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# Gingerols and shogaols: Important nutraceutical principles from ginger

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ABSTRACT

Gingerols are the major pungent compounds present in the rhizomes of ginger (*Zingiber officinale* Roscoe) and are renowned for their contribution to human health and nutrition. Medicinal properties of ginger, including the alleviation of nausea, arthritis and pain, have been associated with the gingerols. Gingerol analogues are thermally labile and easily undergo dehydration reactions to form the corresponding shogaols, which impart the characteristic pungent taste to dried ginger. Both gingerols and shogaols exhibit a host of biological activities, ranging from anticancer, anti-oxidant, antimicrobial, anti-inflammatory and anti-allergic to various central nervous system activities. Shogaols are important biomarkers used for the quality control of many ginger-containing products, due to their diverse biological activities. In this review, a large body of available knowledge on the biosynthesis, chemical synthesis and pharmacological activities, as well as on the structure–activity relationships of various gingerols and shogaols, have been collated, coherently summarised and discussed. The manuscript highlights convincing evidence indicating that these phenolic compounds could serve as important lead molecules for the development of therapeutic agents to treat various life-threatening human diseases, particularly cancer. Inclusion of ginger or ginger extracts in nutraceutical formulations could provide valuable protection against diabetes, cardiac and hepatic disorders.



## 1. Introduction

*Zingiber officinale* Roscoe (Zingiberaceae), commonly known as ginger, is indigenous to tropical Asia, probably to southern China or India. The rhizomes of the plant have a powerful aroma and are extensively used as a spice and as medicine. Precise information concerning the plant's origin has been lost, due to its long history of cultivation in these regions. The history of ginger is beautifully related by Elzebroek and Wind (2008). According to these authors, ginger is mentioned in the earliest recordings of Chinese herbals and is firmly entrenched in the culinary and medicinal practises of natives of Asian countries. The plant was well known by the Greeks and was mentioned by the Ancient Greek physician, botanist and apothecary Dioscorides (40–90 AD), in his works (Elzebroek and Wind, 2008). After an orgy, the Greeks are said to have eaten ginger wrapped in bread to combat nausea. The Roman writer, naturalist and philosopher Plinius Secundus (23–79 AD 79), known as Pliny the Elder, also described the medicinal use of ginger in his works, *Naturalis Historia* (Elzebroek and Wind, 2008). The spice was known in Germany and France by the 9th century. Marco Polo, introduced to ginger while visiting China and Sumatra in the 13th century, transported some to Europe. During the same period, ginger spread to East Africa from India by the Arabs. Later, in the 16th century, the Portuguese introduced ginger to West Africa. Elzebroek and Wind (2008) also discuss how the cultivation of ginger in Mexico was initiated by the Spaniard, Francesco de Mendoza. Throughout the Middle Ages, ginger was used to flavour beer. The English botanist William Roscoe named the plant *Zingiber officinale* in 1807. The genus name is from the Greek word 'zingiberis', which is derived from the Sanskrit word 'shringavera', aptly meaning 'shaped like a deer's antlers', while *officinale* pertains to the medicinal properties of the rhizomes (Elzebroek and Wind, 2008). Ginger is

*Abbreviations:* BSA, bovine serum albumin; COX, cyclooxygenase; GN, gingerol; HepG2, human hepatoma G2; iNOS, inducible NO synthase; LPS, lipopolysaccharide; MBC, minimum bactericidal concentration; MIC, minimal inhibitory concentration; NF-κB, nuclear factor-kappa B; NO, nitric oxide; OVA, ovalbumin; PG, prostaglandin; ROS, reactive oxygen species; SERCA, sarco-endoplasmic reticulum $Ca^{2+}$-ATPase; SG, shogaol; SR, sarcoplasmic reticulum; TPA, 12-O-tetradecanoylphorbol-13-acetate; TRPV1, transient receptor potential cation channel subfamily V member 1.

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commercially cultivated throughout the world and is a common crop in Africa, Latin America and south-east Asia.

Infusions prepared from ginger are reputed folk remedies in many countries for a wide range of conditions, but primarily to treat coughs, colds and flu (Khaki and Fathiazad, 2012). Beer containing ginger is used to settle stomach upsets. In Burma, a mixture of ginger and palm tree juice is taken to alleviate flu, whereas in Colombia, ginger mixed with hot panela is used to treat colds and flu. An infusion of ginger rhizomes with brown sugar is administered to relieve common colds, while scrambled eggs with powdered ginger is taken as a home remedy to reduce coughing in China. A mixture of ginger and mango juice is considered to be a panacea (medicine to cure all) in the Congo. Khaki and Fathiazad (2012) also mention the use of ginger rhizomes, prepared as a paste, for external application to cure headaches and taken orally to offer relief of colds in India and Nepal, while its mixture with lemon and black salt is extensively used to combat nausea. In Indonesia, ginger is believed to reduce fatigue, prevent rheumatism and improve digestion, whereas in the Philippines, it is taken to sooth a sore throat. Ginger is used in the United States as a remedy to alleviate motion sickness and morning sickness during pregnancy and to reduce heat cramps. Peruvians take ginger infusions to reduce stomach cramps, while the Japanese use ginger to improve blood circulation. Ginger plays an important role in Ayurvedic, Chinese, Arabic and African traditional medicines used to treat headaches, nausea, colds, arthritis, rheumatism, muscular discomfort and inflammation (Baliga et al., 2011; Dehghani et al., 2011).

Ginger is well known for its nutraceutical value, which can be ascribed to a variety of bioactive compounds, including the gingerols, zingiberene and the shogaols (Butt and Sultan, 2011). The pungent taste of fresh ginger rhizome is attributed to the presence of the gingerols (GNs), a group of volatile phenolic compounds. Gingerol (6-GN) is the major compound of the rhizome responsible for the pungency, while other GNs, such as 4-, 8-, 10- and 12-GN, are present in lesser concentrations. These compounds are thermally labile and are transformed at high temperatures to shogaols (SGs), which impart a pungent and spicy-sweet fragrance (Wohlmuth et al., 2005). During the preparation of dried ginger, GNs are also rapidly converted to the corresponding SGs, of which 6-SG is the most common dehydration product (Ok and Jeong, 2012). In many cases, 6-SG has been reported to have better biological activities than 6-GN. In the plant, GNs co-occur with various analogues, including the gingerdiones (Wang et al., 2011a). The concentrations of 6-, 8- and 10-GN were found to diminish when fresh ginger was roasted, dried and charred, whereas the concentrations of 6-SG increased with the corresponding treatments (Zhang et al., 2012). Although some reports have claimed that 6-SG occurs in fresh ginger rhizome (Wang et al., 2011b), this has not been conclusively proven. Park and Jung (2012) developed a sensitive high performance liquid chromatography-time-of-flight mass spectrometry method for the quantification of ginger-related compounds in fresh and dry ginger and in a hot water extract. They concluded that fresh ginger is devoid of the shogaols, but suggested that these compounds are artefacts formed from the corresponding gingerols through heat-catalysed dehydration reactions. In contrast, Bhattarai et al. (2007) are of the opinion that 6-GN and 6-SG undergo reversible first-order dehydration and hydration reactions to form 6-SG and 6-GN, respectively.

Thresh first isolated 6-GN, a volatile yellow oil at room temperature, in 1879 from the rhizomes of ginger (Thresh, 1879; Wohlmuth, 2008). After the discovery of 6-GN, various studies focussed on determining its structure (Lapworth et al., 1917; Nelson, 1917). Although the rhizomes of ginger are the primary source of GNs, many species of the Zingiberaceae, in addition to others, produce GNs as major compounds. These compounds have been reported to be present in other species in the genus *Zingiber* and also in related genera, including *Zingiber zerumbet* (L.) Smith (Zingiberaceae) (Chang et al., 2012) and *Aframomum melegueta* K. Schum. (Zingiberaceae) (Groblacher et al., 2012). However, the presence of gingerol and zingerone was reported in seeds of *Trigonella foenum-graecum* L. (Leguminosae) (Al-Daghri et al., 2012). Gas chromatography–mass spectrometry was used to identify the two analytes, but retention indices and the use of reference standards were not mentioned. Since no other accompanying gingerol metabolites were identified, this report should perhaps be viewed with some degree of caution until further research supports the findings. A range of gingerols and shagaols were isolated from the roots of *Lycianthes marlipoensis* C.Y. Wu & S.C. Huang (Solanaceae) and their structures elucidated using NMR spectroscopy (Guo and Li, 2011). Although the Solanaceae is taxonomically distant from *Zingiber*, this report seems more credible. The biotransformation of 6-GN and 6-SG by *Aspergillus niger* in the rhizomes of ginger to form their tasteless metabolites, a primary alcohol from 6-GN and both a ketoalcohol and a diol from 6-SG, was described by Takahashi et al. (1993). A recent study (Chari et al., 2013) revealed the roles of specific enzymes, including α-amylase, viscozyme, cellulase, protease and pectinase, in increasing the yield of GN in the rhizomes of ginger.

In this paper, the biosynthesis, chemical synthesis and biological properties of 6-gingerol ((5*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one), 8-gingerol ((5*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one), 10-gingerol ((5*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)tetradecan-3-one), 6-shogaol ((*E*)-1-(4-hydroxy-3-methoxyphenyl)dec-4-en-3-one), 8-shogaol ((*E*)-1-(4-hydroxy-3-methoxyphenyl)dodec-4-en-3-one) and 10-shogaol ((*E*)-1-(4-hydroxy-3-methoxyphenyl)tetradec-4-en-3-one) (Fig. 1) are comprehensively reviewed.

