize and document the phytochemistry, phytochemical, pharmacological and molecular work done on ginger. The data was compiled to provide consolidated information covering different aspects of the plant, to provide a basis on which to plan future studies and to promote sustainable use of *Z. officinale.*

Keywords: *Zingiber officinale,* Gingerol, Shogaol, Molecular marker

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INTRODUCTION

Ginger (*Zingiber officinale* Roscoe) is an important tropical valued medicinal plant, over the world as a spice and for its therapeutic properties. Ginger belongs to the family Zingiberaceae, which contains about 1300 species in 50 genera, along with four other families is positioned in the order Zingiberales which belong to class *Monocotyledones*. The plant is sterile in nature (produce no seed) and only propagated by rhizomes [1-2]. Different members of the family have been distributed in the tropics of the south and south-eastern Asia specially Indomalaysia [3-4]. This plant is also cultivated throughout the tropical and sub-tropical region. It is thought to be first vegetative cultivated plant among them [5]. These plants contain a wide variety of biologically active, nonnutritive compounds known as phytochemicals [6]. Ginger is widely used around the world in foods as a spice. For centuries, it has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani herbal medicines for the treatment of catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes [7-8]. In recent year several reviews have come out about this plant, and this may replicate the popularity of the subject and its common use as a spice and a medicinal plant [9-10]. The literature showed that very few or no reviews are available which correlate the data of phychemistry, phytochemical, pharmacological and molecular properties of ginger together. Here, the aim was to recapitulate the more recent and common actions including phytochemistry, phytochemical, pharmacological and molecular aspect of *Zinger officinale.*

Phytochemistry of *Z. officinale*

Ginger rhizome contains two classes of constituents: (i) the essential oils which give the aroma, and (ii) the main pungent principles called gingerols. Ginger contains 1-2% volatile oil, 5-8% resinous matter, starch and mucilage. The oil of ginger is a mixture of over 24 constituents, consisting of monoterpenes (phellandrene, carnphene, cineolc, citral, and borneol) and sesquiterpenes (zingiberine and bisabolene) etc [11]. It contains the secondary metabolites found in the rhizome of ginger that are of primary attention. It can generally be divided into volatile compounds and nonvolatile phenolic compounds, the major ones of which have pungent properties. It is believed that the pharmacological activity of ginger rhizome is due to non-volatile pungent phenolic compounds. The term oleoresin refers to the volatile oil, the pungent compounds and other compounds extracted by means of solvents ethanol or acetone [11-12].

Non-volatile compounds of ginger

The pungency of ginger is due to the presence of phenolic compounds. In the fresh rhizome, the major type comprises a series of homologous phenolic alkanones known as gingerols and derivatives gingerdiols. The principal of these compounds is 6-gingerol 8-and 10-gingerol occurring in lower concentrations [13-14]. When subjected to heat or alkali treatment, gingerols are converted to a corresponding series of homologous shogaols by dehydration and or to the compound zingerone [11, 13]. The shogaols found to possess greater pungency than the corresponding gingerols [14]. Although gingerol is usually an oily substance, Connell and Sutherland [13] were able to obtain a crystalline solid when storing the gingerol in hexane at–30 °C. This solid was shown to consist of a mixture of homologous phenolic ketones, identified as 6-, 8-and 10-gingerol.

Degradation products of gingerol

Connell [15] suggested that chemical changes occurred in ginger reflected in the different therapeutic applications of fresh and processed ginger in oriental medicine. The main pungent compounds in fresh ginger, 6-, 8-and 10-gingerol, are thermally unstable and can undergo at least two reactions [11, 13].

Firstly, 6-, 8-and 10-gingerol can undergo dehydration and convert to 6-, 8-and 10-shogaol, respectively, when exposed to high temperature or subjected to prolonged storage [16]. Secondly, a retro-aldol reaction can give rise to zingerone and a series of aliphatic aldehydes, which can cause undesirable flavours in the oleoresin [11]. It was found that aldehyde formation occurred when oleoresin was heated to temperatures above 200 °C [17]. Jolad and his co-worker [18] have reported many novel compounds. These include paradols, dihydroparadols, acetyl derivatives of gingerols, 3-dihydroshogaols, gingerdiols, mono and diacetyl derivatives of gingerdiols, 1-dehydro-gingerdiones, diarylheptanoids, methyl [8]-paradol, methyl [6]-isogingerol, methyl [4]-shogaol, [6]-isoshogaol, 6-hydroxy-[8] shogaol, 6-hydroxy-[10]-shogaol, 6-dehydro-[6]-gingerol, three 5-methoxy-[*n*]-gingerols (*n* = 4, 8 and 10),3-acetoxy-[4]-gingerdiol,5-acetoxy [6] gingerdiol, diacetoxy-[8]-gingerdiol, methyldiacetoxy-[8]-gingerdiol, 5-acetoxy-3-deoxy-[6]-gingerol, 1-hydroxy-[6]-paradol and others [19].

