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Phytochemical and Pharmacological Review of Red Ginger Extracts *(Zingiber Officinale var Rubrum)*

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Abstract:
Background: *Red ginger rhizome is widely used in traditional medicine because it is known to contain essential oils (2.58-3.90%) which is higher than other types of ginger. The purpose of this review is to increase knowledge of the phytochemical content and pharmacological activity of the red ginger extract.*
Methods*: The literature search was carried out systematically using 3 databases, namely Google Scholar, Research Gate, and Pubmed with the search keywords as follows: Red ginger, chemical compounds, and pharmacology. A total of 358 articles have been identified, and by the final analysis, 15 articles can be used in this review.*
Results*: From the results of several studies used, it is shown that red ginger extract contains phytochemicals in the form of flavonoids, quinones, monoterpenes, sesquiterpenes, b-caryophyllene, camphene, geranial, geranyl acetate, gingerols, alkaloids, steroids/triterpenoids, and phenolics. Pharmacologically red ginger extract has antibacterial, antioxidant, antifungal, antihypertensive, analgesic, and antitussive properties*
Conclusion: *It can be concluded that Red Ginger Extract (Zingiber Officinale var rubrum) is one of the plants rich in chemical compounds that are spread in the rhizomes and leaves and has benefits for treating various diseases.*
Key Word*: Red ginger, phytochemical content, pharmacological activity.*

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I. Introduction

Red ginger or *Zingiber officinale var. rubrum* (Zingiberaceae) was first cultivated in Asia (Indonesia and Malaysia) which has medicinal benefits, one of which is found in the rhizome. Red ginger rhizome is used as a cooking spice, food flavoring, and herbal medicine[1]. Other advantages of ginger are used as anti-inflammatory, antiemetic, antitumor, analgesic, antihemorrhagic, nerve cell protection, antirheumatic, antifungal, and antibacterial agents [2].

The content of chemical compounds in red ginger is an essential oil (2.58-3.90%) which is the highest compared to other types of ginger[3]. The chemical compounds contained in red ginger are carbohydrates (50-70%), lipids (3-8%), terpenes *(zingiberene, -bisabolene, -farnesene, -sesquiphellandrene, and -curcumene)*, phenolic compounds *(gingerol, paradol, and shogaol)* and essential oils. The essential oil content in red ginger is higher than other types of ginger, which are used as raw materials for medicine. It is characterized by the presence of a distinctive smell and taste of ginger caused by a mixture of essential oils such as *shogaol and gingerol*. Gingerol and shogaol were found in higher amounts in red ginger with an average gingerol content (23-25%), shogaol (18-25%)[4] which are known to have pharmacological activities such as antioxidant, antifungal, antibacterial, antihypertensive, analgesic and antitussive[12,7,8,11,9,13,14,15].

The chemical structure of gingerols and shogaols can be seen in Figure 1 below :

[a] [b]

Figure 1: a. Gingerol chemical structure
b. Chemical structure of shogaol[5].

Plant Classification

The classification and morphology of Red Ginger *(Zingiber Officinale var Rubrum)* are as follows:

Kingdom : Plantae
Division : Magnoliophyta
Class : Liliopsida
Order : Zingiberales
Family : Zingiberaceae
Genus : *Zingiber*
Species : *Zingiber Officinale*
Variety : *Zingiber Officinale* var. *Rubrum* [5].

Plant Morphology

Red Ginger *(Zingiber Officinale var Rubrum)* is an annual plant that can grow up to 50-100 cm in height. Red ginger leaves are 5-25 cm long and 1.5-2 cm wide, the tips of the leaves are pointed and green. Red ginger *(Zingiber Officinale var Rubrum)* has stems that grow upright and round flat, not branched. Red ginger flowers are oval and purple flower crowns measuring 2-2.5 cm. Red ginger has a thick rhizome and reddish-brown color. Red ginger root has a single root that gets bigger according to its growth or age, to form rhizomes and shoots that will grow into new plants [5].

