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Review

Potential bangle (*Zingiber montanum* J.König) rhizome extract as a supplement to prevent and reduce symptoms of Covid-19

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ABSTRACT

The morbidity and mortality rates due to Covid-19 are increasing day by day, to overcome this, we urgently need a better treatment strategy, therefore various ways and strategies for this must be pursued. The purpose of the present review is to explain that the rhizome of bangle (*Zingiber montanum*) has great potential to increase antibodies and reduce symptoms of acute respiratory distress syndrome (ARDS), which also seems suitable for treating Covid-19. Method: This review is looking for the results of scientific research from various sources, regarding the efficacy of bangle (*Zingiber montanum*) rhizome which is strongly suspected to be able to prevent, and reduce the symptoms that occur in COVID-19. The results showed that the bangle rhizome extract had activity as immunomodulatory, antiviral and reduced symptoms such as what happened in COVID-19. Conclusion: Bangle rhizome extract has dozens of nutritious substances and has multifunctional activities, and it can be postulated that among the benefits of bangle rhizome extract it is able to prevent and reduce symptoms that occur in Covid-19, and preclinical studies and clinical studies are needed to prove this postulate.

Contents

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1. Introduction

As is well known, the main cause of death from Covid-19 is due to acute respiratory distress syndrome (ARDS), this occurs due to cytokine storms that eventually lead to multi-organ failure. People who can recover from Covid-19 are generally people who have strong antibodies or get drugs or herbs that are suitable for defeating Covid-19. On the other hands, according to several reports from China, that the success rate of treatment against Covid-19 is actually better, when pharmaceutical drugs are combined with herbal medicines rather than just pharmaceutical drugs, and the results have statistically significant differences (Yen and Ye, 2019).

The Chinese government has implemented this policy in all regions of China, and several formulas of traditional Chinese medicine (TCM) to combat COVID-19 that are widely used include Huoxiang Zhengqi, Lianhuaqingwen, Shuanghuanglian, and others (Runfeng et al., 2020; Su et al., 2020; Xiao et al., 2020).

The results of this policy are very encouraging, where based on data published online on Worldometer, China's position for the number of infected and dead due to Covid-19 at the end of April 2020, was still ranked number 1 or the highest in the world. On 4 November 2020, China's position for the number of infected and died moved to position no. 57 in the world (Worldometer, 2020).

Traditional Chinese Medicine (TCM) formula to combat COVID-19 contains many plants and mostly only grows in the area of China, if there is one plant that has properties such as the TCM formula to combat COVID-19 and is easily available, and has a cheap price, it will certainly be better, one of the plants to replace TCM in our view is bangle rhizome (*Zingiber montanum*). This plant grows in some areas of South Asia, Indonesia, Malaysia, Myanmar, Thailand, and Vietnam (Lim, 2016).

Bangle has long been used by some people, especially in Indonesia, Malaysia, Thailand, and in some areas of South Asia to treat asthma, pneumonia, anti-inflammatory, antiviral, antibacterial, immunomodulatory, and others (Iswantini et al., 2011; Jantan et al., 2008; Kaewchoothong, 2009). Likewise, according to the results of scientific research that bangle rhizome extract has dozens of nutritious substances, and has multifunctional activities, and it can be strongly suspected that among the benefits of bangle extract is that it seems to be able to prevent and reduce the symptoms that occur in Covid-19.

Traditional Chinese medicine (TCM) which is suitable to prevent and treat Covid-19 is from plants that have activities as antiviral, immunomodulatory, anti-inflammatory, and can reduce the symptoms produced by the effect of the cytokine storm (Runfeng et al., 2020; Su et al., 2020; Xiao et al., 2020) The bangle is a plant that has many nutritious substances and has multifunctional activities (Lim, 2016). Its activity is almost the same as TCM drugs to prevent and combat COVID-19 As we explain below.

2. Material and methods

2.1. Material

The material used for the drug of bangle generally is extract of the bangle rhizome (Fig. 1), while the synonyms of *Zingiber montanum* J.König, among others are *Amomum cassumunar* (Roxb.), *Zingiber cassumunar* (Roxb), *Zingiber cliffordiae* (Andrews), *Zingiber luridum* (Salisb), *Zingiber purpureum* (Rosc), *Zingiber xantorrhizon* (Steud) (Lim, 2016).

Bangle plant (*Zingiber montanum*) in Indonesia is also called Banggele, Banglai, Bengle, Bungle, Mungle, Kunit Bolai but is most commonly called bangle. In Malaysia, this plant is also called Bangle, Bolai, Boleh, Bonglai, but most commonly it is called Bangle, while in Thailand it is most commonly called Phlai or Plai (Lim, 2016).