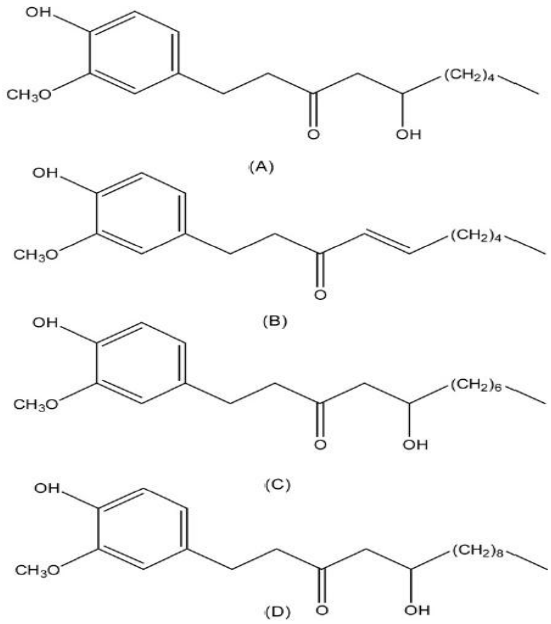

Fig. 1: Chemical structures of 6-gingerol (A), 6-shogaol (B), 8-gingerol (C), and 10-gingerol (D)

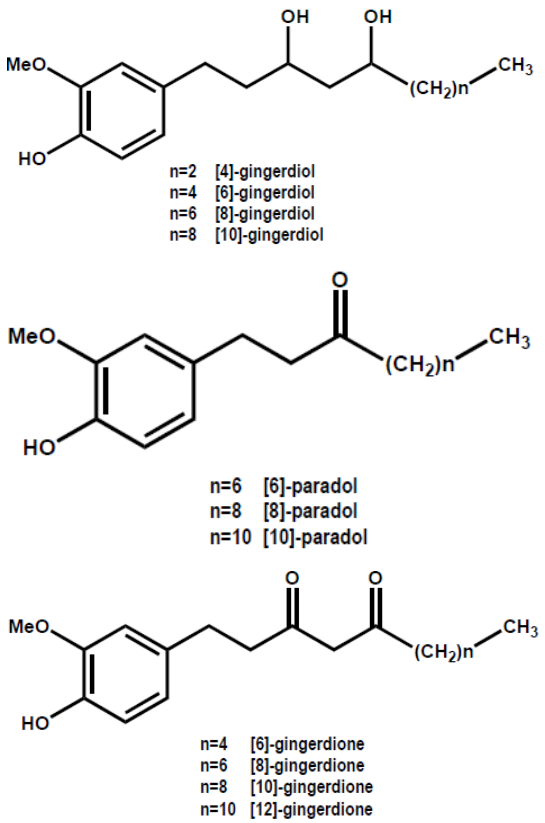

Fig. 2: Structures of paradols, gingerdiols and gingerdiones in *Z. officinale*

Volatile oil in ginger

Ginger oil distilled from the dry material is characterised by a high proportion of sesquiterpene hydrocarbons and relatively small amounts of monoterpene hydrocarbons and oxygenated compounds [12]. The major sesquiterpene hydrocarbons are zingiberene, *ar*-curcumene, β-bisabolene, (-) β-sesquiphellandrene and (*E, E*)-α-farnesene [20] fig. 3 (E-J).

Both zingiberene and (-)-β-sesquiphellandrene can be oxidised to *ar*-curcumene in oil stored under unfavourable conditions [12]. Other constituents of ginger essential oil widely reported include α-pinene, camphene, 6-methyl-5-hepten-2-one, myrcene, α-and β-phellandrene, limonene, 1,8-cineole, linalool, borneol, α-terpineol, citronellol, neral, geraniol, geranial, bornyl acetate, 2 undecanone, citronellyl acetate, α-copaene and geranyl acetate [21].

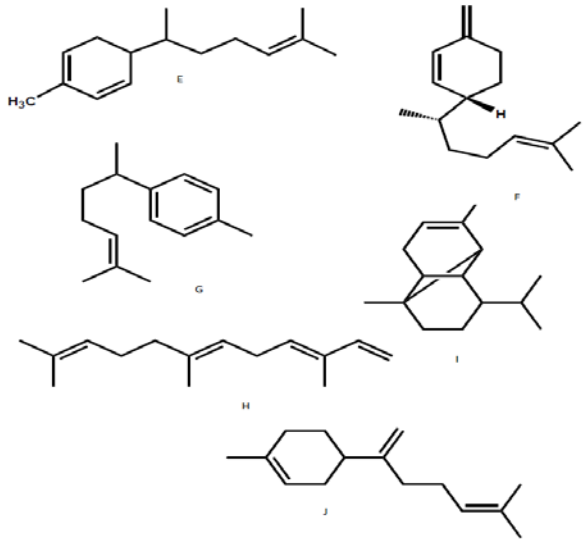

Fig. 3: E=zingiberene, F=β-sesquiphellandrene, G=ar-curcumene, H= (E, E)-α-farnesene, I=α-copaene, J=β-bisabolene

Some of the monoterpenoids in the oil of ginger are shown in fig. 4 (K-Q).