The morphology of Red Ginger can be seen in Figure 2 below :

[a]

[b]

Figure 2: a. Rhizome of Red Ginger *(Zingiber Officinale var Rubrum)*
b. Flowers from Red Ginger *(Zingiber Officinale var Rubrum)*

II. Data Collection

The preparation of this review article used a literature study of National and International articles with a span of 10 years (2011 - 2021). The data search in this article review was done using online media through trusted sites such as Google Scholar, Research Gate, and Pubmed with the search keywords as follows: red ginger, chemical compounds, and pharmacology. The process and stages of the systematic review in this article use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analysis) diagram as documentation of the process of searching, filtering and selecting articles so that articles can be obtained that can be used in this systematic review. The PRISMA diagram can be seen in Figure 3 :

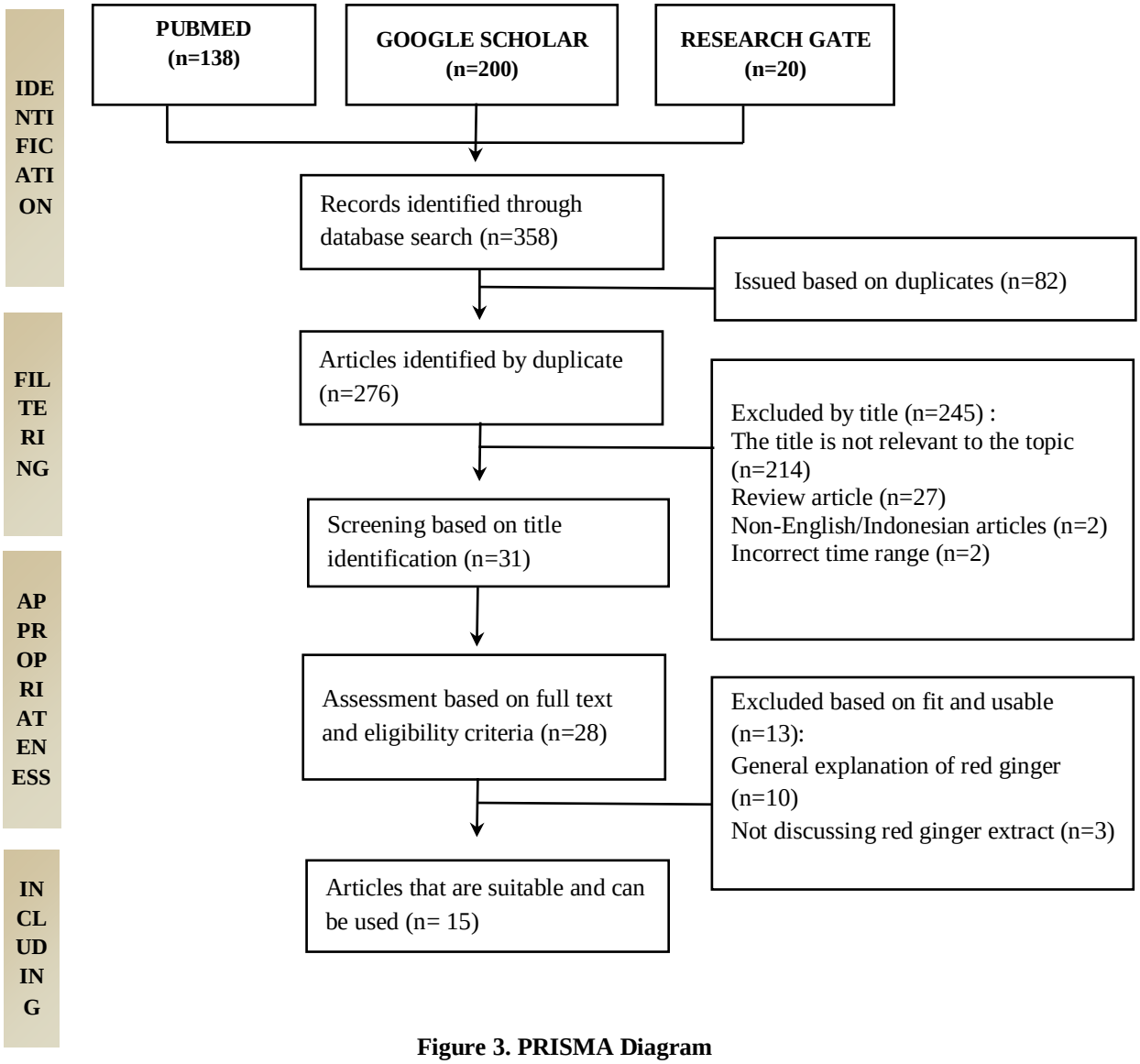

Figure 3. PRISMA Diagram

III. Results

The first step in the PRISMA diagram is identification. A total of 358 articles were found through 3 databases used (PubMed, Google Scholar, Research Gate) based on keywords that matched this review. Then further identification was carried out to remove 358 articles based on duplication. A total of 82 articles were found to have similar articles, thus these articles were removed, and the remaining were 276 articles. Subsequently, a screening stage was carried out based on the title of the article, as many as 245 articles were omitted due to several reasons such as the title was not in accordance with the topic, review articles, articles that used other than English/Indonesian language, and the time span that was not appropriate. From the title screening, 31 articles were obtained and then an assessment was carried out based on the full text and eligibility criteria, 28 articles were included and 3 articles were omitted. And the last stage obtained as many as 15 articles that were suitable and could be used for further review. The PRISMA diagram is used in this review as evidence and documentation of the steps taken by the author in identification, screening until articles meet the eligibility criteria for use in this article review.

