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Review Article

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EXPERIMENTAL ADVANCES IN PHARMACOLOGY OF GINGEROL AND ANALOGUES

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ABSTRACT

Ginger rhizome has a long history of use in traditional systems of medicine. The primary pungent agents are chemically defined as phenylalkylketones or vanillyl ketones. Gingerol and shogaol seems to be active constituents of ginger based preparations. They are reported to demonstrate analgesic, antiemetic, antipyretic, antiarthritic, and anti-inflammatory activities. Mutagenic potential of gingerol has been discussed. The review article focuses on experimental advances in pharmacology of gingerol and analogues.

Keywords: Ginger, pharmacology, phenylalkylketones, gingerol, shogoal.

INTRODUCTION

Native to tropical Asia, ginger is a perennial cultivated in the tropical climates of Australia, Brazil, China, India, Jamaica, West Africa, and parts of the United States.[1] Ginger rhizome has a long history of use in Chinese and Ayurvedic medicine as an antiemetic and anti-inflammatory agent, and several pharmaceutical or natural health companies have produced products that have ginger (usually 500 mg) as a main active ingredient.[2]

Phytochemistry of ginger

Over 400 different compounds have been identified in ginger. Oleoresin provides 4% to 7.5% of pungent substances. The primary pungent agents (phenylalkylketones or vanillyl ketones) of ginger are gingerol, with other gingerol analogues such as the shogoals, paradol and zingerone also found in high levels in rhizome extracts. The major pharmacological activity of ginger appears to be due to gingerol and shogaol (Duke and Beckstrom 1999). phenylalkylketones or vanillyl ketones of ginger includes [6]-gingerol (Figure **1**), [8]-gingerol (Figure **2**), and [10]-gingerol (Figure **3**), [6] – shogaol (Figure **4**), [8]-shogaol, [10] – shogaol and zingerone (Figure **5**). [6]-paradol (Figure **6**), [6]- and [10]-dehydrogingerdione and [6]- and [10]-gingerdione have also been identified[3].

Compounds isolated from the ginger rhizome have been studied in numerous *in vitro* and animal experiments.[4] Gingerol and shogaol are reported to be responsible for the analgesic, antiemetic, antipyretic, antitussive, hypotensive and cardio depressant, mutagenic, prostaglandin suppression, and enter mobility enhancing activities of ginger.[5]

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Figure 1. Structure of [6]-gingerol

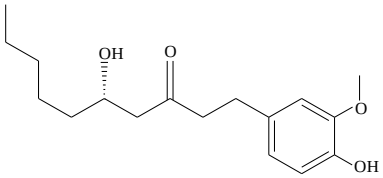


Figure 2. Structure of [8]-gingerol

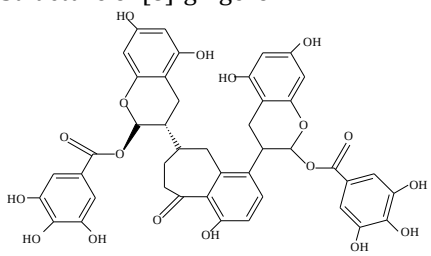


Figure 3. Structure of [10]-gingerol

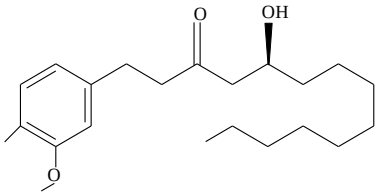


Figure 4. Structure of [6]-shogoal

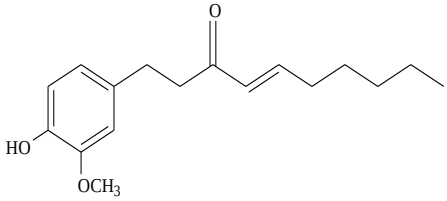


Figure 5. Structure of Zingerone

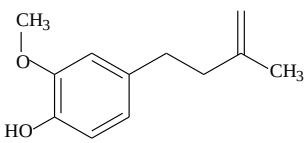
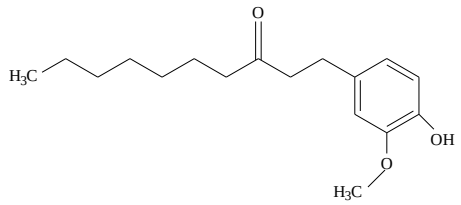