## 2. Biosynthesis

Macleod and Whiting (1979) stressed the importance of dihydroferulic acid and hexanoic acid in the biosynthesis of (*S*)-6-GN in ginger. The roles of these compounds were further elucidated when the complete route of biosynthesis of (*S*)-(+)-6-GN in ginger was proposed by Denniff and Whiting (1976a) and Denniff et al. (1980). According to these researchers, phenylalanine is converted to dihydroferulic acid, which subsequently participates in a biological Claisen reaction with malonate and hexanoate to form 6-dehydrogingerdione, which is finally converted to 6-GN (Scheme 1). Ramirez-Ahumada et al. (2006) suggested an alternative pathway for 6-GN biosynthesis in ginger, in which particular enzymes, including phenylalanine ammonia lyase, *p*-coumaroyl shikimate transferase, *p*-coumaroyl quinate transferase, caffeic acid *O*-methyltransferase and caffeoyl-CoA-*O*-methyltransferase, play key roles in the process (Scheme 2).

## 3. Chemical synthesis

The commercial value of the GNs prompted the development of a large number of efficient and cost-effective procedures for their synthesis. The first procedure was reported by Hirao et al. (1973) for the synthesis of *dl*- and *d*-GN *via* *dl*-benzylgingerol, which was produced by the condensation of benzylzingerone with caproic aldehyde. Denniff and Whiting (1976b) and Denniff et al. (1981) synthesised (±)-2-, 4-, 6-, 10- and 12-GN by deprotonation of trimethylsilyl zingerone and trimethylsilyl vanillylacetone with lithium di-isopropylamide at −78 °C. The resulting anions were then used to produce GNs by condensation reactions with aldehydes and acylimidazoles. Enders et al. (1979) achieved an enantioselective synthesis of both (−)-(*R*) and (+)-(*S*)-6-GN by an aldol

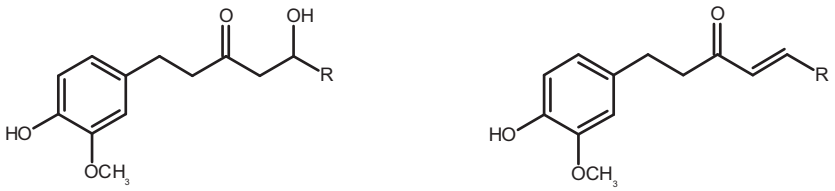
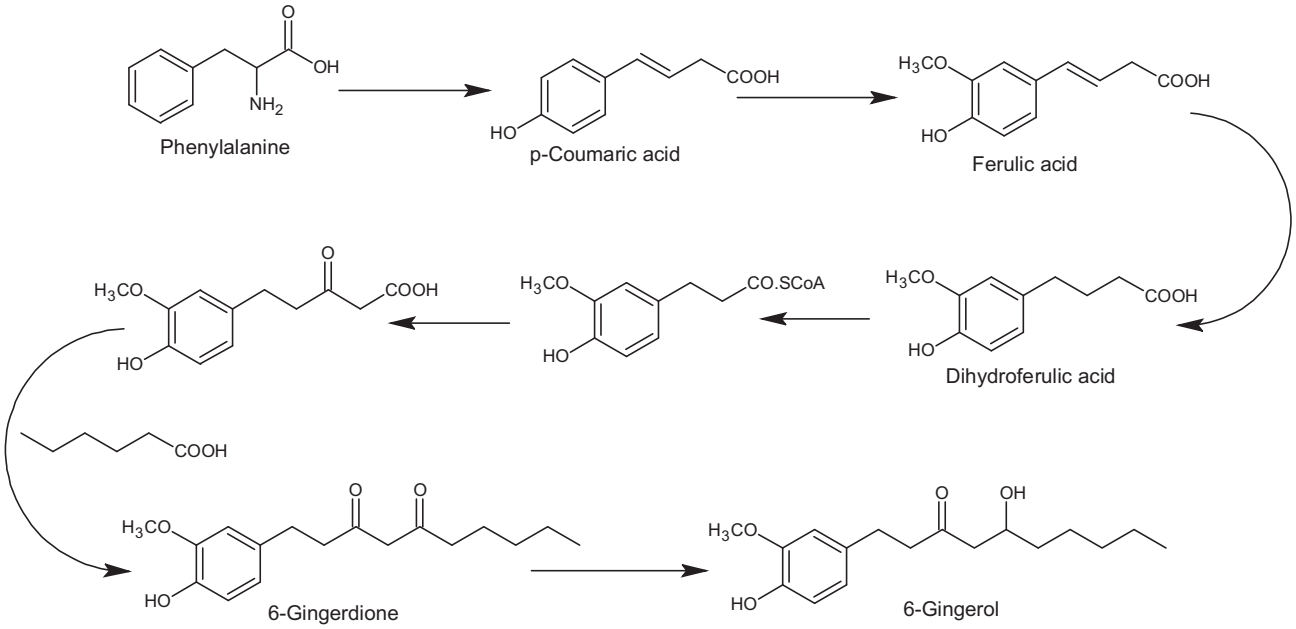



**Fig. 1.** Chemical structures of the various gingerol and shogaol analogues isolated from ginger rhizome.




**Scheme 1.** Biosynthetic pathway for 6-gingerol as proposed by Denniff et al. (1980).

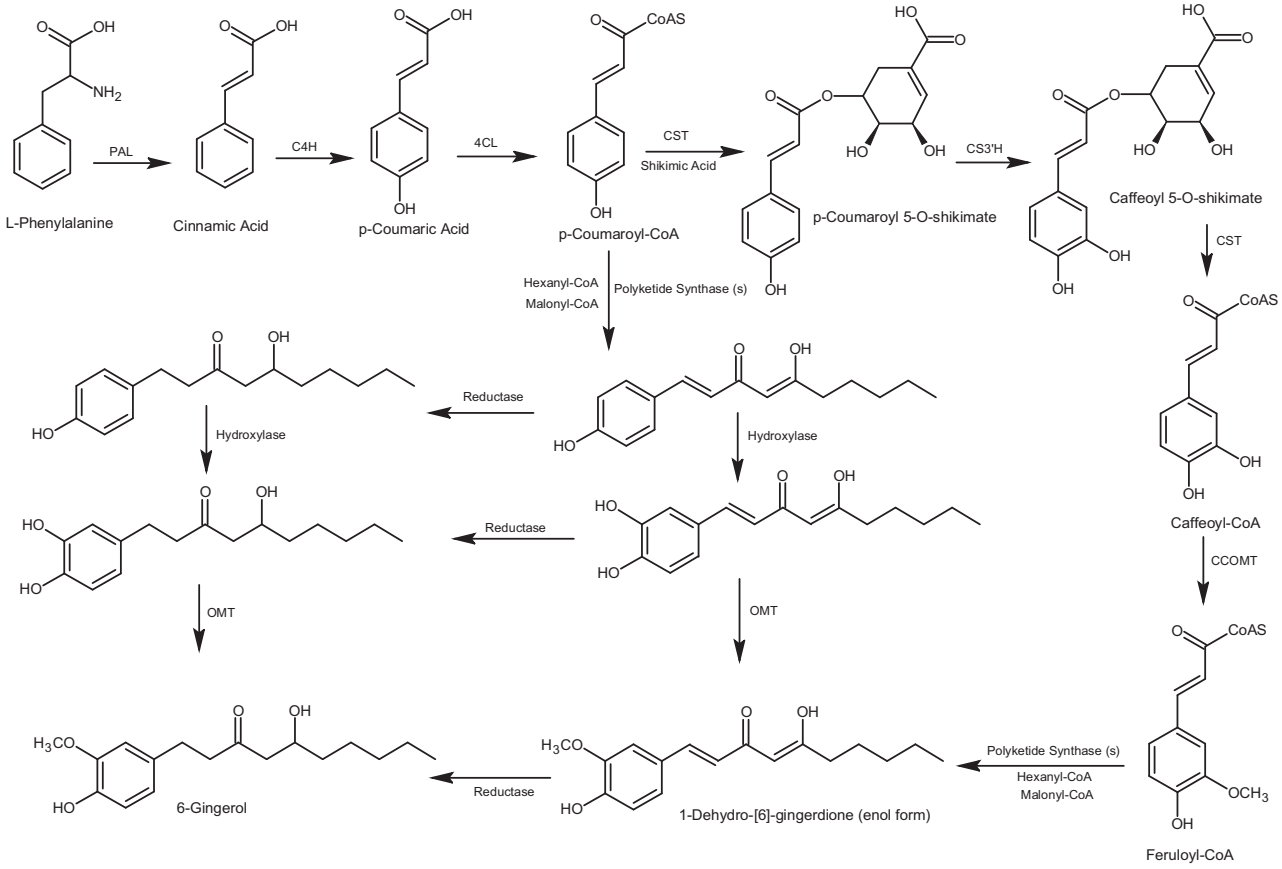
reaction of the chiral hydrazone anion and *n*-hexanal. An alternative route for (±)-6-GN synthesis was reported by Barco et al. (1981) using a 3,5-disubstituted isoxazole derivative, which served as an equivalent for the β-hydroxyketone unit. In contrast, Giovanni et al. (1982) synthesised (±)-6-GN, in addition to (+)-(*S*)-6-GN, making use of 3,5-disubstituted isoxazoles as masked β-ketols. In the first step, isoxazoles were used to produce enamino-ketones *via* reductive fission of the N–O bond, which were then converted to vinylogous imides with N-tosyl-L-prolyl chloride. A diastereoisomeric mixture of the alcohols were subsequently obtained by reduction of the vinylogous imides, which were finally hydrolysed with aqueous $CH_3COOH$ to yield GNs (β-ketols) with optical yields of 30–40%. Le Gall et al. (1989) developed an efficient synthesis of (+)-(*S*)-6-GN by the stereoselective cycloaddition of nitrile oxide and a chiral iron-complexed triene. Tsuge et al. (1987) succeeded in synthesising a racemic mixture of GNs by employing the Horner–Emmons olefination of 4-hydroxy-2-oxoalklyphosphonates. A similar procedure was later used by Martin and Guibet (1991) for the preparation of the (−)-(*R*) and (+)-(*S*) enantiomers of 8-GN. Solladie and Ziani-Cherif (1993) prepared (+)-(*S*)-6-, 8- and 10-GNs from ferulic acid, but a chiral β-keto sulphoxide was used for the asymmetric synthesis of GNs with high yields (Scheme 3).