Photochemical Review

Phytochemical review of the red ginger plant and the extraction process using specific solvents and chemical constituents contained in red ginger can be seen in Table 1 below.

Table 1: Phytochemical content of red ginger rhizome and leaves *(Zingiber Officinale Var. Rubrum)*

No	Part of plant used	Extraction method	Instrument	Solvent	Compounds contained	Reference
1.	Rhizome	Colorimetric	-	TMPD (N,N,N',N'-tetra methyl-p-phenylendiamine)	Flavonoids, Quinones, Monoterpenes and Sesquiterpenes	(6)
2.	Leaf	Microdilution	Capillary GC and GC-MS (Gas Chromatography–Mass Spectrometry)	Ethanol	B-caryophyllene	(7)
3.	Rhizome	Microdilution	Capillary GC and GC-MS (Gas Chromatography–Mass Spectrometry)	Ethanol	Monoterpenoid, with Camphene, Geranial, and Geranyl acetate	(7)
4.	Rhizome	TLC densitometry	-	Ethanol	Gingerol	(8)
5.	Rhizome	Maceration	-	Ethanol	Flavonoids, alkaloids, quinones, steroids/triterpenoids	(9)
6.	Rhizome	Drying	-	Ethanol	Phenolic and flavonoids,	(10)

Phytochemical testing of red ginger *(Zingiber Officinale var. Rubrum)* was carried out using the Colorimetric COX Inhibitor Screening Assay method using *TMPD (N,N,N',N'-tetra methyl-p-phenylendiamine)* as a reagent. Then the treatment was spotted on TLC with three detectable points using chloroform: methanol as the mobile phase (5:5). Phytochemical screening showed that presence of secondary metabolites namely flavonoids, quinones, and monoterpenoids/sesquiterpenoids were detected in both dried herbs and aqueous extracts[6].

In the ethanol extract test, essential oils were obtained by hydrodistillation method on the leaves and rhizomes of *Zingiber Officinale var. Rubrum* as it was analyzed by capillary GC and GC-MS. Forty-six constituents were identified in the leaf oil, while 54 were identified in the oil from the rhizome. Leaf oil was dominated by β-caryophyllene(31.7%), while oil from rhizome was dominated by monoterpenoids, such as camphene (14.5%), geranial (14.3%), and geranyl acetate (13.7%)[7].