Figure 1. Structure of 6-paradol



REPORTED PHARMACOLOGY OF GINGER

Ginger in crude or standardized extract form has been subjected to several animal studies and cardiotonic,[6] antiplatelet,[7] antiemetic,[8] anxiolytic,[9] anti-diabetic,[10] antidyslipidaemic,[11] anti-inflammatory,[12] anti-obesity,[13] and immunomodulator,[14] have been reported.

There are many traditional uses for ginger, but more recent interest in the use of ginger centers on the prevention and management of nausea. However, there is limited clinical information to support these uses. Limited number of clinical trials have justified efficacy of ginger in the treatment of antiplatelet,[15,16] symptomatic gonoarthritis,[17] pregnancy-induced nausea and vomiting,[18-21] osteoarthritis and chronic low back pain.[3]

PHARMACOLOGY OF GINGER ANALOGUES

Action on gastrointestinal system

Gastro sedative

[6]–shogaol inhibited the traverse of charcoal meal through the intestine in contrast with [6]-gingerol after intravenous administration of 3.5 mg/kg, but [6]-gingerol facilitated such an intestinal function after oral administration of 35 mg/kg. Both [6]-gingerol and [6]–shogaol suppressed gastric contraction *in situ*. The suppression by the [6]–shogaol was more intensive.[22]

Antiemetic

[6]-gingerol, [8]-gingerol, [10]-gingerol and [6] – shogaol have been shown in different *in vivo* studies to be partly responsible for the ginger's anti-emetic properties. These compounds exert their anti-emetic effect at least partly by acting on the 5-HT_3 receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin binding site. This may include indirect effects via receptors in the signal cascade behind the 5-HT_3 receptor channel complex such as substance P receptors and muscarinic receptors.[23]

Action on central nervous system

Antitussive

Intravenous administration of [6]-gingerol (at 1.75-3.5 mg/kg) or (6)-shogaol (at 1.75-3.5 mg/kg) and oral administration of them (at 70-140 mg/kg) resulted in inhibition of spontaneous motor activity, an antipyretic and analgesic effects, prolonged hexobarbital-induced sleeping time. The effects of [6] – shogaol were mostly more intensive than that of [6]-gingerol. [6] –shogaol showed an intense antitussive effect in comparison with dihydrocodeine phosphate.[22]

Anti-inflammatory and analgesic

The anti-inflammatory effect of ginger is thought to be due to inhibition of cyclooxygenase and 5-lipoxygenase, resulting in reduced leukotriene and prostaglandin synthesis.[24] In a study, the analgesic and anti-inflammatory effects of [6]-gingerol were investigated. Intraperitoneal administration of [6]-gingerol) (25 mg/kg-50 mg/kg) produced an inhibition of acetic acid-induced writhing response and formalin-induced licking time in the late phase. [6]-gingerol (50 mg/kg-100 mg/kg). It also resulted in inhibition of paw edema induced by carrageenin.[25]

Hypothermic

A study investigated the effects of systemic administrations of ginger or its pungent constituent, [6]-gingerol on resting body temperature in rats. Rats given ginger-containing rat chow for 5 days showed no changes in their day-night cycle of body temperature or physical activity. However, a single intraperitoneal injection of [6]-gingerol) (2.5 or 25 mg/kg) induced a rapid, marked drop in body temperature in a dose-related manner, with no change in physical activity. A significant decrease in metabolic rate was observed immediately after intraperitoneal injection of [6]-gingerol (25 mg/kg).[26]

Action on cardiovascular system

Antihypertensive

In the cardiovascular system, both [6]-gingerol and [6]–shogaol demonstrated hypotensive response at lower doses. At high doses, both drugs resulted in three phase pattern.[22]