Sharma et al. (1998) achieved a chemoenzymatic synthesis of (*R*)-8-GN in which the required chiron was prepared by the enantioselective lipase-catalysed esterification of a 2-hydroxy acid. Fleming et al. (1999) explored the feasibility of a one-step synthesis of (±)-6-, 8- and 10-GN by the low temperature addition of a dianion of zingerone to hexanal, octanal and decanal, respectively (Scheme 4). The corresponding SGs were obtained by acidic treatment of different GNs.

Sabitha et al. (2011) made use of Keck allylation, the Crimmins' aldol reaction, aldehyde coupling with acetylene and chelation-controlled reduction to synthesise 6-GN. Kumar et al. (2012) synthesised 6-GN, together with 7- and 9-GN, using eugenol as starting material. In this procedure, the nitro-derivative of eugenol reacts with terminal alkenes to afford intermediate isoxazolines, which then yield the corresponding GNs through catalytic hydrogenation with Raney nickel. A series of analogues of (±)-6-GN displaying TRPV1 and TRPA1 agonist properties were synthesised by Morera et al. (2012).

## 4. Pharmacological significance

Apart from culinary uses, ginger and its major components, GNs and SGs, are known to have beneficial medicinal properties. Numerous pre-clinical studies have supported their value in the treatment of diabetes, obesity, diarrhoea, allergies, pain, fever, rheumatoid arthritis, inflammation and various forms of cancer. Tumours induced in the bowel, breast, ovaries and pancreas were successfully treated by GNs in various animal models. Liver-, CNS- and cardiovascular disorders have been effectively treated




**Enzymes:** PAL= phenylanaline ammonialyase; C4H= cinnamate 4-hydroxylase; 4CL= 4-coumarate:CoA ligase; CST= p-coumaroyl shikimate transferase; CS3'H= p-coumaroyl 5-O-shikimate 3'-hydroxylase; OMT= O-methyltransferase; CCOMT= caffeoyl-CoA O-methyltransferase

**Scheme 2.** Biosynthesis of 6-gingerol as proposed by Ramirez-Ahumada et al. (2006).

in animal models with GNs and SGs. Ginger and its metabolites have been recognised as potent anti-oxidants due to their ability to inhibit the oxidation of various free radicals and the production of nitric oxide. The biological activities of GNs and SGs, together with their possible mechanisms of action and structure–activity relationships, as elucidated through selected *in vitro* and *in vivo* models, are discussed in the following sections.

### 4.1. Anticancer activity

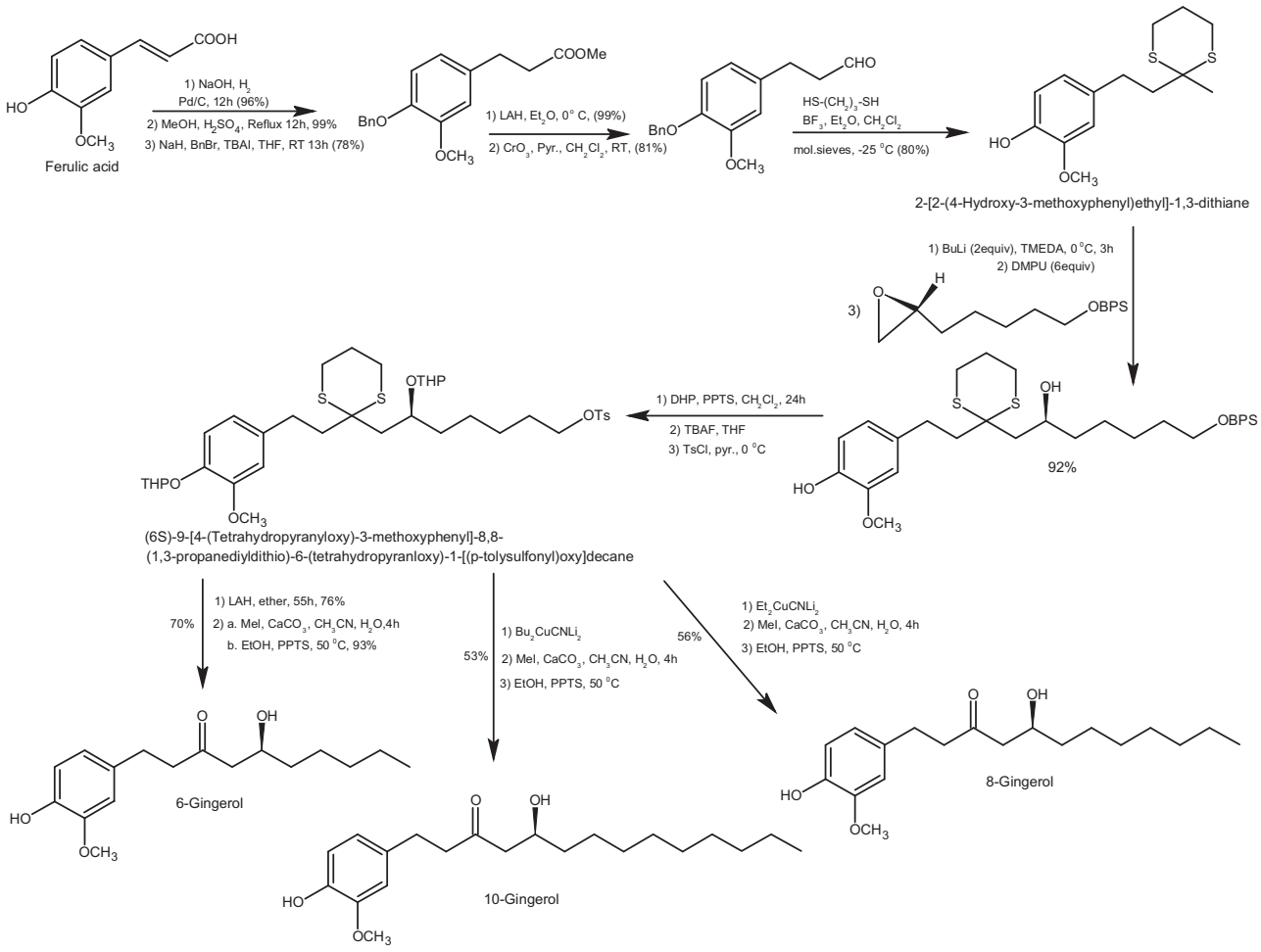
A continued increase in the incidence of cancer has alerted consumers to the use of functional foods that protect against, and reduce the acceleration of the disease. The beneficial effects of ginger and its metabolites against a variety of carcinomas and cell lines of the lung, colon, skin, pancreas, prostate, liver, ovary, colon, breast, kidney, etc. have been recognised by many researchers over the past 20 years. In spite of the huge body of *in vitro* evidence available in the literature (Table 1), *in vivo* assays to establish the therapeutic effects of individual secondary metabolites from ginger against malignant tumours are conspicuous in their absence.

In spite of the GNs and SGs exhibiting anticancer activities towards numerous cell lines, ginger metabolites were found to be mutagenic towards certain *Salmonella typhimurium* strains, upon metabolic activation (Nagabhushan et al., 1987), and towards *Escherichia coli* Strain Hs30 (Nakamura and Yamamoto, 1983). Ginger extract was found to be weakly mutagenic towards some of the *S. typhimurium* strains (TA 100 and TA 1535) and 6-GN proved to be more mutagenic than 6-SG (Nagabhushan et al., 1987). However, zingerone was not only non-mutagenic against all the strains, but actually suppressed the mutagenicity of the other metabolites when tested as a mixture. This led to the logical conclusion that the antimutagenic metabolites probably negate the action of the mutagenic metabolites when ginger is consumed in food. When tested against *E. coli* Hs30, 6-GN and 6-SG caused $1 \times 10^7$ and $1 \times 10^3$ revertants/$10^8$ viable cells/700 μM concentration, respectively, while exposure of histidine-dependent *S. typhimurium* to zingerone, caused only 40 revertants for the same concentration of test substance (Nakamura and Yamamoto, 1983). The aliphatic chain and hydroxyl moieties present in 6-GN and 6-SG were found to be responsible for the mutagenic activities. These findings caution against the use of pure metabolites as nutraceuticals, rather than whole extract of ginger.