The ethanol extract of red ginger *(Zingiber Officinale var. Rubrum)* contains gingerol which has the potential as an antioxidant. This test uses the FRAP method. These results obtained Ginger-Ethanolic Extract (MGE) which is 2.8%, the antioxidant activity is 1.96 mmol Fe(II)/100g. Determination of gingerol content in MGE was carried out by TLC densitometry. The maximum wavelength of gingerol was obtained at 525 nm, and the r-value of the standard gingerol calibration curve equation was close to 1. The eluent that gave the best separation in MGE TLC was n-hexane-ethyl acetate (13:7) with an Rf value of 0.3[8].

In the phytochemical screening of red ginger extract *(Zingiber Officinale var. Rubrum)* using 96% ethanol in the maceration extraction procedure, several compounds were found as follows: flavonoids, alkaloids, quinones, steroids/triterpenoids in dried plants, and extracts[9].

In ethanol extraction of red ginger *(Zingiber Officinale var. Rubrum)* with stirring at 100 rpm at different temperatures (ambient temperature, 40, and 50^{o} C) and various extraction times (30, 60, and 90 minutes). Analysis of the chemical content tested was total phenolic and total flavonoid. Based on the test results, the highest total flavonoid content (5.17% w/w) was produced at 40^{o}C for 90 minutes, while the total phenolic content was not affected by temperature or extraction time. The total phenolic content ranged from 2.39% to 2.65% w/w[10].

Pharmacological Review

A pharmacological review of the red ginger plant and the extraction process using specific solvents as well as the testing methods and activities contained in red ginger can be seen in Table 2 below.

Table 2 : Use of Red Ginger rhizome *(Zingiber Officinale Var. Rubrum)* in Pharmacology

No	Plant Part	Extraction Method	Solvent	Test Method	Activity	Reference
1.	Rhizome	Capillary GC and GC-MS (Gas Chromatography-Mass Spectrometry)	Ethanol	Micro Dilution	Antibacterial	(7)
2.	Leaves	Capillary GC and GC-MS (Gas Chromatography–Mass Spectrometry)	Ethanol	Micro Dilution	Antibacterial	(7)
3.	Rhizome	Maceration	Ethanol	Duncan multiple range test (DMRT)	Antibacterial	(12)
4.	Rhizome	Maceration	Ethanol	FRAP	Antioxidant	(8)
5.	Rhizome	Vacuum oven drying	Ethanol	DPPH and FRAP	Antioxidant	(11)
6.	Rhizome	Maceration	Ethanol	Microdilution	Antifungal	(9)
7.	Rhizome	Maceration	Aquadest	Isolated in vitro	Antihypertensive	(13)
8.	Rhizome	Maceration	Ethanol	Ionic	Gelation	(14)
9.	Rhizome	Maceration	Ethanol	Orally	Antitussive	(15)

Antibacterial

One of the pharmacological activities contained in Red Ginger extract *(Zingiber Officinale Var Rubrum)* is antibacterial, antibacterial is a compound that can control the growth of bacteria. This study was used to assess the antibacterial potential of red ginger to treat mastitis. In dairy farming, mastitis is one of the common health problems found in dairy farms. Mastitis not only causes a significant reduction in the milk production of dairy cows but also affects the composition and quality of milk. Subclinical mastitis is more common in dairy cattle. The bacteria survive in the mammary glands and nipple ducts. In the mammary glands, bacteria produce toxins that destroy cell membranes and directly damage milk-producing tissues, thereby reducing the quantity and quality of milk produced. This undoubtedly causes considerable economic loss to dairy farms. Several bacteria, including *Staphylococcus aureus, Staphylococcus epidermidis,* and *Streptococcus agalactiae* were tested with each red ginger extract concentration, namely, 50, 25, 12.50, and 6.25%. with methanol solvent and it was found that (1) S. epidermidis was most affected by red ginger extract, followed by S. aureus and S. agalactiae, (2) the higher the concentration of red ginger extract, the higher the inhibition effect of bacterial growth, and (3) the effect of inhibiting the growth of red ginger extract on isolates of *S. aureus, S. epidermidis, and S. agalactiae* was significantly different at < 0.0001. Therefore, red ginger is effective in inhibiting antibacterial activity against these three bacteria [12].