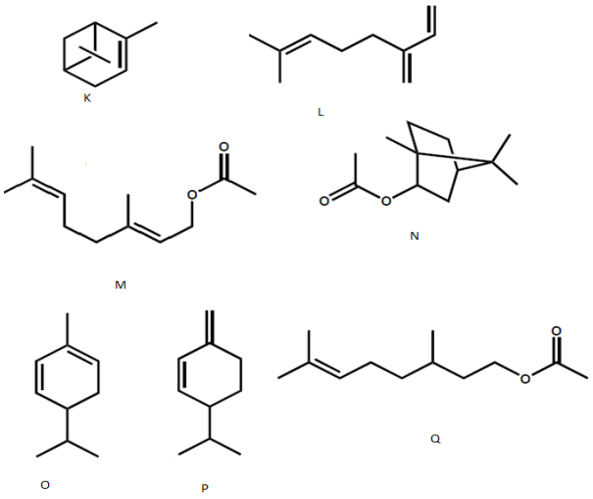

Fig. 4: K=α-pinene, L=myrcene, M=geranylacetate, N=bornyl acetate, O= α-phellandrene P= β-phellandrene,, Q=citronellyl acetate

Varieties of ginger

Suprabha, Suruchi, Suravi, Himgiri, Varada, Mahima, Rejatha, Karthika, Athira.

Phytochemical analysis of *Z. officinale*

Plants produce phytochemicals in order to protect themselves against environmental threats like predator insects, pollution and disease. In the past years, several phytochemical analysis works have been carried out. A number of studies have been reported to separate gingerols by thin layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), and column

chromatography (CC). Characterization of cultivars of Jamaican ginger (*Zingiber officinale* Roscoe) were carried out by HPTLC and HPLC. HPTLC fingerprints of the ginger cultivars showed chemical homogeneity with small qualitatively observed differences in the intensities of the gingerol and shogaols zones. Quantification of these compounds by high-performance liquid chromatography (HPLC) revealed significant differences in total pungency among the cultivars [22]. Imran and his co-worker [23] have developed and validated fast, accurate, specific and reproducible HPTLC method for quantification of 6-, 8-and 10-gingerols in fresh ginger rhizomes. The separations of the gingerols were performed with mobile phase acetonitrile–water–formic acid (7:2:1 v/v/v). The densitograms were further scanned for their in situ UV spectra from 300 to 800 nm. Lower limit of detection (LOD) obtained for 6-, 8-and 10-gingerols were 23, 32 and 21 ng/spot, respectively, with good linearity ranging from 0.9992 to 0.9937, whereas the LOQ obtained were 140, 168 and 136 ng/spot, respectively. In another experiment, Pawar and his co-worker [24] have reported variations in the content of 6-gingerol in different ginger cultivars. The separation of the TC extract was conducted in a C18 column (Delta Pak), 5 lm, and 3.9 x 150 mm, 300 Å. A mobile phase consisting of A (water) and B (acetonitrile) was used for separation, and the gradient range varied linearly from 50% to 90% B in 4 min with injection volume 2 ml for the RRHT column. Detection wavelength of the diode array detector (DAD) was set at 280 nm. Metabolic fingerprinting from the leaves of three micro-propagated ginger cultivars Bukit Tinggi, Tanjung Sepat and Sabah have been done by using a gas chromatography-mass spectrometry (GC-MS) [25]. Analysis of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol in ginger-containing dietary supplements, spices, teas, and beverages was extracted from various ginger-containing products with ethyl acetate and then analyzed by HPLC on a C-8 reversed phase column at 282 nm. The recoveries of 6-, 8-, and 10-gingerol, and 6-shogaol from the ginger dietary supplements and ginger-containing products were 94.7±4.1, 93.6±3.4, 94.9±4.0, 97.1±3.8%, respectively [26]. In another study, determination of 6-gingerol in methanolic extract of ginger rhizome was carried out. Separation occurred in n-hexane and diethyl ether (40:60 v/v) as the mobile phase. The calibration plot shows the linearity in the range of 250–1200 ng. The method permits reliable quantification of 6-gingerol and good resolution and separation of 6-gingerol from other constituents of ginger [27]. Characterization of gingerol-related compounds in ginger rhizome (*Zingiber officinale* Rosc.) was carried out by high-performance liquid chromatography/ electrospray ionization mass spectrometry. This study reported the utility of liquid chromatography/electrospray ionization tandem mass spectrometry (LC/ESI-MS/MS) coupled with diode array detection in identifying gingerol-related compounds from crude extracts of ginger rhizome. In this study, total 31 gingerol-related compounds were identified from the methanolic crude extracts of fresh ginger rhizome [28]. In a similar study, Ashraf and his co-worker [29] have developed and validated UPLC-MS/MS method for determination of gingerols in several ginger varieties of India. They also reported that Patna and Lucknow varieties are the superior among all accessions. Wei *et al.* [30] have showed how 6-Paradol and 6-shogaol, the pungent compounds of ginger, promote glucose utilization in adipocytes and myotubes, and 6-paradol reduces blood glucose in high-fat-diet-fed mice. In another study, Kamal *et al.* [31] developed reverse phase stability indicating HPLC method for the determination of 6-gingerol in polyherbal formulations. Separation of 6-gingerol was achieved with a mobile phase containing methanol: 0.05% orthophosphoric acid in water (60:40, *v/v*) at 280 nm using UV-visible detector. The linear regression analysis data showed a good linear relationship (r^2 = 0.9989 ± 0.0010) for 6-gingerol in the concentration range of 0.5 µg to 500 µg/ml. This proved the method can be employed for the determination 6-gingerol even in nanogram levels.