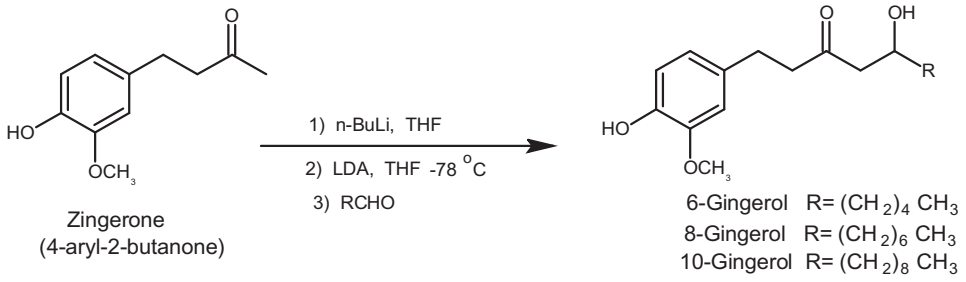
### 4.2. Anti-oxidant activity

Gingerol analogues, 6-, 8-, 10-GN, as well as 6-SG, displayed anti-oxidant activities with $IC_{50}$ values ranging from 8.05 to 26.3 μM for the DPPH radical, 0.85–4.05 μM for the superoxide radical and 0.72–4.62 μM for the hydroxyl radical (Dugasani et al., 2010). The anti-oxidant activity of 6-GN was established by determining the decrease in phospholipid liposome peroxidation in the presence of $Fe^{3+}$ and ascorbate. The compound was found to be a good scavenger of the trichloromethyl peroxyl radical ($CCl_3O_2$), with a rate constant of $10^6$ $M^{-1}$ $s^{-1}$, as calculated by pulse radiolysis (Aeschbach et al., 1994).

6-Gingerol (25 μM) has been reported to inhibit NO production and reduce iNOS in LPS-stimulated J774.1 macrophages, cultured in RPMI1640 medium supplemented with 10% heat-inactivated




**Scheme 3.** Multi-step synthesis of gingerols as proposed by Solladie and Ziani-Cherif (1993).




**Scheme 4.** One-step synthesis of gingerols as proposed by Fleming et al. (1999).

fetal calf serum, 100 U/mL penicillin and 100 μg/mL streptomycin (Ippoushi et al., 2003). It was also found to suppress the peroxynitrite-induced oxidation of dichlorodihydrofluorescein, oxidative single strand breaks in supercoiled pTZ 18U plasmid DNA and the formation of 3-nitrotyrosine in BSA and J774.1 cells. A later mechanism-based study by the same group (Ippoushi et al., 2005) revealed that 6-GN scavenges peroxynitrite-derived radicals and inhibits peroxynitrite-induced oxidation and nitration reactions. The compound, at a concentration of 30 μM, caused a decrease in UVB-induced intracellular ROS levels and activated caspase-3, -8, -9 and Fas expression. In addition, 6-GN stimulated UVB-induced expression and transactivation of COX-2 (Kim et al., 2007). It also inhibited the translocation of NF-κB from the cytosol to the nucleus in HaCaT cells, following the suppression of IκBα phosphorylation.

Lee et al. (2011a) demonstrated the ability of 6-GN to protect against Aβ25-35-induced cytotoxicity and apoptotic cell death, by suppressing the Aβ25-35-induced intracellular accumulation of ROS and reactive nitrogen species and by restoring Aβ25-35-depleted endogenous anti-oxidant glutathione levels. The compound also reduces ROS production in transforming growth factor β1-induced nasal polyp-derived fibroblasts (Park et al., 2012). In addition, it was found to prevent myofibroblast differentiation, collagen production and the phosphorylation of Smad2/3.

### 4.3. Analgesic, antipyretic and anti-inflammatory activities

At intravenous and oral dosages of 1.8–3.5 mg/kg and 70–140 mg/kg, respectively, 6-GN and 6-SG displayed antipyretic and analgesic effects, but caused the inhibition of spontaneous

**Table 1**
Anticancer activity of various metabolites of ginger.

| Cell line | Metabolite | Effect | Reference |
|---|---|---|---|
| *Blood cancer* | | | |
| Promyelocytic HL-60 (leukemia) | 6-GN and 6-paradol | Cytotoxic and antiproliferative activities associated with apoptotic cell death (effective concentration 500 μM) | Lee and Surh (1998), Park et al. (1998), Surh et al. (1999) |
| | 6-GN | Cytotoxic, ROS mediation and inhibition of Bcl-2 expression in cells | Wang et al. (2003) |
| | 6-SG and 10-GN | Cytotoxic ($IC_{50}$ = 10 μM) | Peng et al. (2012) |
| Chronic myeloid K562 (leukemia) | 6-GN | Inhibition of cell proliferation ($IC_{50}$ 11.2–22.9 μg/mL) | Zeng et al. (2010b) |
| Human acute T lymphoblastic MOLT4 (leukemia) | 6-GN | ROS levels reduced in cells | Zeng et al. (2010a) |
| Human lymphocytes | 6-GN | Antigenotoxic effect and amelioration of *in vitro* genotoxic damage induced by norethandrolone and oxandrolone (at 30 and 40 μM) | Beg et al. (2008) |
| *Breast, cervix and ovarian cancer* | | | |
| MDA-MB-231 (human breast cancer) | 6-GN | 16% reduction of cell adhesion at a concentration of 10 μM | Lee et al. (2008a) |
| | 6-, 8- and 10-GN | Inhibition of the proliferation of cells ($IC_{50}$ 666, 136 and 12 μM, respectively). All GNs inhibited human fibroblast cell proliferationat 500 μM | Silva et al. (2012) |
| NCI-60 cell line (human breast MCF7 cells) | 6-SG | Induction of peroxisome proliferator activated receptor γ (PPARγ) transcriptional activity, suppression of NFκB activity and induction of apoptosis in cancer cells at 100 μM | Tan et al. (2013) |
| HeLa cells (human cervical cancer cells) | 6-GN | Externalisation of phosphatidyl serine, DNA degradation and increase in TUNEL in cancer cells. Down-regulation of the over-expression of NFkβ, AKT and Bcl2 genes in cancer cells. IC50 values for 24 and 48 h treatment were found to be 126 and 114 μg/mL, respectively | Chakraborty et al. (2012a) |
| SK-OV-3 (human ovarian cancer cells) | 6-SG, 10-GN | Cytotoxic ($ED_{50}$ = 1.1 μg/mL for 6-SG and 4.5 μg/mL for 10-GN) | Kim et al. (2008) |
| Mouse ovarian cancer cell lines, C1 (genotype: $p53^{-/-}$, c-myc, K-ras) and C2 (genotype: $p53^{-/-}$, c-myc, Akt) | 6-SG | Inhibited the proliferation ($ED_{50}$ of 0.6 and 10.7 μM, for C1 and C2, respectively) | Kim et al. (2008) |
| *Colon cancer* | | | |
| HT29 cells (human colon cancer cells) | 6-SG | Induction of PPARγ transcriptional activity, suppression of NFκB activity and induction of apoptosis in cancer cells at 100 μM | Tan et al. (2013) |
| HCT15 (human colon cancer cells) | 6-SG, 10-GN | Cytotoxic ($ED_{50}$ = 1.76 μg/mL for 6-SG and 6.57 μg/mL for 10-GN) | Kim et al. (2008) |
| HCT 116 (human colon carcinoma cells) | 4- and 6-SG | Apoptosis by inducing aberrant mitosis through the attenuation of cell cycle and spindle assembly checkpoint proteins at 100 μM | Gan et al. (2011) |
| | 6-GN and 6-SG | Inhibition of growth of cancer cells ($IC_{50}$ 8 μM for 6-SG and 150 μM for 6-GN) | Sang et al. (2009) |
| | 6-GN | Suppression of anchorage-independent cancer cell growth through the inhibition of leukotriene A4 hydrolase activity in cancer cells | Jeong et al. (2009) |
| | 6-GN | Inhibition of cancer cell growth ($IC_{50}$ = 160.4 μM) | Lv et al. (2012) |
| COLO 205 (human colon cancer cells) | 6-GN | Inhibition of growth and induced apoptosis in cancer cells due to the modulation of mitochondrial functions through regulation of ROS | Pan et al. (2008b) |
| SW480 (human colorectal cancer cells) | 10-GN | Induced an early signalling effect in cancer cells by increasing intracellular calcium concentration, $[Ca^{2+}]i$ | Yi et al. (2009) |
| LoVo (human colon cancer cells) | 6-GN | Reduced cell viability of cancer cells by inducing G2/M phase arrest with slight effect on the sub-G1 phase | Lin et al. (2012) |
| HCT-116, SW480, HT-29, LoVo, and Caco-2 (Human colorectal cancer cells) | 6-GN | Cytotoxic at 10–100 μM.<br>Suppressed the expression of cyclin D1, while enhancing that of NAG-1 apoptosis in cancer cells stimulated through the upregulation of NAG-1 and the arrest of the G1 cell cycle through downregulation of cyclin D1 | Lee et al. (2008b)<br>Lee et al. (2008b) |
| CT26 (mouse colon carcinoma) | 6-GN | Increased tumour-infiltrating lymphocytes in mouse tumours (*in vivo*) at 3 μg/mL orally it caused massive infiltration of CD4 and CD8 T-cells and B220 + B-cells, but reduced the number of CD4 + Foxp3 + regulatory T-cells in tumour-bearing mice | Ju et al. (2012) |
| *Lung cancer* | | | |
| A-549 (human lung cancer cells) | 6-SG, 10-GN | Cytotoxic ($ED_{50}$ = 1.47 μg/mL for 6-SG and 5.09 μg/mL for 10-GN) | Kim et al. (2008) |
| H-1299 (human lung cancer cells) | 6-GN and 6-SG | Inhibition of growth of cancer cells ($IC_{50}$ 8 μM for 6-SG and 150 μM for 6-GN) | Sang et al. (2009) |
| | 6-GN | Cytotoxic against cancer cells ($IC_{50}$ = 136.73 μM) | Lv et al. (2012) |
| *Skin cancer* | | | |
| SK-MEL-2 (human skin cancer cells) | 6-SG, 10-GN | Cytotoxic ($ED_{50}$ = 1.1 μg/mL for 6-SG and 5.92 μg/mL for 10-GN) | Kim et al. (2008) |
| B16F1 (mouse skin melanoma) | 6-GN | Increased tumour-infiltrating lymphocytes in mouse tumours (*in vivo*).<br>It caused massive infiltration of CD4 and CD8 T-cells and B220 + B-cells, but reduced the number of CD4 + Foxp3 + regulatory T-cells in tumour-bearing mice | Ju et al. (2012) |