Cardiac tonic

A. The purpose of the study was to compare the effects of [6]-gingerol and ellagic acid, on the kinetics of the sarcoplasmic reticulum Ca^{2+} pump with those of PKA-catalyzed phospholamban phosphorylation to elucidate their mechanisms of Ca^{2+} pump regulation. An inhibition of Ca^{2+} uptake by gingerol at micromolar MgATP concentrations was overcome with increasing MgATP concentrations. The stimulation of Ca^{2+} uptake attributable to gingerol in unphosphorylated microsomes at saturating Ca^{2+} was 30% to 40% when assayed at 0.05 to 2 mM MgATP and only about 12% in phosphorylated microsomes as well as in rabbit fast skeletal muscle light SR.[27]

B. [8]-gingerol produced a concentration-dependent positive inotropic effect on guinea pig isolated left atria at concentrations of 1 X 10(-6) to 3 X 10(-5) M. [8]-gingerol exhibited positive inotropic and chronotropic effects on guinea pig right atria. The time to peak tension and relaxation time within a single contraction were shortened by (2) (1 X 10(-5) M) as well as isoproterenol, whereas they were prolonged by BAY K 8644. In guinea pig isolated atrial cells. [8]-gingerol (3 X 10(-6) M) caused an increase in the degree and the rate of longitudinal contractions.[28]

C. In yet another study, [10]-gingerol. isoproterenol (0.1, 1 mumol/l) and ouabain exerted significant positive inotropic effects under basal experimental conditions and normalized post-rest behavior. In addition, gingerol increased sarcoplasmic reticulum Ca (2+)-uptake significantly in myocardial homogenates. +/Ca (2+)-exchange.[29]

Action on endocrine system

Two experimental groups receiving doses of either 2 or 8 mg/kg/day zingerone for 10 days were compared with young rats (6 months old) and an age-matched control group. For molecular work, the endothelial cell line YPEN-1 was used. Both the 2 and 8 mg/kg/day dose of zingerone significantly increased. Zingerone partially prevented the age-related decline in PPAR expression. *In vitro* experiments revealed zingerone (10 μM) increased PPAR expression (2.5-fold) to a similar extent as the PPAR

agonist fibrate (5 μM) and suppressed pro-inflammatory transcription factor NF-κB activity.[30]

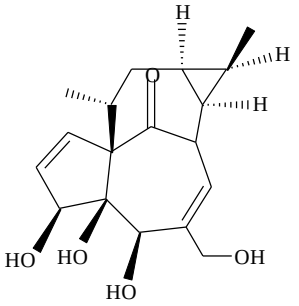
Antiarthritic effect

A study investigated the antiarthritic effects of ginger and its bioactive constituents. A well-characterized crude ginger extract was compared with a fraction containing [6]-gingerol and their derivatives to inhibit joint swelling in an animal model of rheumatoid arthritis, streptococcal cell wall-induced arthritis. Both extracts demonstrated anti-inflammatory activity. The crude dichloromethane extract, containing essential oils and more polar compounds, was more efficacious, when normalized to [6]-gingerol content, in preventing, both joint inflammation and destruction. Non-gingerol components enhance the antiarthritic effects of the more widely studied [6]-gingerol.[31]

Antimicrobial activities

Ingenol (Figure 7) and [6]–shogaol, isolated from ginger rhizome, demonstrated antiviral activity.[32] [10]-gingerol has been reported as active inhibitor of *M. avium* and *M. tuberculosis in vitro.* [33] Gingerol and related compounds have been investigated for antimicrobial activities. [6]-gingerol and [12]-gingerol, isolated from ginger rhizome, demonstrated antibacterial activity against periodontal bacteria.[34]

Figure 7. Structure of Ingenol



Anticancer activities

A. [6]-gingerol has been reported to possess a strong anti-inflammatory activity, which is considered to be closely associated with its cancer chemo preventive potential. [6]-Paradol, another pungent phenolic substance found in ginger, also has a vanilloid structure found in other chemo preventive phytochemicals including curcumin.[35]

