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Red ginger (*Zingiber officinale* Roscoe var *rubrum*): a review

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Abstract

Red ginger (*Zingiber officinale* Roscoe var *rubrum*) has been widely used as traditional medicine in many countries, especially in Indonesia, China, and Malaysia. The traditional use of red ginger is in accordance with its pharmacological activity and chemical content. Many studies have shown that red ginger exhibited pharmacological activities as an immunomodulator, antihypertensive, antihyperlipidemia, tonic, acetylcholine esterase inhibitor, antihyperuricemia, antimicrobial agent, and cytotoxic agent. Several studies have also indicated that some of the pharmacological activities of red ginger were superior to that of white ginger. This review aimed to examine the development of studies concerning red ginger from its ethnopharmacology to pharmacological activity.

Keywords: red ginger, *Zingiber officinale Roscoe* var *rubrum*, gingerol, shogaol.

Introduction

Ginger is a plant widely used in Indonesia as a food preservative, seasoning, and in traditional remedies [1]. Based on the size and color of the rhizome, ginger is divided into three varieties, namely elephant-sized or white ginger (*Z. officinale* var. *officinale*), *emprit* or small ginger (*Z. officinale* var. *amarum*), and red ginger (*Z. officinale* var *rubrum*) [2][3][4].

According to the modern system of taxonomy, red ginger is biologically categorized into the Spermatophyta division, Angiospermae subdivision, Monocotyledoneae class, Zingiberales order, Zingiberaceae family, and *Zingiber officinale* Roscoe var. *rubrum* Theilade species [5]. It is synonymous with *Zingiber officinale* Roscoe var *Sunti* Val., *Zingiber amomum* L., *Zingiber cholmondeleyi* (F.M.Bailey) K.Schum., *Zingiber missionis* Wall., *Zingiber officinale* var. *macrorhizonum* Makino, *Zingiber officinale* var. *rubens* Makino, *Zingiber sichuanense* Z.Y.Zhu, S.L.Zhang & S.X.Chen [6]. An annual plant that can grow to up to 50-100 cm high, it has thick, reddish-brown rhizomes but is smaller than white ginger. The leaves are narrow and lancet-shaped with a length of 5-25 cm and a width of 8-20 mm. The plant has an ovoid-shaped composite that emerges from the rhizomes, with a stem length of 10-25 cm and small leaves at the base of the flower. The corollas are funnel-shaped, 2-2.5 cm long, and have a dark purple colour with creamy-yellow spots. The petals are small, tubular, and tridental [7].

Red ginger is known by many names in many countries and languages, such as Canton ginger, East Indian ginger, and stem ginger in England; zenjabil and zingibil in Arabic; chiang, ganjiang, and kanchiang in China; and jahe blasa or jahe merah in Indonesia [6].

Materials and Methods

The journals were searched through online search engine powered by Scopus, Science Direct, Google Scholar and Pubmed with pharmacological activities and scientific name as key words.

Results

Ethnopharmacological studies

Ginger is believed to have originated in Southeast Asia. It can only be grown from cultivation and is not found in the wild [8]. In India, ginger decoctions are widely used in the Ayurvedic medicine systems, Unani and Siddha. These decoctions have a wide variety of uses, including as stimulants, contraceptives, aphrodisiacs, abortion, hypoglycemic agents, hypolipidemic agents, tonics, carminatives, and stomach pain relievers. Fresh ginger is also used to treat flu, arthritis, pneumonia, infertility, helminth infections, toothache, tuberculosis, vomiting, cough, asthma, bronchitis, sore throat, diarrhea, headache, wound infections, and malaria [6]. In China, ginger has been known since the 4th century BC and is used in traditional Chinese medicine as anti-worm and anti-malarial agents [9][10].

In its place of origin, Southeast Asia, red ginger has also had a long history of use in traditional medicine. For instance, red ginger has been extensively used by the indigenous peoples of Indonesia (such as the Tolitoli, Java, Banjar, Madura, Batak, Dayak, Bugis, and Sunda tribes [11][12], to treat nausea, vomiting, impotence, colds, flatulence, and coughs [13. The pungent smell and spicy taste of red ginger was believed to have better efficacy than other subspecies of ginger, and its cultivation was encouraged [14].

Although ginger first originated and was mostly cultivated in Asia, it has also spread to other parts of the world, including Europe and America. The first European to discover this plant was the Venetian merchant, Marco Polo, in 1285. After that, ginger became an essential commodity in Europe, leading the Venetian merchants to build businesses in Constantinople and Sudak, situated on the shores of the Red Sea, to monopolize the ginger trade brought by caravans from the Silk Road. The Venetians' monopoly of the ginger trade continued until the 15th century but started to collapse when Portuguese sailors were able to sail directly to Calicut, India, to obtain ginger. Another prominent figure involved in the ginger trade was Francisco Mendoza who brought ginger to South America to be cultivated and then exported to Spain in early 1547 [15].