(*continued on next page*)

**Table 1** (*continued*)

| Cell line | Metabolite | Effect | Reference |
|---|---|---|---|
| JB6 (mouse epidermal cells | 6-GN and 6-paradol | Induction of cell death at 50 μM (6-parabol) and 300 μM (6-GN) blocked cell transformation induced by epidermal growth factor | Bode et al. (2001) |
| Benzo[a]pyrene-induced skin tumourigenesis in mice | 6-GN | Reduced cumulative number of tumours, and reduced tumour volume (*in vivo*) at a dose of 2.5 μM/mouse, topically chemopreventive effect attributed to an increase in p53 levels, which had initially been suppressed following exposure to benzo[a]pyrene | Nigam et al. (2010) |
| TPA-induced skin tumourigenesis in mice | 6-GN | Topical application at 25 μM/mouse inhibited COX-2 expression (*in vivo*) suppression of NF-κB DNA binding activity in mouse skin and inhibition of phosphorylation of p38 mitogen-activated protein kinase and TPA-stimulated interaction of phospho-p65-(Ser-536) with the cAMP response element binding protein | Kim et al. (2004, 2005a,b) |
| | 6-SG | Inhibition of TPA-induced tumour promotion in mice (*in vivo*) by 50% at oral doses of 3 μg/mL in 60 days inhibition of TPA-stimulated transcription of iNOS and COX-2 mRNA expression by reducing the TPA-induced nuclear translocation of the NF-κB subunits | Wu et al. (2010) |
| A431 (human epidermoid carcinoma cells) | 6-GN | Anti-apoptotic activity and cytotoxicity against A431 cells mediated *via* generation of ROS | Nigam et al. (2009) |
| *Kidney cancer* | | | |
| MDCK cells (dog renal tubular cells) | 6-GN | Stimulation of influx of extracellular $Ca^{2+}$ and release of thapsigargin-sensitive intracellular $Ca^{2+}$ in cells at concentrations ranging from 5 to 20 μM | Chen et al. (2008) |
| Renca (murine renal cell carcinoma) | 6-GN | Increase in tumour-infiltrating lymphocytes in mouse tumours (*in vivo*) when administrated topically with 1.0 and 2.5 μM. Massive infiltration of CD4 and CD8 T-cells and B220 + B-cells, but reduction in number of CD4 + Foxp3 + regulatory T-cells in tumour-bearing mice | Ju et al. (2012) |
| *Liver cancer* | | | |
| AH109A (rat ascites hepatoma cells) | 6-GN | Inhibition of proliferation and invasion of hepatoma cells at concentrations of 6.25–200 and 50–200 μM, respectively. Reduction of ROS-potentiated invasive capacity and intracellular peroxide levels in cells | Yagihashi et al. (2008) |
| HepG2 and Hep3B (human liver carcinoma cells) | 6-SG and 6-GN | Reduction in the migratory and invasive abilities of phorbol-12-myristate-13-acetate (PMA)-treated HepG2 and PMA-untreated Hep3B cells | Weng et al. (2010) |
| HepG2 (human liver carcinoma cells) | 6-GN | Induction of genotoxicity by increasing DNA migration and micronuclei frequencies in HepG2 cells at concentrations of 20–80 and 20–40 μM, respectively reduction of lysosomal membrane stability and mitochondrial membrane potential, while increasing ROS and glutathione levels | Yang et al. (2010) |
| | 6-GN | Chemoprotective effects against patulin-induced genotoxicity in HepG2 cells, by reducing DNA strand breaks and micronuclei formation reduction in patulin-induced elevation in intracellular ROS formation and concentrations of 8-hydroxydeoxyguanosine | Yang et al. (2011) |
| | 6-GN | Cathepsin D found to be a positive mediator of 6-GN-induced apoptosis in HepG2 cells apoptosis found to be associated with oxidative stress | Yang et al. (2012) |
| Human liver microsomes | 6-GN | Inhibition of cytochrome P450 enzymes in human liver microsomes at $IC_{50}$ values ranging from 36 to 2499 μM | Joo and Lim (2011) |
| HuH-7 (human hepatocellular carcinoma cells) | 6-GN | Induction of a transient rise in $[Ca^{2+}]i$ and rapid NFB activation through TRPV1 in cancer cells. Increased the mRNA levels of NFB target genes | Li et al. (2013b) |
| *Pancreatic cancer* | | | |
| BxPC-3 and HPAC (human pancreatic cancer cells) | 6-GN | Inhibition of growth of HPAC-expressing wild-type p53 and BxPC-3-expressing mutated p53 cell lines (at 400 μM) apoptotic cell death of the highly resistant mutant p53 cells and cytostatic effect on wild-type p53-expressing cells through temporal growth arrest | Park et al. (2006) |
| *Prostate cancer* | | | |
| LNCaP (human prostate adenocarcinoma cells) | 6-GN | Modulatory effects on testosterone-induced alterations of apoptosis-related proteins in androgen-sensitive LNCaP cells and in the ventral prostate of Swiss albino mice at 10 mg/kg, b.w. orally for 15 days protective effect against prostate cancer by modulating specific proteins involved in the apoptosis pathway | Shukla et al. (2007) |
| *Neuroblastoma cancer* | | | |
| SH-SY5Y (human neuroblastoma cells) | 4-GN and 6-GN | Inhibition of cancer cell colony formation under anchorage-independent conditions at 100 μM | Gan et al. (2011) |

motor activity and prolonged hexobarbital-induced sleeping time (Suekawa et al., 1984). The analgesic property of 6-GN was affirmed by intraperitoneal administration at 25 and 50 mg/kg in an acetic acid-induced writhing response assay and by measuring formalin-induced licking time in the late phase (Young et al., 2005). An *i.p.* injection of 6-GN, at 2.5 or 25 mg/kg in rats, induced an antipyretic effect by decreasing body temperature without changing any physical activity. The compound also decreased the metabolic rate at 25 mg/kg with no change in heat-loss responses (Ueki et al., 2008).

The use of ginger infusions to alleviate rheumatism and arthritis (Baliga et al., 2011; Dehghani et al., 2011; Khaki and Fathiazad, 2012) have prompted researchers to investigate the anti-inflammatory activities of secondary metabolites of ginger. Tripathi et al. (2007) attributed the anti-inflammatory activity of 6-GN to the inhibition of pro-inflammatory cytokines and antigen presentation by LPS-activated macrophages. The compound inhibited LPS-induced NOS and COX-2 in murine RAW 264.7 cells. Lee et al. (2009) reported that 6-GN displayed anti-inflammatory activity by decreasing inducible NO synthase and TNF-α expression through the suppression of I-κBα phosphorylation, NF-κB nuclear activation and PKC-α translocation. The compound was also found to control TLR-mediated inflammatory responses. It inhibited NF-κB activation and COX-2 expression by inhibiting the LPS-induced dimerisation of TLR4 (Ahn et al., 2009). Lee et al. (2011b) reported that 10-GN, 6-SG and 8-SG exhibited anti-inflammatory activity, by inhibiting direct binding between intercellular adhesion molecule-1 and lymphocyte function-associated antigen-1 of the THP-1 cells, with $IC_{50}$ values of 57.6, 27.1 and 65.4 μM, respectively. Recently, Li et al. (2013c) explored the mechanism of anti-inflammatory action of *S*-6-GN in liver HuH7 cells stimulated by IL1β. The study indicated that 6-GN reduces inflammation and oxidative stress by decreasing mRNA levels of inflammatory factor IL6, IL8, and SAA1. Moreover, the compound decreased IL1β-induced COX-2 upregulation and NFB activity. 10-Gingerol was also found to inhibit neuro-inflammation in a LPS-activated BV2 microglia culture model. The same gingerol analogue, together with other SGs at a concentration of 20 μM, inhibited the production of NO, IL-1β, IL-6 and TNF-α, as well as their mRNA levels, in LPS-activated BV2 microglia (Ho et al., 2013). The inhibition of pro-inflammatory gene expression was ascribed to attenuation of NF-κB activation. Research by Ha et al. (2012) indicated that 6-SG has therapeutic effects on microglia activation in BV-2 and primary microglial cell cultures by inhibiting NO and the expression of NO synthase that is induced by LPS. The production of NO was attenuated by 6-GN, but the compound was a weaker inhibitor than 6-SG, which displayed anti-inflammatory activity by inhibiting the production of prostaglandin E2 and pro-inflammatory cytokines.