B. In one study**,** [6]-gingerol and [6]-paradol were found to exert inhibitory effects on the viability and DNA synthesis of human promyelocytic leukemia (HL-60) cells. The cytotoxic and antiproliferative effects of both compounds were associated with apoptotic cell death. The above results suggest that [6]-gingerol and [6]-paradol possess potential cytotoxic/cytostatic activities. The antioxidative effects of [6]-gingerol) were detected by DPPH and DCFH assays and, as predicted, [6]-gingerol as an antioxidant was shown to protect HL-60 cells from oxidative stress.[36]

C. The leukotriene A_4 hydrolase (LTA_4H) protein is regarded as a relevant target for cancer therapy. *In silico* prediction using a reverse-docking approach suggested LTA_4H as a potential target of [6]-gingerol. The prediction was supported by the fact that [6]-gingerol suppresses anchorage-independent cancer cell growth by inhibiting LTA_4H activity in HCT116 colorectal cancer cells. It showed that [6]-gingerol effectively suppressed tumor growth *in vivo* in nude mice, an effect that was mediated by inhibition of LTA_4H activity.[37]

D. A study examined the early signaling effects of [10]-gingerol on human colorectal cancer cells. [10]-gingerol caused a slow and sustained rise of $[Ca^{2+}]_i$ in a concentration-dependent manner. (3) induced a $[Ca^{2+}]_i$ rise when extra cellular Ca^{2+} was removed, but the magnitude was reduced by 38%. In a Ca^{2+}-free medium, the [10]-gingerol induced $[Ca^{2+}]_i$ rise was partially abolished by depleting stored Ca^{2+} with thapsigargin. [10]-gingerol killed cells in a concentration-dependent manner.[38]

Antioxidant activity

A. In a study, thymol, carvacrol, [6]-gingerol and hydroxytrosol decreased peroxidation of phospholipid liposomes in the presence of iron (III) and ascorbate, but zingerone**)** had only a weak inhibitory effect on the system. However, thymol, carvacrol, [6]-gingerol and hydroxytrosol and zingerone were not able to accelerate DNA damage in the bleomycin-Fe (III) system.[39]

B. Gingerol related compounds and diarylheptanoids are considered to be possible antioxidant constituents if ginger extracts. In this study, structure-activity relationship of gingerol related compounds, substituted with an alkyl group bearing 10-, 12- or 14-carbon chain length were isolated from the dichloromethane extract of rhizomes.

The antioxidant activities of these compounds were evaluated by the following measurements;

1. 1, 1-diphenyl-2-picrylhydrazyl radical scavenging activity,
2. Inhibitory effect on oxidation of methyl linoleate under aeration and heating by the Oil Stability Index (OSI) method
3. Inhibitory effect on oxidation of liposome induced by 2,2'-azobis(2-amidinopropane) dihydrochloride.

These findings suggests that the substituents on the alkyl chain might contribute to both radical scavenging effect and inhibitory effect of autoxidation of oils, while inhibitory effects against the AAPH-induced peroxidation of liposome was somewhat influenced by the alkyl chain length.[40]

C. In order to study the nephroprotective activity of gingerol against cisplatin- on cisplatin-induced oxidative stress and renal dysfunction. [6]-gingerol in dosages of 12.5, 25, 50 mg/kg was administered 2 days before and 3 days after cisplatin administration. Renal injury was assessed by measuring serum creatinine, blood urea nitrogen, creatinine, urea clearance and serum nitrite levels. Renal oxidative stress was assessed by determining renal malondialdehyde levels, reduced glutathione levels and enzymatic activities of superoxide dismutase and catalase. A single dose of cisplatin resulted in marked renal oxidative and nitrosative stress and significantly deranged renal functions.[41]