The popularity of red ginger in society, as well as its ethnopharmacological studies, is thought to have triggered the many further research into this subspecies of ginger.

Chemical constituents

Although the chemical constituents of red ginger vary depending on the cultivation site, a ginger rhizome typically contains 1-2% of volatile oils, 5-8% of resinous substancesand also starch and gum [9][16]. The composition of volatile oils in ginger is characterized by a high percentage of sesquiterpene hydrocarbons such as α-zingiberene, ar-curcumene, β-bisabolene, and β-sesquiphellandrene [10][17][18][19][20].

In 2011, Sivasothy *et al.* mapped the volatile oil composition in the leaves and fresh rhizomes of red ginger obtained from Negeri Sembilan, Malaysia [21]. Forty-six compounds were detected in the leaves and 54 compounds in the rhizomes, the main constituents of which were monoterpenoids (81.9%), with the highest

being camphene (14.7%), followed by geranial (14.3%), geranyl acetate (13.7%), neral (7.7 %), geraniol (7.3%), and 1.8-cineole (5%). Neral and geranial are suspected to cause the scent of lemon found in red ginger rhizomes, similar to gingers from Australia, while borneol, bornyl acetate, and 1,8-cineole contribute to their camphor-like aroma [10][22].

Pharmacological activities

Studies have shown that red ginger exhibits several pharmacological activities, such as immunomodulators, antihypertensives, antihyperlipidemia, tonics, acetylcholine esterase inhibitors, antihyperuricemia, antimicrobial, and cytotoxic agents [23][24][25][26][27][28][29][30].

Immunomodulator in psoriasis

The immunomodulator properties of red ginger were studied by Nordin *et al.* [23]. The active fraction of red ginger rhizome chloroform extract containing 6-shogaol and 1-dehydro-6-gingerdione effectively inhibited the production of nitric oxide (NO) and prostaglandin E2 (PGE2) by activating macrophages. At a concentration of 20 µg/ml, this active fraction also reduced mRNA levels of iNOS, IL-12p40, and IL-23p19 in pre-treatment experiments of activated macrophages. Additionally, inhibition of polymorphonuclear neutrophil (PMN) migration through human vascular endothelial cells (HUVEC), presumably by influencing CD11b expression and CD62L shedding, and activation of the expression of CD8 + cytotoxic T-lymphocytes, CD25, and CD69, were observed. Inhibition of cytokines IL-20 and IL-8 expression, as well as inhibition of the proliferation of keratinocytes, were also observed through *in vitro* studies.

Antihypertensive

In vitro studies have shown that red ginger aqueous extracts (1:20 w/v) inhibit the action of Angiontensin-I converting enzyme (ACE), and Fe^{2+}- and sodium nitroprusside (SNP)-induced lipid peroxidation in rats' hearts. The red ginger aqueous extracts were also compared to those of white ginger and were shown to have a higher inhibitory effect, with an EC_{50} value of 0.027 mg/ml. In the incubation period, the reduction of malondialdehyde levels by red ginger aqueous extract followed a dose-dependent trend [24].

The ACE inhibitor activity of red ginger was also demonstrated in *in vivo* studies conducted using HDL cholesterol-induced rats. Rats given feed containing 4% red ginger showed a significant decrease in blood HDL-Cholesterol levels, as well as malondialdehyde levels in the liver and heart tissues. These results indicate that **the** antihypertensive effect of red ginger is due to the inhibition of ACE and lipid peroxidation [31].

Antihyperlipidemia

A recent study conducted by Hapsari and Rahayuningsih (2014) showed the antihyperlipidemia effect of red ginger [25]. Thirty-four female subjects who suffered from hyperlipidemia were given red ginger drinks with a dose of 3.2 ml/kg bw for 21 days. The results showed that the low density lipoprotein cholesterol (LDL-C) levels of the subjects decreased by 12% at the end of the treatment period. The antihyperlipidemia activity of red ginger extract is believed to arise from 6-gingerol, 6-shogaol, and gingerdione, the concentration of which are higher in red ginger compared to other ginger varieties [32][33].

Tonicum

An *in vivo* study using male Swiss mice showed that the ethanol extract of red ginger had a higher tonic effect than other ginger varieties. The average tonic effect of red ginger ethanol extract was 5.6711 minutes compared to the 4.0300 minutes of white ginger ethanol extract. The compounds thought to be responsible for this tonic or stimulant effect in extracts of ginger is oleoresin [26].