Although anti-inflammatory assays were mostly *in vitro* models, some *in vivo* models have been used to study the anti-inflammatory activities of 6-GN. Doses of 50 and 100 mg/kg exhibited anti-inflammatory activity in a carrageenan-induced mouse paw oedema assay (Young et al., 2005). Topical application of 6-GN to the shaven TPA-treated backs of mice resulted in the inhibition of iNOS and COX-2 protein expression (Pan et al., 2008a). It reduced the LPS-induced nuclear translocation of the NFκB subunit and the dependent transcriptional activity of NFκB, by blocking the phosphorylation of inhibitor κBα and p65.

### 4.4. Antidiabetic activity

Glucose uptake was enhanced by (*S*)-6- and (*S*)-8-GN, as demonstrated by radioactively labelled 2-[1,2-$^3$H]-deoxy-D-glucose in L6 myotubes. The higher activity of (*S*)-8-GN was linked to an increase in the surface distribution of GLUT4 protein on the L6 myotube plasma membrane (Li et al., 2012). Chakraborty et al. (2012b) reported that the ability of 6-GN to reduce blood sugar and ease oxidative stress is due to stimulation of superoxide dismutase, catalase, glutathione peroxidase and GSH activities. Treatment with 6-GN resulted in increased plasma insulin levels in mice with sodium arsenite-induced type 2 diabetes, by improving impaired insulin signalling. An *in vivo* assay in streptozotocin-induced diabetic mice revealed that 6-GN acts as a SERCA activator by improving diabetes-induced myocardial diastolic dysfunction and by enhancing the relaxation and the $Ca^{2+}$ transient decay rate (Namekata et al., 2013).

The growth of osteoblastic MC3T3-E1 cells was increased in the presence of 0.1 μM 6-GN and 30 mM 2-deoxy-D-ribose, as a result of elevating the alkaline phosphatase activity, collagen content and osteocalcin secretion of the cells. At concentrations of 1 and 100 nM, 6-GN increased the osteoprotegerin secretion in osteoblastic cells and decreased the protein carbonyl contents of osteoblastic cells, which is of importance in bone diseases related to diabetes (Choi and Kim, 2007). At a concentration of 50 μM, 6-SG and 6-GN caused inhibition of the TNF-α mediated downregulation of adiponectin expression in mouse 3T3-L1 adipocytes *in vitro* (Isa et al., 2008). The study indicates that 6-SG and 6-GN could assist in preventing diabetes *via* the improvement of adipocyte dysfunction.

### 4.5. Anti-obesity activity

Okamoto et al. (2011) reported that 6-GN counteracts body weight gain and fat accumulation in mice. A study conducted by Tzeng and Liu (2013) revealed that 6-GN inhibits rosiglitazone-induced adipogenesis by suppressing oil droplet accumulation and by decreasing the droplet size in 3T3-L1 cells. Histochemical staining also permitted the detection of oil droplets in adipocytes at concentrations ranging from 5 to 15 μg/mL. A reduction in the levels of fatty acid synthase and adipocyte-specific fatty acid binding protein was also reported.

### 4.6. Antimicrobial activity

There is not much data available regarding the antimicrobial activities of ginger or its metabolites. However, some studies have indicated that the metabolites actually augment the activities of other antimicrobial compounds, thereby increasing their effectiveness. It may be argued that this ability of ginger-related compounds may be related to increased disintegration of the bacterial cell walls, which could possibly interfere with the build-up of resistance of pathogens, thereby increasing the useful lifetime of antibiotics.

The gingerol analogues, 10- and 12-GN, displayed potent inhibitory activity against three oral pathogens, *Porphyromonas gingivalis*, *Porphyromonas endodontalis* and *Prevotella intermedia*, with MICs ranging from 6 to 30 μg/mL and MBCs ranging from 4 to 20 μg/mL (Park et al., 2008). Inhibitory activities were displayed by 6-, 8-, 10-GN and 6-SG against *Helicobacter pylori* with MICs ranging from 1.6 to 25 μg/mL. This organism is responsible for gastric cancer in humans. Among all constituents tested, 10-GN was found to be the most active, whereas 6-SG was the least active (Mahady et al., 2003). These results were confirmed by Zhang et al. (2013), who reported an MIC of 0.02 mg/mL for 6-GN against *H. pylori* when compared to amoxicillin as positive control and 50% PEG400 as the negative control.

The addition of 10-GN enhanced the antimicrobial activities of several aminoglycosides, including arbekacin, bacitracin and polymixin B, against vancomycin-resistant enterococci (Nagoshi et al., 2006). The MIC of arbekacin against *Enterococcus faecalis* was lowered from 64 μg/mL to 4 μg/mL, and from 16 μg/mL to 2 μg/mL

against *Enterococcus faecium*, in the presence of 10-GN (20 μg/mL). The compound was also reported to be a potent inhibitor of *Mycobacterium avium* and *Mycobacterium tuberculosis* (Hiserodt et al., 1998). Tintu et al. (2012) reported that 6-GN, at an effective concentration of 0.1 mM, acts as a natural inhibitor of fungal α-amylase, by affecting binding affinity. However, few reports of antifungal activity of ginger metabolites are available.

Cholera is a serious disease that is increasingly difficult to treat due to the development of pathogen resistance to the available drugs (Saha et al., 2013). The antidiarrheal activity of 6-GN has been accredited to its ability to bind to the toxin (CT) produced by *Vibrio cholera*, rather than due to antibacterial activity. This mode of action hinders the interaction of the virulence factor (toxin) with the GM1 receptor present on the epithelial cells of the intestine (Saha et al., 2013). The inhibitory activity on binding was quantified ($IC_{50}$ 10 μg/mL). Further validation of anti-binding activity was achieved *in vitro* by incorporating CHO, HeLa, and HT-29 cell lines, as well as *in vivo* with a rabbit ileal loop assay.

### 4.7. Renoprotective activity

6-Gingerol displays renoprotective activity to alleviate cisplatin-induced oxidative stress and renal dysfunction in rats. The compound aids in restoring renal functions, reducing lipid peroxidation and enhancing the levels of reduced glutathione, superoxide dismutase and catalase activities at doses of 12.5, 25, and 50 mg/kg, respectively (Kuhad et al., 2006).

### 4.8. Activity on the central nervous system

Injection of 10 μg of 6-GN into the rat spinal cord was found to be effective in alleviating neuropathic pain (Gauthier et al., 2013). The compound was also found to block prion peptide-mediated neurotoxicity by protecting mitochondrial function, which is associated with the expression of hypoxia-inducible factor 1α (Jeong et al., 2013). 6-Gingerol and SG were predicted *in silico* to be strong antidepressants, using Argus lab 4.0.1 docking software, when compared to the standard drug, imipramine (Ittiyavirah and Paul, 2013).

Specific primary sensory neurons contain a functional vanilloid receptor that is responsible for transmitting pain or itch stimuli to the central nervous system (Someya et al., 2003). This receptor is activated by vanilloids, such as capsaicin, and by high temperatures. When these capsaicin-sensitive neurons are activated, contraction of the ileum may occur. The *in vitro* contraction of guinea pig ileum was induced by 6-GN immediately after treatment with 30 and 100 μM. However, the induced contraction could be inhibited by tetrodotoxin and atropine, which are antagonists of the vanilloid receptor, indicating that 6-GN binds to the receptor. In addition, 6-GN inhibited capsaicin-induced contraction at a dose above 3 μM confirming the interaction of the compound with the receptor.

### 4.9. Immuno-modulatory activity

The beneficial effects of ginger in treating coughs, colds and flu (Khaki and Fathiazad, 2012) is probably linked to immune-boosting properties of the plant. However, researchers have evaluated the role of gingerols as an immunosuppressant in a quest to find therapeutic agents for treating auto-immune diseases (Lu et al. (2011). It was reported that 8-GN exhibited *in vitro* and *in vivo* immuno suppression of immune responses to OVA in mice by reducing OVA-specific IgG, IgG1 and IgG2b levels at doses of 50 and 100 mg/kg. The compound was found to also suppress LPS- and concanavalin A-induced splenocyte proliferation, while decreasing the percentages of CD19 + B and CD3 + T cells.

An oral dose of 6-GN of 400 mg/kg/day for 7 days, indicated immunomodulatory potential in mice exposed to 5 Gy of γ-radiation. The compound increased spleen relative weight and macrophage survival, while reducing splenocyte survival and proliferation in mice (Zhu, 2009). Farhath et al. (2013) reported that 6-GN exerted an immunomodulatory effect on humoral and cell-mediated immune responses in rats. Oral administration of 800 mg 6-GN per kg body weight for 7 days increased haemagglutinating antibody titre (88.2) and delayed type hypersensitivity (3.5) response in rats when compared to the control (8.9 and 0.2, respectively). It also increased humoral antibody response to the antigen and significantly enhanced cellular immunity by facilitating foot pad thickness response to RBCs in rats, immunised with sheep RBCs.