In a recent study, Ashraf and his co-workers [32] have carried the quantitative analysis of 6 gingerol in ginger by the RP-HPLC method. He reported very good separation of 6-gingerol on mobile phase acetonitrile and water in isocratic mode. Park and Jung [33] have carried out UHPLC-ESI-MS/MS for the quantification of eight major gingerols and shogaols in ginger products and showed the effects of ionization polarity and mobile phase modifier on the sensitivity. This reported method was successfully applied to analyze the compounds in fresh and dried powdered gingers, and dietary supplements. In a very recent study, Gaikwad *et al.* [34] have isolated and standardized gingerol from ginger rhizome by using TLC, HPLC, and identification tests. He also checked the purity of ginger extract by HPLC analysis method.

Recently Ashraf *et al.* [35] have developed and validated HPTLC method for the analysis of 10-gingerol in ginger and found that Patna and Lucknow samples are reported to have a high content of 10-gingerol among all accessions. In another study, Alam [36] developed and validated the densitometric HPTLC analysis of 8-gingerol in *Zingiber officinale* extract and ginger-containing dietary supplements, teas and commercial creams by using n-hexane: ethyl acetate 60: 40 (v/v) as the mobile phase. This system was found to give a compact spot of 8-gingerol at retention factor (Rf) value of (0.39±0.04) and linearity was found in the ranges 50-500 ng/spot (r^2=0.9987).

Ghasemzadeh *et al.* [37] in an experiment applied response surface methodology for optimizing reflux extraction conditions for getting high 6-gingerol and 6-shogaol contents, and high antioxidant activity in *Zingiber officinale* var. *rubrum Theilade.* The 6-gingerol and 6-shogaol contents were measured using ultra-performance liquid chromatography. Results indicated that the pharmaceutical quality of ginger could be improved significantly by optimizing of extraction process using response surface methodology.

In a recent study, Gan *et al.* [38] have showed separation and preparation of 6-gingerol from molecular distillation residue of yunnan ginger rhizomes by high-speed counter-current chromatography technique in semi-preparative scale. He successfully performed separation and purification of 6-gingerol from MD-R by using a two-phase solvent system composed of n-hexane-ethyl acetate-methanol-water (10:2:5:7, v/v/v/v).

Pharmacological actions of *Z. officinale*

Anti-cancer effects

The anticancer activity of *Z. officinale* are believed to be accredited to a range of constituents including vallinoids, viz. 6-gingerol and 6-paradol shogaols, zingerone, and Galanals A and B [39-41]. Galanals A and B reported to be powerful apoptosis inducers of human T lymphoma Jurkat cells [39]. The ratio of gingerols to shogaols is important as earlier literature showed. So far activity of dried to steamed ginger, there was also increased anti-tumour potency and a move towards higher shogaol ratios in steamed ginger. 6-, 8-, and 10-gingerols were shown to inhibit proliferation of the breast cancer cell line, MDA-MB-231, with an effectiveness order of 10-gingerol>8-gingerol>6-gingerol. Remarkably, 10-gingerol was about 50-fold more potent (IC50 = 12 versus 670 µM, respectively) than 6-gingerol [39]. Ginger and its bioactive molecules are effective in regulatory the degree of colorectal, gastric, ovarian, liver, skin, breast, and prostate cancers [40, 42-47]. Kim *et al.* [45] have carried out an experiment in mouse models and administered Zerumbone orally and observed inhibition in a multiplicity of colonic adenocarcinomas through suppression of colonic inflammation in a dose-dependent manner. The mechanism includes inhibition of proliferation, induction of apoptosis, and suppression of NFκB and heme oxygenase (HO) expression. Yagihashi *et al.* [48] have stated that 6-gingerol can inhibit both proliferation and invasion of hepatoma cells. Cell cycle arrest and apoptosis induction are the main causes of [6] gingerol in these cancerous cells. Habib and his co-worker [45] in an experiment reported that ginger extract can reduce the raised expression of NFκB and TNF alpha in rats with liver cancer [49]. 6-gingerol showed substantial cytotoxicity by growth inhibition of human epidermoid carcinoma cells interceded through reactive oxygen species (ROS) induced apoptosis [50]. Treating of skin cancer by the ginger on the mechanism based on Inhibition of angiogenesis in the mouse skin [45].