Radio protective activity

In vitro, pre-treatment with [6]-gingerol reduced UVB-induced intracellular reactive oxygen species levels, activation of caspase-3, -8, -9, and Fas expression. It also reduced UVB-induced expression and transactivation of

COX-2. Translocation of NF-κB from cytosol to nucleus in HaCaT cells was inhibited by [6]-gingerol via suppression of IκBα phosphorylation (ser-32). Examination by EMSAs and immunohistochemistry showed that topical application of [6]-gingerol (30 μM) prior to UVB irradiation (5 kJ/m2) of hairless mice, also inhibited the induction of COX-2 mRNA and protein, as well as NF-κB translocation.[42]

Antigenotoxic activity

Norethandrolone and oxandrolone were investigated for their genotoxic effect on human lymphocyte chromosomes using chromosomal aberrations and sister chromatid exchanges as parameters and subsequently Genistein and [6]-gingerol were used as antigenotoxic agents to ameliorate the genotoxicity induced by the steroids. Norethandrolone and oxandrolone were studied at 5, 10, 20, 30 and 40 μM, respectively and were found to be significantly genotoxic at 30 and 40 μM. Genistein and [6]-gingerol proved to be equally effective in reducing genotoxic damage at appropriate doses.[43]

Mutagenicity

A study was performed to discover the active part in mutagenesis of [6]-gingerol and [6]-shogoal. [6]-shogoal was much less mutagenic (1×10^3 revertants/10^8 viable cells/700 μM) than [6]-gingerol (1×10^7 of the same units). Mutation frequencies of their related compounds were 4×10^1 for zingerone, 1×10^7 for 3-hydroxymyristic acid and 3×10^2 for 12-hydroxystearic acid.[44]

PHARMACOKINETICS OF GINGER ANALOGS

Oral or intraperitoneal dosage (100mg/kg) of zingerone resulted in the urinary excretion of most metabolites within 24 h, mainly as glucuronide and/or sulphate conjugates. While zingerone itself accounted for roughly 50—55% of the dose, reduction to the corresponding carbinol (11-13%) also occurred. Appreciable (40% in 12 h) biliary excretion occurred.[45]

The metabolic fate of [6]-gingerol was investigated using rats. The bile of rats orally administered [6]-gingerol was shown to contain a major metabolite. The total cumulative amount of [6]-gingerol excreted in the bile and 2-7 in the urine during 60 h after the oral administration of [6]-gingerol were approximately 48% and 16% of the dose, respectively. The excretion of 2-7 in the urine decreased after gut sterilization. On the other hand, the incubations of [6]-gingerol with rat liver showed the presence of 9-hydroxy [6]-gingerol, gingerdiol, and (S)-[6]-gingerol-4'-O-β-glucuronide.[46]

A study investigated the *in situ* jejunal absorption of [6]-gingerol) to determine the extent of its intestinal absorption after administering the drug solution (2 mg in 0.9% NaCl solution containing 5% Tween 80) into the closed jejunal loop in rats. Initially, the blood cell-plasma partition of [6]-gingerol was investigated following intravenous administration (3 mg/kg) in rats to calculate the drug levels in whole blood from the plasma levels measured in the absorption experiments. The blood cell-plasma concentration partition ratio (K) for [6]-gingerol after instantaneous equilibrium was achieved was estimated as 0.489. The cumulative percentage of [6]-gingerol absorbed into the mesenteric venous blood by 60 min was estimated to be 10.86±2.61% of the initial dose.

The recovery of [6]-gingerol was calculated by dividing the sum of the cumulative amount of [6]-gingerol absorbed in the mesenteric blood, the amount of the drug taken up by the jejunal mucosa and muscle at 60 minutes, and the remaining amount of [6]-gingerol) in the closed loop by the initial dose, and was estimated as 58.7±9.2%. The residual 40% of the initial dose was not recovered as [6]-gingerol.[47]

CONCLUSION

This article has outlined some of the current thinking with regard to the experimental advances in gingerol and analogues. Animal studies done so far, reveals the empirical use of ginger in several aryurvedic medicinal products.

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