### 4.10. Anti-allergic activity

The anti-allergic activities of 6-, 8-SG and 8-GN were confirmed by their abilities to inhibit histamine release from rat peritoneal mast cells (Yamahara et al., 1995). Both 6-GN and 6-SG inhibited 48-h passive cutaneous anaphylaxis in rat. In addition, 6-GN displayed antihypersecretory activity by suppressing IL-1β-induced MUC5AC gene expression in human airway epithelial cells at 10 μM. The suppression was mediated *via* the extracellular signal-regulated kinase and p38 mitogen-activated protein kinase-dependent pathways (Kim et al., 2009). Ingestion of 6-, 8-GN and 6-SG reduced asthma activity at doses ranging from 100 to 300 μM, by inducing the rapid relaxation of precontracted airway smooth muscle (Townsend et al., 2013). A 100 μM treatment of human cells with these compounds revealed inhibition of $Ca^{2+}$ in response to bradykinin and *S*-(−)-Bay K 8644.

### 4.11. Antinausea and antigastric activity

It is a well-known folk-lore that ginger alleviates nausea, causing pregnant women with so-called "morning sickness" to nibble on ginger biscuits until they can face food. It therefore comes as no surprise that 6-, 8-, 10-GN and 6-SG were found to inhibit guinea pig M3 and 5-HT3 receptors, which are responsible for nausea and vomiting, at an antagonist concentration of 10 μM (Pertz et al., 2011). Furthermore, an anti-emetic effect was exerted by 6-GN against the acute and delayed phases of cisplatin-induced nausea and vomiting in rats. It was also found to improve their appetites (Wang et al., 2012). A 1.5–50 mg/kg *p.o* dose of 6-GN inhibited basal acid secretion in conscious mice. A combined dose of capsaicin and 6-GN also restricted gastric acid secretion by activating TRPV1 (Okumi et al., 2012).

### 4.12. Suppressive activity on hair growth

6-Gingerol was found to suppress hair growth within follicles in culture. The compound also caused *in vitro* inhibition of proliferation of cultured human dermal papilla cells, which play an important role in nourishing hair follicles by transporting nutrients and oxygen to the epidermal cells (Miao et al., 2013). In addition to prolonging the telogen (resting) phase of hair growth *in vivo*, 6-GN exhibited inhibitory and pro-apoptotic effects against dermal papilla cells *in vitro*.

### 4.13. Anti-angiogenic activity

Kim et al. (2005a,b) reported that 6-GN exhibited anti-angiogenic activity by inhibiting the vascular endothelial growth factor- and basic fibroblast growth factor-induced proliferation of human endothelial cells in the rat aorta. Their study suggested that 6-GN

has potential for the treatment of tumours and other angiogenesis-dependent diseases.

Both 6-GN and 6-SG regulated matrix metalloproteinases-2/-9 transcription in Hep3B cells. Whereas 6-GN reduced urokinase-type plasminogen activator (PA) expression, 6-SG caused up-regulation of the PA inhibitor-1, thereby decreasing PA. Both compounds, at concentrations of 2.5–10 μM, inhibited the phosphorylation of mitogen-activated protein kinase and PI3K/Akt signalling and the activation of NF-κB and STAT3 (Weng et al., 2012).

### 4.14. Anti-platelet aggregation activity

Significant anti-platelet aggregation activity was displayed by 6-GN and 6-SG, while 10-GN inhibited $Ca^{2+}$-dependent contractions in media high in $K^+$ (Liao et al., 2012). The aggregation and release reaction of arachidonic acid and collagen-induced rabbit platelets were inhibited by 6-GN at 0.5–20 μM. It also inhibited thromboxane B2 and PG D2 formation, caused by arachidonic acid, at 0.5–10 μM 6-GN (Guh et al., 1995).

### 4.15. Hepatoprotective activity

The lowering of total bilirubin and several hepatic marker enzymes, including aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase, in blood serum indicated that 6-GN possesses hepatoprotective activity at a dose of 30 mg/kg, against acetaminophen-induced hepatotoxicity (Sabina et al., 2011). These effects were similar to those achieved with silymarin, the positive control, at a dose of 25 mg/kg. In addition. 6-GN and 6-SG imparted a protective effect against diclofenac sodium-induced hepatotoxicity following intra-peritoneal injection of 10 mg/kg for 6 days in rats (Alqasoumi et al., 2011). Joo and Lim (2011) reported that 6-GN inhibits cytochrome P450 in human liver microsomes.

A study based on antihepatotoxic activity by Hiroshi et al. (1985), to establish the mode of action of GNs and SGs. revealed that they are highly active in mitigating $CCl_4$-induced cytotoxicity in primary cultured rat hepatocytes. The length of the side chain and the position of hydroxyl substituents on the molecule were found to play a crucial role in the activity.

### 4.16. Cardiovascular activity

8-Gingerol, at concentrations from $1 \times 10^{-6}$ to $3 \times 10^{-5}$ M, exerted a positive inotropic effect on a left atrium isolated from guinea pig, suggesting that the compound could act as a cardiotonic (Kobayashi et al., 1987, 1988). Although the degree and rate of longitudinal contractions were increased in isolated atrial cells at 3 μM, at concentrations of 3–30 μM, the compound stimulated the $Ca^{2+}$-pumping activity of fragmented sarcoplasmic reticulum in rabbit skeletal and dog cardiac muscles (Ohizumi et al., 1996).

Administering of 0.3 mM of (±)-6-GN suppressed spontaneous spikes in $Ca^{2+}$ concentration and isometric contractions of isolated portal veins of mice, while (±)-8-GN, at the same concentration, inhibited contractions, but had no effect on the $Ca^{2+}$ concentration (Kimura et al., 1988). A study by Maier et al. (2000) indicated that 10-GN, at 0.1 μmol/L, also exerts a positive inotropic effect by increasing sarcoplasmic reticulum $Ca^{2+}$ uptake in human myocardial homogenates. The maximum contraction response, induced by PGF(2α) in the presence of intact vascular endothelium, was achieved in mouse mesenteric veins, following treatment with 0.3 mM (±)-6-GN (Hata et al., 1998). This effect was inhibited by the COX inhibitors aspirin and indomethacin. It was proposed that the COX-dependent release of vasoconstrictors, or the inhibition of vasorelaxants released from endothelial cells, are responsible for the stimulatory effect of 6-GN. An increase in $K$(max(Ca)) was induced by 6-GN in phosphorylated vesicles, in which $Ca^{2+}$ uptake was further increased at a saturated level of $Ca^{2+}$ (Antipenko et al., 1999). The compound stimulated $Ca^{2+}$ uptake in unphosphorylated microsomes in isolated rabbit skeletal muscle by 30–40%, at a saturated level of $Ca^{2+}$, using MgATP concentrations of 0.05–2 mM.

6-Gingerol, at an oral dose of 10 mg/kg, was found to ameliorate the doxorubicin-induced elevation of cardiac enzymes in albino rats (El-Bakly et al., 2012). The reduction in the levels of sRAGE, NF-κB and cardiac caspase-3 following treatment, is helpful in cardioprotection against doxorubicin-induced cardiotoxicity. Liu et al. (2013) reported that 6-GN is able to inhibit the activation of the angiotensin II type 1 receptor as reflected by the $IC_{50}$ value of 8.2 μM, when compared to the positive control, angiotensin II (1 μM). The compound could therefore be helpful in regulating blood pressure and strengthening of the heart. The S-enantiomer of 6-GN was found to exhibit a potent anti-atherosclerotic activity, by inhibiting the incorporation of [35S]-Met/Cys into proteoglycans and total proteins in human vascular smooth muscle cells. It also inhibited TGF-β-stimulated proteoglycan core protein synthesis and biglycan mRNA expression (Kamato et al., 2013).

### 4.17. Miscellaneous activities

6-Gingerol and 6-SG proved lethal to anisakis larvae at a minimal effective dose of 62.5 and 250 μg/mL, respectively (Goto et al., 1990). This finding indicates that these compounds could have potential to treat anisakiasis, a human parasitic infection of the gastrointestinal tract. Heatstroke-induced endotoxemia in mice was ameliorated by 6-GN (Nie et al., 2006). The compound was also found to increase the metabolic concentrations of macrophages, phagocytic abilities and superoxide dismutase activity, while decreasing the concentration of malondialdehyde in the plasma.

Hypoxia-induced embryotoxicities were suppressed by 6-GN in cultured mouse embryos at $1 \times 10^{-9}$ μg/mL, *via* the upregulation of hypoxia-inducible factor 1α and intracellular superoxide dismutases (Yon et al., 2011). The gingerol, at $1 \times 10^{-8}$ or $1 \times 10^{-7}$ μg/mL, provided protection against ethanol-induced teratogenicity during mouse embryogenesis, by controlling the mRNA levels of antioxidant enzymes and superoxide dismutase activity (Yon et al., 2012). At doses ranging from 25 to 100 μM, 6-GN suppressed murine tyrosinase activity and reduced the amount of melanin and intracellular ROS levels (Huang et al., 2011). The suppression of intracellular tyrosinase activity and melanin concentrations in B16F10 and B16F1 cells by 8-GN, at doses of 5–100 μM, was attributed to down-regulation of signalling pathways for protein kinase A and mitogen-activated protein kinases. The abilities of both 6- and 8-GN to reduce the levels of intracellular reactive species and ROS imply that these compounds could be used as a skin-whitening agent (Huang et al., 2013). Complete metabolism of 10-GN to (3*S*,5*S*)-10-gingerdiol and (3*R*,5*S*)-10-gingerdiol was observed in zebrafish embryos and humans after 24 h of treatment (Chen et al., 2013). Both metabolites, as well as 10-GN, displayed hematopoietic effects on zebrafish embryos.