Anticoagulant effects

Ginger was reported to have an inhibitory action on platelet aggregation [51] and also causes to reduce platelet thromboxane production *in vitro*. 8-Gingerol, 8-shogaol, 8-paradol, and gingerol

analogues show antiplatelet actions [52]. Although *in vivo* effects of ginger is not well studied yet. Ginger is liable for the decrease in platelet aggregation [53]. Lumb [54] has reported that ginger has no effect on platelet count, bleeding time, or platelet aggregation.

Antiemetic effect

Effect of ginger on nausea and vomiting is diffident. Yet, there are a number of anticipated mechanisms. Constituents of ginger like gingerols, shogaols, and galanolactone, a diterpenoid of ginger are believed to be responsible for the antiemetic effect [55-56]. *In vitro* studies (new animal models) was found to have antiserotoninergic and 5-HT3 receptor antagonism effects, which take part in an important role in the etiology of postoperative nausea and vomiting [56]. The women in early pregnancy are largely affecting by nausea and vomiting. It is believed that up to 80% of women have nausea and vomiting in some degree during the first trimester of pregnancy, and for the majority of women, symptoms typically tenacity by 12–14 w gestation [57-58]. If we see in morning sickness of women in a small percentage of pregnancies (0.2%–5%), persistent and excessive nausea and vomiting resulting in dehydration, electrolyte imbalance, and weight loss (termed hyperemesis gravidarum) can occur and is a leading cause of hospital admissions during the first half of pregnancy [59].

Anti-inflammatory effects

Ginger was found to possess anti-inflammatory and numerous of its constituents were known as anti-inflammatory properties [60]. Ginger was reported to inhibit prostaglandin biosynthesis [61]. Srivastava and Mustafa [62] have reported that ginger can also impede with them inflammatory cascade and the vanilloid nociceptor. Ginger was shown to have pharmacological properties with non-steroidal anti-inflammatory drugs (NSAIDs) because it reduces prostaglandin synthesis by the reducing cyclooxygenase-1 and cyclooxygenase-2. Study of Habib and his co-workers have found that extract of ginger can reduce the elevated expression of NFκB and TNF-α in rats with liver cancer [63-64]. A number of inflammatory diseases, including cancer, atherosclerosis, myocardial infarction, diabetes, allergy, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, septic shock, and AIDS has been linked by activation of NF-κB [60]. Lantz *et al.* [65] revealed that gingerols can prevent LPS-induced COX-2 expression while shogaol containing extracts have no effect on COX-2 expression. These data demonstrate that important compounds in ginger are capable of inhibiting PGE (2) production.

Antinociceptive effects

In ginger, 6-shogaol was formed anti-nociception and obstructed the discharge of substances in rats, it appears identical receptor to which capsaicin binds. But, it was seen to be 100 times less effective and to obtain half the maximal result of capsaicin [67]. In another experiment, Sepahvand *et al.* [68] were carried experiment of ginger root extract on the nociceptive threshold and morphine-induced analgesia in male Wistar rats. Analgesia, ginger extract (200, 400, and 600 mg/kg i. p.) was injected before a sub-effective dose of morphine (2.5 mg/kg i. p.) for the determination the effect of ginger on morphine. The radiant heat tail-flick test was used to assess the nociceptive threshold before and at different times after drug administration. Results showed that ginger extract provoked a significant ant nociceptive effect.

Antioxidant effects

The antioxidative properties of ginger and its constituents have been explored in various *in vitro* and *in vivo* tests. Reinforcement the body's defenses by improving the antioxidant status will certainly protect human against many chronic diseases [69-70]. 6-Shogaol has showed the most potent antioxidant and anti-inflammatory properties in ginger, which can be accredited to the existence of alpha, beta-unsaturated ketone moiety [71]. Animal modelling indicated that ginger considerably lowered induced lipid peroxidation and raised the levels of antioxidant enzymes, together with serum glutathione [72]. Additionally, feeding ginger to rats at 1% w/w during the administration of malathion (20 ppm) for 4 w considerably lessened malathion induced lipid peroxidation [73]. Ginger was found to show speantioxidant effects also [74]. In another study, 6-gingerol of ginger showed the antioxidant property and it also defends HL-60 cells from oxidative stress [75]. In a research conducted by Mallikarjuna *et al.* [76] found that ethanol considerably decreases the superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione content in the hepatic tissue. This effect was further enhanced by a treatment with 1% dietary ginger 1 mo in rats which recommend that ginger may have a protective role against the ethanol-induced hepatotoxicity.