Alzheimer's disease therapy

A study by Oboh *et al.* investigated the effect of red ginger rhizome aqueous extracts on sodium nitroprusside-induced mice, and the results showed that the extracts inhibited the activity of acetylcholine esterase (AChE) in the mice's brains. This anti-AChE activity was caused by the flavonoids, tannins, alkaloids and terpenoids present in the extract that prevented lipid peroxidation [27].

Antihyperuricemia

The antihyperuricemia activities of red ginger rhizome methanol extract were studied by Hariyanto *et al.* [28]. A reduction in uric acid levels by 78.76% was observed when administered orally in Wistar rats for 9 days at a dose of 0.0305 g/kg bw. This effect is associated with rutin, kaempferol, and quercetin as flavonoids that inhibit xanthine oxidase activity. Epicatechin and catechin in extracts were also reported to have antioxidant activity against free radicals.

Antimicrobial activity

Some of the volatile oils contained in red ginger, namely trimethyl-heptadien-ol, ar-curcumene, camphene, carbaldehyde, sesquiphellandrene, and nerol, were found to inhibit the growth of test bacteria with MIC values

ranging from 2.65 to 3.97 mg/ml and MBC values from 3.10 to 5.29 mg/ml. Based on the MIC and MBC values, *Bacillus cereus* was the most sensitive to red ginger volatile oils, followed by *Escherichia coli, Salmonella typhimurium,* and *Pseudomonas aeruginosa* [29].

Cytotoxic agent

In vitro studies of red ginger rhizome extract showed cytotoxicity against myeloma and WiDr cells with IC_{50} values of 28 mg/ml and 74 mg/ml. Additionally, immunohistochemical results showed an increased expression of p53 in cell apoptosis, and inhibition of p53 expression in HeLa, T47D, and MCF-7 cell lines [30].

Pharmacokinetic activity

The pharmacokinetic profiles of the chemical constituents of red ginger have never been investigated. However, a pharmacokinetic study of similar compounds, namely 6-shogaol and 6-gingerol, has been conducted. The tests were carried out using both ^{14}C-labeled 6-shogaol and unlabeled 6-shogaol. The study showed that the blood concentration of these compounds (AUC) is dose-dependent. When administered orally at a dose of 10mg/kg, 20% of 6-shogaol (labeled) is excreted via urine, 64% in feces, and 12.9% through the respiratory tract. Meanwhile, orally-administered 6-shogaol (unlabeled) had a low plasma concentration and excretion. This suggests that 6-shogaol is largely metabolized in the body and is excreted in the form of metabolites [34]. Furthermore, 6-gingerol has an elimination half-life of 7.23 minutes with CrCl 16.8 ml/min/kg and 92.4% protein binding. Also, gut flora and liver enzymes play a key role in the metabolism of 6-gingerol [35][36].

Red ginger is a superior ginger variety in terms of its shogaol and gingerol contents and pharmacological activities. For instance, its 6-gingerol and 6-shogaol contents were proven to have a superior antihyperlipidemic effect without any side effect due to inhibition of prostaglandin. Red ginger also shows promising results as immunomodulator, antihypertensive, tonicum, treatment of Alzheimer's disease, antihyperuricemia and cytotoxic agent. The immunomodulator activity showed red ginger extract affected the lymphocyte T activity and its secreted cytokine that contribute to psoriasis. The extracts also express inhibitory activity to ACE higher than white ginger. Oleoresin compound of red ginger, considered as the active compound, acts in a superior tonicum effect compared to white ginger. The flavonoids, tannins, alkaloids and terpenoids present in the red ginger ethanol extract contributed as inhibitor AchE by preventing lipid peroxidation. Rutin, kaempferol, and quercetin as flavonoids that express inhibitor xanthine oxidase activity, also epicatechin and catechinin as antioxidants were responsible in the antihyperuricemia activity of red ginger. The extract also acts as apoptosis promoter in some *in vitro* studies related to various cancer cells. Although the red ginger extract also indicates microbial activity, it is still inferior compared to other Zingiberaceae plants such as turmeric and zedoary. The pharmacokinetic study that has been conducted is 6-shogaol and 6-gingerol. It is similar to the red ginger compound found in oleoresin.

There is still high potential for further research on red ginger regarding its chemical contents, mainly gingerol, shogaol, and their derivatives, and mapping the chemical constituents such as oleoresin. Current studies on red ginger are still in the preclinical stage and need to be further developed in terms of pharmacological effects, toxicity, mechanism of actions and signaling, compound modification, and also clinical trials in order to establish red ginger as a therapeutic agent.

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