Subcutaneous injection of 6-,8- and 10-GN and SGs at 5–10 mmol/L increased the intracellular calcium concentration in rat TRPV1-expressing HEK293 cells by inducing nociceptive responses (Iwasaki et al., 2006). Gingerol analogues, 6-, 8- and 10-GN, inhibited human cytochrome P450, P2C19 and P3A4 activities. Among them, 8-GN was the most active with $IC_{50}$ values ranging from 6.8 to 8.7 μmol/L (Li et al., 2013a). Treatment with 6-GN reduced iNOS and TNF-α expression by suppressing IκBα phosphorylation and NF-κB nuclear translocation (Oyagbemi

et al., 2010). It was found that ingestion of 6-GN at a dose of 0.30 mg/kg combated fatigue in mice by increasing glycogen storage in the muscles and liver. After oral administration, mice were able to swim for longer and had better lactic acid recovery rates in the blood than the controls (Huang and Peng, 2012).

## 5. Pharmacokinetic studies

Many pharmacokinetic studies have been carried out to determine the efficacy and bioavailability of GNs and SGs, using a variety of analytical tools, including high performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC–MS), gas chromatography–mass spectrometry (GC–MS) and high performance thin layer chromatography (HPTLC).

Ding et al. (1991) developed and validated a HPLC method to determine 6-GN in the plasma of rats that had been intravenously dosed with 3 mg/kg of the compound (Ding et al., 1991). Naora et al. (1992) investigated the pharmacokinetics of 6-GN in rats with bilateral nephrectomy-induced acute renal failure and carbon tetrachloride-induced acute hepatic failure, to elucidate the roles of the kidney and liver in the elimination process of 6-GN. The study revealed that 6-GN can be partially eliminated by the liver. A study of the metabolism in livers of rats treated with phenobarbital revealed that the enzymatic reduction of *S*-(+)-6-GN gives rise to a second asymmetric carbon centre, thereby producing *S*,*S*- and *R*,*S*-gingerdiol metabolites of 6-GN (Surh and Lee, 1994). The gut flora and enzymes were thought to be responsible for the metabolism of 6-GN to (*S*)-6-gingerol-4′-O-β-glucuronide, which was identified as the major metabolite in rat liver (Nakazawa and Ohsawa, 2002). Bhattarai et al. (2007) studied the degradation kinetics of 6-GN and 6-SG in simulated gastric and intestinal fluids. They found that 6-GN and 6-SG undergo first-order reversible dehydration and hydration reactions to form 6-SG and 6-GN, respectively. These degradation processes were found to be catalysed by hydrogen ions and reached equilibrium after approximately 200 h.

The distribution of 6-GN in plasma and other tissues of rats was monitored by HPLC with ultraviolet (UV) detection. After oral administration of a ginger extract (containing 53% 6-GN) at a dose of 240 mg/kg, 6-GN was absorbed into the plasma within 10 min at concentrations as high as 4.23 μg/mL. However, the biggest proportion was confined to the gastrointestinal tract (Jiang et al., 2008). Wang et al. (2009) developed a LC–MS method for the quantitative analysis of 6-GN in plasma and various tissues of rats, with recoveries ranging from 72.5% to 90.4%. 6-Gingerol-glucuronide was identified as the major metabolite of 6-GN following β-glucuronidase hydrolysation. A quantitative LC–MS/MS for the determination of 6-GN in rat tissues was developed and validated by Gauthier et al. (2011). They proposed that phase I metabolism may not be a major contributor to GN clearance from the liver, owing to its slow degradation (163 min half-life). 6-Gingerol-glucuronide, a main metabolite of GN, was found to be excreted in rat urine.

## 6. Toxicity

The ginger metabolites, 6-, 8- and 10-GN and 6-SG, were found to be safe for healthy human subjects up to doses of 2000 mg (Zick et al., 2008). This value is below the recommended guidelines set by the U.S. National Cancer Institute Common Toxicity Criteria. A few individuals experienced minor gastrointestinal symptoms, including eructation, heartburn and indigestion at the highest doses.

## 7. Bioactive markers for quality control of various products

Many commercial products derived from ginger are available. These products originate mainly from China, Korea, India and Japan. Since GNs and SGs are the principle active components of the rhizomes of *Z. officinale*, they are used as marker compounds for the quality control of ginger raw materials and commercial products. The isolation or synthesis of pure reference standards is necessary for any quantitative work. Modern instrumentation can assist in the rapid and cost-effective isolation of GNs and their metabolites from plant material. Zhan et al. (2011) used HPCCC to achieve single-step separation of 200 mg of crude extract. Yields of 30, 41 and 51 mg were obtained for 6-, 8- and 10-GN, respectively. A pre-purified extract (360 mg), resulting from silica gel column chromatography, was further purified using HPCCC to yield 132, 31 and 61 mg of 6-, 8- and 10-GN, respectively (Wang et al., 2011b).

Liquid chromatography is the logical choice for the determination of the GNs, due to their labile nature. Many HPLC-UV methods, with low detection limits, have been developed and validated (Rafi et al., 2013) for the determination of GNs in fresh and roasted ginger (Zhang et al., 2012) and in medicinal products (Kim et al., 2002; Wang et al., 2002). Electrochemical array detection has also been used for the quantification of 6-, 8-, 10-GNs and SGs in various commercial products by RP-HPLC. The method developed by Shao et al. (2010) was found to have detection limits as low as 7.3–20.2 pg for various gingerols.

Hyphenation with mass spectrometry allows the unequivocal identification of the individual gingerols. He et al. (1998) identified 6-, 8-, 10-GNs and SGs by HPLC-UV-ESI-MS, following isolation from ginger extract. The method was found to be suitable for the quality control of raw ginger products. Park and Jung (2012) developed an LC-TOF/MS method to quantify GNs, SGs and other related compounds in fresh and dry ginger. They found that dried ginger contained GNs in higher levels (7126–13,790 μg/g) than fresh ginger (2008–2790 μg/g) whereas SGs were only detected in dry ginger. Jiang et al. (2005) reported the use of LC–ESI-MS/MS for the determination of thermally labile ginger constituents. The advent of UPLC provides the opportunity for fast analysis of medicinal ginger products. Han et al. (2013) also used UPLC for the determination of 6-, 8- and 10-GN in a study aimed at optimising the processing temperature and time for the ginger rhizome preparation.

Although extremely effective, the use of highly sophisticated instruments are expensive and require highly skilled technicians for operation. For this reason, HPTLC methods for quality control of ginger products have been investigated. This technique is appropriate to industrial environments, since non-chemists can be trained to operate the equipment and make decisions from the results. An HPTLC method was developed for the determination of 6-GN (Rf 0.40) in ginger rhizomes using a 40:60 (v/v) mixture of *n*-hexane and diethyl ether as developing solvent (Rai et al., 2006). Rout and Mishra (2009) reported an HPTLC method to determine 6-GN (Rf 0.23) in various marketed Ayurvedic products, as well as in the oleoresin of ginger rhizomes, using *n*-hexane–acetone (7.2:2.8, v/v) as eluent.

## 8. Conclusions and future perspectives

Although many people are aware of the health benefits of ginger, few people realise that pre-clinical studies have indicated that this natural product may have value as a complementary treatment for various forms of cancer. In recent years, nutraceutical compounds have gained wide acceptance as preferred alternatives to various synthetic drugs available on the market, particularly

against cancer and diabetes. The long-term use of synthetic drugs is often associated with serious side effects that can even result in death. Important metabolites of ginger, GNs and SGs, are widely available and safe to use. There are indications that 6-, 10-GNs and SGs (1.6 μmol/kg, *i.v.*) may influence energy consumption in the body, since the compounds were able to promote adrenal catecholamine secretion in rats. An increase in the appetite of rats was noted after administration of GN, alone and in combination with dexamethasone (Wang et al., 2012). These findings indicate that ginger metabolites may have value as ingredients of functional foods. Various studies have also revealed that they possess a myriad of pharmacological activities, including anti-inflammatory, anti-oxidant, antidiabetic and antiproliferative potential. These compounds are promising chemopreventive, hypoglycaemic, anti-aging and anti-inflammatory pain-killing agents. Although numerous studies have been conducted to understand the mechanisms and signalling pathways associated with their anti-oxidant, anticancer and other properties, detailed pharmacokinetic studies are required to determine the mechanism of action and stability in animal systems. There is still a need to further explore the structure–activity relationship of GNs and SGs and to fully map the route of their administration. Gingerols and SGs are effective against various types of cancer *in vitro*, including colon, lung, skin and breast cancer. However, few studies have been done to confirm *in vivo* efficacy of these compounds. Further clinical studies are warranted to assess their efficacy and safety and, consequently, minimise any risks associated with their use. Structural modification of GNs and SGs may further enhance their chemopreventative potential and therapeutic benefits.

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