Vitamin E and in combination with ethanol extract of *Z. officinale* moderately ameliorated cisplatin prompted nephrotoxicity. This protection is mediated by renal antioxidant defence system [77]. Protective effect of the ginger extract was also examined on CCl(4) and acetaminophen-induced liver damage and it showed that *Z. officinale* could be useful in preventing acute liver injury [78].

Action on cardiovascular and lipid-lowering effects

Ginger extract have hypocholesterolemic, hypolipidemic, and antiatherosclerotic effects in cholesterol-fed rabbits if taken orally [79]. There has been the development of atherosclerosis in apolipoprotein E-deficient mice due to inhibition of LDL oxidation [80]. Both 6-shogaol and 6-gingerol, and the gingerdiones, are reportedly potent enzymatic inhibitors of prostaglandin, thromboxane, and leukotriene biosynthesis [81]. In another study, 'methanolic' extract of fresh ginger shows a hypotensive effect in anesthetized rats via blockade of Ca++channels whereas here in this investigation report a cholinergic receptor-mediated hypotensive activity of 'aqueous' ginger extract. The variance in activity could be a result of the different solvent systems used for extraction as it is known that organic solvents extract non-polar while distilled water would extract polar compounds [82-83]. Remarkably, the potency of the CCB activity was less in this study when equated with the previous study carried out with the ginger methanolic extract [81]. A change in activity was also reported between methanolic and aqueous ginger extracts for their vascular effects by Pancho *et al.* [84]. In contrast, Weidner and Sigwart [85] have showed that an 'ethanol extract of dried ginger' was lacking of any effect on the BP or heart rate of 'conscious rats'. In another study, it was examined the effects of ginger supplementation on serum lipids and lipoproteins in peritoneal dialysis PD patients. It was randomized, double-blind, placebo-controlled trial, in which 36 PD patients were randomly assigned to either the ginger or the placebo group. The patients in the ginger group received 1,000 mg ginger daily for 10 w, while the placebo group received corresponding placebos. At baseline and at the end of week 10, 7 ml of blood were obtained from each patient after a 12-to 14-hour fast, and serum concentrations of triglyceride, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and lipoprotein (a) [Lp (a)] were measured. Serum triglyceride concentration decreased significantly up to 15% in the ginger group at the end of week 10 compared with baseline ($p<0.01$), and the reduction was significant in comparison with the placebo group ($p<0.05$). This study indicates that daily administration of 1,000 mg ginger reduces serum triglyceride concentration, which is a risk factor for cardiovascular disease, in PD patients [86]. In another experiment Akinyemi *et al.* [87] have assessed the effect of two ginger varieties (*Zingiber officinale* and *Curcuma longa*) on the arginase activity, atherogenic index, levels of liver thiobarbituric acid reactive substances (TBARSs), and plasma lipids in rats fed with a high-cholesterol (2%) diet for 14 d. It was found that feeding a high-cholesterol diet to rats caused significantly ($p<0.05$) increases in arginase activity, atherogenic index, levels of TBARS, total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C) with a concomitant decrease in high-density lipoprotein cholesterol (HDL-C).

Gastrointestinal effects

Ginger rhizome (root) enhances stomach acid secretion. It is acted by hindering antacids, sucralfate (Carafate), H2 antagonists, or proton pump inhibitors. Other animal study discovered gastro defensive actions [88]. Additionally, 6-shogaol, is usually more effective than 6-gingerol, has repressed intestinal motility in intravenous preparations. Ginger extract was also found to delay the

growth of *Helicobacter pylori in vitro* [89]. The ginger extract showed sensitivity to atropine, a standard cholinergic antagonist in intestinal propulsive activity [90-91]. The muscarinic receptors mediate human circular and longitudinal colonic smooth muscle contractions and so are significant in regulating the gastrointestinal smooth muscle tone [92]. These are supposed to present in the myenteric plexus, circular and longitudinal muscles, oesophagus, stomach, ileum, and colon [93]. It also maintaining the path and intensity of peristalsis [94]. Ginger is usually used as a stomachic, laxative, prokinetic and digestive aid [97].

Weight loss effects

Herbal drinks or spiced foods such as those that contain ginger was found to show significant effects on metabolic targets, such as satiety, thermogenesis, and fat oxidation. Importantly clinical results for a while could appear easily but also depends too powerfully on the full fulfilment of subjects. Thermogenic ingredients, such as ginger, may be considered as useful agents that could help reinstate" constructive energy equilibrium" and stop fatness [98].

Antiarthritic effect

Ginger also shows antiarthritic effects. 6-gingerol and their derivatives were found to reduce joint inflammation in an animal model of rheumatoid arthritis, streptococcal cell wall-induced arthritis. Both extracts of ginger were found to possess anti-inflammatory activity. The crude dichloromethane extract, containing essential oils and more polar compounds, was more useful, in preventing, both joint inflammation and destruction [99].