According to another study tested using the microdilution technique, it was shown that both leaf oil and rhizome oil were quite active against Gram-positive bacteria such as the *Bacillus licheniformis, Bacillus spizizenii* and *Staphylococcus aureus*, and Gram-negative bacteria scuh as the *Escherichia coli, Klebsiella pneumoniae*. and *Pseudo monas stutzeri*. Leaf and rhizome oils were tested against three Gram-positive *(B. licheniformis, B. spizizenii, S. aureus)* and three Gram-negative. *(E. coli, K. pneumoniae, P. stutzeri)* bacteria. The results revealed that the leaf oil and oil from the ginger rhizome had moderate antibacterial activity (MIC value 0.16-0.63 mg/ml) against all tested bacterial strains, which may have resulted from the presence of *caryophyllene oxide, a-pinene, a- terpineol, linalool, 1,8-cineole and geraniol*, compounds known to have antibacterial activity. Although present in low concentrations, these constituents can exert a significant effect on the antibacterial activity of the oil through a synergistic effect. In general, both oils showed better antibacterial activity against Gram-positive bacteria (with MIC values of 0.16-0.31 mg/ml) than against Gram-negative bacteria (with MIC values of 0.31-0.63 mg). /ml). The low MIC values of leaf, rhizome, and root oils seen here against *B. licheniformis, B. spizizenii, S. aureus and E. coli* would suggest that oil from ginger coals might be used as a natural preservative against food-borne pathogens or to delay food spoilage. However, further investigations on the activity of this oil against other foodborne pathogens (Listeria sp., Salmo nella sp.) should be carried out [7].

Antioxidant

Red Ginger *(Zingiber officinale var. Rubrum)* ethanol extract has an antioxidant activity which was tested using the FRAP method and compared with gallic acid activity. The results obtained by the ethanol extract of red ginger *Ginger-Ethanolic Extract (*MGE) was 1.96 mmol Fe(II)/100g, while the gallic acid was 9.34 mmol Fe(II)/100 g. These results indicate that MGE has lower antioxidant activity than gallic acid used as a comparison [8].

Red ginger *(Zingiber Officinale var. Rubrum)* has antioxidant activity from the ethanol extract of red ginger rhizome. Rhizomes dried by vacuum oven drying method showed the highest DPPH (52.9%) and FRAP activity (566.5 M Fe(II)/g DM)[11].

Antifungal

Red ginger *(Zingiber Officinale var. Rubrum)* has antifungal activity. The antifungal activity was calculated using the minimum fungicide concentration using the agar diffusion method. Extract-antibiotic interaction was carried out using the checkerboard method. The results obtained from zingiber officinale rhizome extract had the best antifungal activity against C. albicans with a MIC value of 2048 g/mL. The antimicrobial interaction between vancomycin and S. rebaudiana against S. aureus and S. mutans showed a synergistic effect. Synergism was also observed in the combination of amoxicillin with B. pandurata or S. rebaudiana against S. aureus and S. mutans. The combination of ketoconazole with each of the plant extracts studied against C. albicans showed a synergistic effect. Additive interactions were observed between amoxicillin and B. pandurata or S. rebaudiana against S. aureus and S. mutans, respectively. No antagonism was observed in this study. Therefore, this study reveals that the use of a combination of plant extracts and antimicrobial agents can be useful in treating oral infections as well as combating the emerging problem of drug resistance, and in vivo trials are needed to confirm microbial eradication using this combination [9].