In a very recent study Thabet *et al.* [100] were carried experiment and prepared the extract in three different doses of 100, 200 and 400 mg/kg/d in two protocols (prophylactic and therapeutic) to a rat model of adjuvant-induced arthritis which was induced by the administration of Freund's adjuvant and squalene. Ethanolic ginger extract in different doses significantly reduced inflammation and pain in adjuvant-induced arthritis of rats as evidenced by the decreased change of ankle diameter and the increased threshold of pain after the mechanical pressure of both inoculated and non-inoculated hind paws of arthritic rats. Ginger extract increased significantly serum levels of the anti-inflammatory cytokine IL-10 in arthritic rats with an insignificant decrease of the pro-inflammatory cytokine TNF-alpha. In another study, it has been proved that ginger is effective against osteoarthritis and rheumatism [101].

Antimicrobial activities

Ingenol and 6–shogaols are reported to have antiviral activity [102].10-gingerol was found to be an inhibitor of *M. avium* and *M. tuberculosis in vitro.* Gingerol and related compounds were shown to produce antimicrobial activities [103]. Onyeagba *et al.* [104] found the synergistic effect of ethanol extract of ginger and garlic against *Bacillus spp*. and *Staphylococcus aureus*. They also reported that antimicrobial activity of the ethanol extract of ginger, lime and garlic against a broad range of bacteria including *Bacillus spp*., *Staphylococcus aureus, Escherichia coli,* and *Salmonella spp.* In another study, Malu *et al.* [105] have carried out the antibacterial activity of ginger extracts. In their experiment, they obtained ginger extracts using solvents, n-hexane, ethyl acetate, ethanolic soxhlet and water. The results showed that all the extracts except the water extract have antibacterial activity and that the inhibition of bacterial growth was dose-dependent.

Recently Islam *et al.* [106] have reported the antimicrobial activity of the soybean extract of ginger different bacterial species. The diameter of the zone of inhibition varied ranging from (8.0±1.73 mm) to (11.67±1.53 mm) for ginger extract as compared to (12.33±7.09 mm) to (19.33±3.51 mm) for gentamicin. The antimicrobial activity of the ginger was reported to be highest against *Salmonella* spp. while lowest activity was found against *Escherichia coli. Staphylococcus aureus* exhibited lower sensitivity to ginger extract as compared to the most other Gram-negative bacteria.

Radioprotective activity

In vitro of animal study pre-treatment with 6-gingerol condensed UVB-induced intracellular reactive oxygen species levels, activation of caspase-3,-8,-9, and F as an expression. It also reduced UVB-induced expression and transactivation of COX-2 [107].

Antigenotoxic activity

Genistein and 6-gingerol were used as antigenotoxic agents to ameliorate the genotoxicity induced by the steroids. Norethandrolone and oxandrolone were investigated for this purpose. Norethandrolone and oxandrolone were studied at 5, 10, 20, 30 and 40 μM, respectively and were reported to be considerably genotoxic at 30 and 40 μM. Genistein and 6-gingerol established to be equally effective in suppressing genotoxicharm at suitable doses [108].

Recently Sradhasini Rout *et al.* [109] have carried out an experiment on the antigenotoxic effect of ginger powder 7, 12-Dimethyl benz (a) anthracene induced genotoxicity in rat bone marrow cells. Six to eight weeks old male Wistar albino rats were divided into six groups (n=6). Group I is control and animals were administered with the standard diet. Group III and IV animals were fed with diet mixed with 5% and 10% ginger powder, for thirty consecutive days. Group II, III and IV rats were injected with 7, 12-Dimethyl benz (a) anthracene (DMBA) 30 mg/kg b.w. intraperitoneally twenty-four hours after the last test dose. Group V and VI animals were kept with a diet containing 5% and 10% ginger powder alone respectively. The animals were sacrificed twenty-four hours after DMBA injection and were injected with colchicine 2 mmol (0.5 ml/100 gm b.w. ip). The occurrence of micronuclei in polychromatic (P) and normochromatic (N) erythrocytes and scoring of chromosomal aberrations were done in rat bone marrow cells. 10% ginger powder mixed diet produced a significant inhibition of DMBA induced modification in P/N ratio and incidence of micronuclei. It decreased the abnormal metaphases as well as total chromosomal aberrations significantly, inhibited the DMBA induced chromosomal breaks, gaps, rings, deletions and other abnormalities in bone marrow cells.

Molecular marker analysis of *Z. officinale*

DNA fingerprinting/profiling is a technique in which combined use of several single locus detection systems used as versatile tools for investigating various aspects of plant genomes. Molecular profiling of ginger revealed different DNA pattern which depends on ecological conditions of environments. Ginger is found to have high medicinal value and India is the place where largest diversity is found. In India, most of the popular commercial varieties are clonal selections from traditional cultivars. Breeding in ginger is seriously handicapped by poor flowering and seed set. Most of the crop improvement programs of these species are confined to evaluation and selection of naturally occurring clonal variations [110-111]. In such species, the extent of genetic diversity is low, unless samples are drawn from diverse agro-ecological conditions [112]. Therefore, diversity analysis and identification of genetically distant clones or genotypes are vital to the ginger improvement program. Recently Ashraf *et al.* [113] have carried out RAPD analysis of 12 accessions of ginger collected from the Indian subcontinent. Ginger undergone genetic diversity due to wide variations in ecological conditions. Thirteen out of twenty primers screened were informative and produced 275 amplification products, among which 261 products (94.90%) were found to be polymorphic. The percentage polymorphism of all 12 accessions ranged from 88.23% to 100%. Out of 275 amplification products 261 was found to be polymorphic 94.90%. In another study Kizhakkayil and Sasikumar [114] have screened 60 RAPD primers, out of this; the 30 which gave reliable pattern were used for amplification. A total of 269 scorable bands were produced, out of which 126 were polymorphic. Seventeen ISSR primers produced 160 scorable bands out of which 76 were polymorphic. The genetic similarity Jaccard's coefficients obtained by the RAPD and ISSR markers were in the range of 0.76–0.97. Though good morphological genetic variability was reported in ginger. But the present molecular diversity study revealed a rather low genetic variability as reported earlier using isozyme markers. Jatoi *et al.* [115] in a study used rice SSR markers as RAPD markers to assess the relationship among the *Zingiber* species and genetic variability in ginger (*Z. officinale*) accessions from Asian countries. Among all molecular plant markers, RAPD is best, suitable tool for poorly studied species such as ginger, because it requires no prior information on the genome and is also cost-effective. Several studies

have reported the successful use of RAPD markers to assess genetic diversity and phylogenetic relationship in different crop species [116-117]. Being a poorly studied genome, little information is available on the molecular characterization of gingers investigated the diversity within and among *Zingiber* species and found that *Z. officinale* from different geographical origin were identical in phylogenetic analysis and metabolic profiling.

There were significant variations reported in 16 elite cultivars of ginger by using cytological and RAPD marker [118-119]. In Malaysian region, Mohd *et al.* [120] were carried out an experiment in three varieties of ginger by RAPD marker and reported variations among samples. Wahyuni *et al.* [121] have carried out an assessment of genetic diversity by AFLP in morphologically distinct Indonesian gingers and found out no clear genetic differentiation between small and big type (morphological variants) gingers. In addition, higher genetic variability was detected in collections from small-scale local farms in comparison to genebank accessions and market collections.

Cultivation of traditional as well as improved clones is common in India. Sanjeev and his co-workers [122] have reported RAPD variation from 44.95 to 72.48 in species of ginger. In another study, Kavitha *et al.* [123] were also observed 40% variations in *Z. officinale* by AFLP marker.

Table 1: Molecular marker studies of ginger

S. No.	Plant	Markers	References
1	*Z. officinale*	AFLP	[124]
2	*Z. officinale*	RAPD	[125]
3	*Z. officinale*	IRAP and REMAP	[126]
4	*Z. officinale*	Isoenzymes	[127]
6	*Z. officinale*	SSR	[128]
7	*Z. officinale*	ISSR, SSR	[129]
8	*Z. officinale*	RAPD and ISSR	[130]
9	*Zingiber officinale*	SCAR	[131]
10	*Zingiber officinale*	SNP	[132]
11	*Zingiber officinale, Z. barbatum and Z. mioga*	RSB-RAPD	[133]
12	*Zingiber barbatum*	PBA	[134]
13	*Zingiber montanum*	RAPD	[135-136]
14	*Zingiber moran*	RAPD	[137]

CONCLUSION

The present review tries to summarize and document the phytochemistry, phytochemical, pharmacological and molecular work done on ginger. Ginger and many of its chemical constituents have strong anti-oxidant actions. Ginger and many of its chemical constituents were shown to have useful pharmacological actions to treat various types of diseases by the action of anti-cancer, anti-inflammatory, antiemetic, anticoagulant property etc. In numerous clinical studies, to be useful in combating post-operative vomiting and vomiting of pregnancy. Molecular study of ginger including fingerprinting by RAPD, SCAR, ISSR, AFLP, etc. plays important role in development of a molecular marker for authenticity and diversity of plants. Different Markers analysis shows that there is a high level of polymorphism among different accessions and pattern varied with respect to environmental factors and genetic parameters.

Future perspective of ginger

Broad traditional knowledge on ginger can be validated by modern pharmacological studies highlighting the chemical nature of ginger, its effects on various parameters and detailed studies of the mechanisms of the observed biological actions.

However, this information alone is not sufficient to provide evidence for safety and efficacy of a natural product and requires further investigation. Studies on molecular, phytochemical and pharmacological effects allow greater understanding of the factors supporting the safe use of the medicine, including interactions with other drugs or nutritional factors. The presented data and documents would helpful in the development of clinically safe and therapeutic valuable formulation to combat various types of ailments as well as cultivation strategies of this valuable plant.

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CONFLICT OF INTERESTS

Declared none

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