Antihypertensive

Hypertension is a metabolic disease in which blood pressure is chronically elevated and is one of the long-term complications of type 2 diabetes. Red ginger *(Zingiber officinale var. Rubrum)* has pharmacological activity as antihypertensive. Antihypertensive testing on red ginger can be seen in animal tests on rat hearts isolated in vitro, using aqueous extracts (0.05 mg/mL) red ginger (*Zingiber officinale var. Rubrum),* and white ginger *(Zingiber officinale Roscoe).* The ability of the extract to inhibit ACE together with Fe^{+2} and SNP-induced lipid peroxidation was determined in the rat heart in vitro. Results revealed that both extracts inhibited ACE in a dose-dependent manner (25–125 lg/mL). However, red ginger extract (EC_{50} = 27.5 lg/mL) had a significantly higher inhibitory effect ($P < 0.05$) on ACE than white ginger extract (EC_{50} = 87.0 lg/mL). Furthermore, incubation of rat heart in the presence of Fe^{+2} and SNPs led to a significant ($P<.05$) increase in the malondialdehyde (MDA) content of the cardiac homogenate, while the introduction of ginger extract (78–313 lg/mL) led to a dose-dependent decrease in the MDA content of the depressed cardiac homogenate. This suggests that the mechanism that allows the ginger to exert its antihypertensive properties may be through inhibition of ACE activity and prevention of lipid peroxidation in the heart. Furthermore, red ginger showed stronger ACE inhibition than white ginger [13].

Analgesic

Red Ginger (*Zingiber officinale var. Rubrum*) has pharmacological activity, one of which is analgesic properties. Analgesic testing on red ginger rhizome extract was done by extracting Red ginger rhizome using maceration method with ethanol as solvent and nanoparticle formulation of the red ginger extract was made using ionic gelation method. Experimental rats were divided into 5 types of treatment and each treatment was repeated 3 times. The analgesic effect test was carried out using the thermal induction method using a water bath and observed 5 times, namely before the administration of the test material, the 30th minute, 60th minute, 90th minute, and 120th minute. Group I as a negative control was given 1% CMC, group II as a positive control was given paracetamol, groups III-V were treated with red ginger extract nanoparticles at a dose of 0.0215g, 0.043g, and 0.086g which gave an analgesic effect on male white rats of Wistar strain. (Rattus norvegicus) after being given red ginger rhizome extract nanoparticles. Based on the ANOVA test, the results of the analgesic effect were significantly different with $p = 0.019$ ($p < 0.05$). This study proves that red ginger has an analgesic effect because it contains alkaloids and flavonoids [14].

Antitussive

Red ginger *(Zingiber officinale var. Rubrum)* has antitussive activity from ethanol extract of red ginger rhizome. The antitussive activity test was carried out by assessing the percentage of cough suppression through the induction of 7.5% citric acid solution in 28 female guinea pigs, divided into seven treatment groups, including treatment with CMC-Na (negative control), codeine 10 mg/kg body weight. (positive control), a single dose of 250 mg/kg BW of 96% ethanol extract of red ginger and purple leaves, a combined dose of 96% ethanol extract of red ginger and purple leaves with a combined ratio of 1:1, 0.5:1, and 1:0 ,5 for 5 days. The study showed that 96% ethanol extract of red ginger and purple leaves in a single dose or in combination had an antitussive activity that was able to increase cough suppression through experimental animals, namely guinea pigs. The comparison of the optimal combination of 96% red ginger ethanol extract and 96% purple leaf ethanol extract was 1:0.5 with a cough suppression percentage of 73.00%. Compounds that play a greater role in this

combination as an antitussive activity are compounds from 96% ethanol extract of red ginger. The pungent compounds in ginger *(gingerol and shogaol)* act on a common group of nerve receptor cells, namely vanilloid receptors. Functioning as an agonist, 6-shogaol can decrease the sensitivity of nociceptive afferents via a phenotypic pathway termed "vanilloid-induced neuronal plasticity", in which receptors involved in pain transduction are downregulated while endogenous analgesics are upregulated [15].

IV. Conclusion

Red ginger *(Zingiber Officinale Var.Rubrum)* is a plant that is rich in chemical compounds found in its rhizomes and leaves. The phytochemical compounds contained in the red ginger rhizome are flavonoids, quinones, monoterpenes, sesquiterpenes, b-caryophyllene, camphene, geranial, geranyl acetate, gingerols, alkaloids, steroids/triterpenoids, and phenolics. The pharmacological effect of red ginger rhizome has a function in the treatment of various diseases such as antibacterial, antioxidant, antifungal, antihypertensive, analgesic and antitussive.

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