2.2. Method

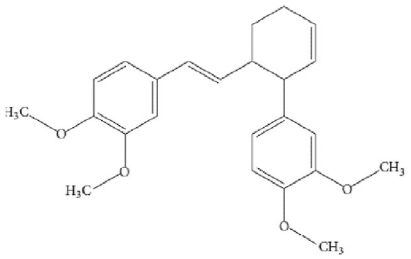
The method used in writing this manuscript is by searching for journal articles from various sources, especially from databases of Medline via Ebscohost, Scopus, and Google Scholar, regarding the efficacy of bangle (Zingiber montanum) rhizome which is strongly suspected to be able to prevent and reduce the symptoms that occur in COVID-19.

3. Result

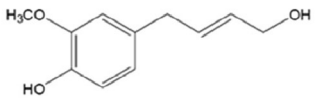
3.1. Ethnobotany and traditional uses of bangle (Zingiber montanum J. König)

Bangle rhizome has been used in traditional medicine as a single plant or as a component of herbal recipes, especially in Indonesia, Thailand, Malaysia, and several Southeast Asian and South Asian countries. This plant is used for the treatment of various diseases such as asthma, pneumonia, muscle pain, influenza, immunomodulatory, diabetes, rheumatism, fever, dysentery and various disorders in the stomach, inflammation, headaches, vertigo, jaundice, intestinal worms, smooth bowel movements, antioxidants, weight loss, sprains, wounds, babies who fainted due to high fever, cleansers for skin diseases, mosquito repellents and others. (Iswantini et al., 2011; Jantan et al., 2008; Kaewchoothong, 2009). Because the symptoms of Covid-19 are

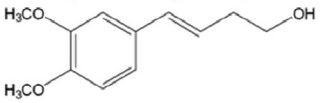
Fig. 1. Rhizome and herbal bangle (*Zingiber montanum* J.König).



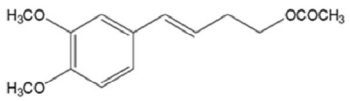
1. cis-3-(3′,4′-dimethoxyphenyl)-4-[(E)-3′′,4′′-dimethoxystyryl] cyclohex-1-ene (cis-banglene)



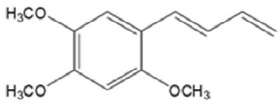
2. (*E*)-4-(4-hydroxy-3-methoxyphenyl) but- 2-en- 1-ol



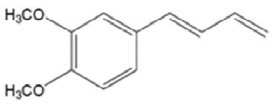
3. (*E*)-4-(3,4-dimethoxyphenyl) but- 3-en-l-ol (compound D)



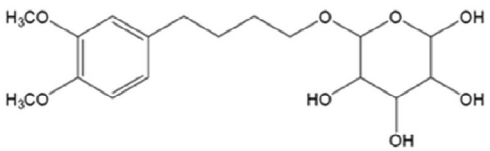
4. (*E*)-4-(3,4-dimethoxyphenyl) but-3-en-l-yl acetate,



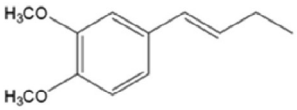
5. (4-(2,4,5-trimethoxyphenyl)-but-1,3-diene



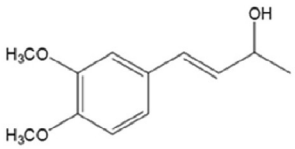
6. (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD)



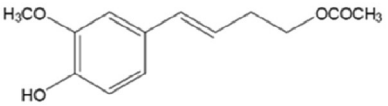
7. (*E*)-4-(3,4-dimethoxyphenyl) but-3-en-l-*O*-*β*-D-glucopyranoside,



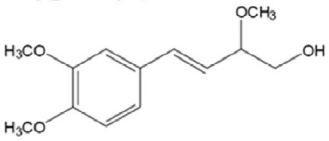
8. (*E*)-1-(3,4-dimethoxy- phenyl) but-1-ene



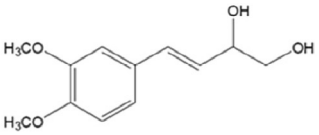
9. (*E*)-3-hydroxy-l- (3,4-dimethoxyphenyl)but-l-ene,



10. (*E*)-4-(4-hydroxy-3-methoxyphenyl) but-3-en-l-yl acetate



11. (E)-2-methoxy-4-(3,4-dimethoxyphenyl)but-3-en-1-ol



12. (E)-2-hydroxy-4-(3,4-dimethoxy-phenyl)but-3-en- 1-ol

Fig. 2. Chemical structure of phenylbutenoid derivatives of bangle rhizome (*Zingiber montaum*).

similar to pneumonia and so far many people use bangle to treat pneumonia, asthma, influenza and to increase endurance by drinking bangle rhizomes, currently many people in Indonesia are drinking bangle to prevent or against Covid-19. Bangle rhizome extract weighing 2–3 g, grated and filtered, then add enough water, drink 1–2 times a day, because bangle rhizome extract has a bitter taste, bangle extract is often drunk with honey or added sugar.

3.2. Dosage and several brands sold

In addition, according to the results of research by Kato et al. (2018), the minimum lethal dose for bangle rhizome extract is estimated to be more than 2000 mg/kg BW per day for humans. Their observations of rats given the bangle extract for 3 months, showed no abnormalities in the rats (Kato et al., 2018).

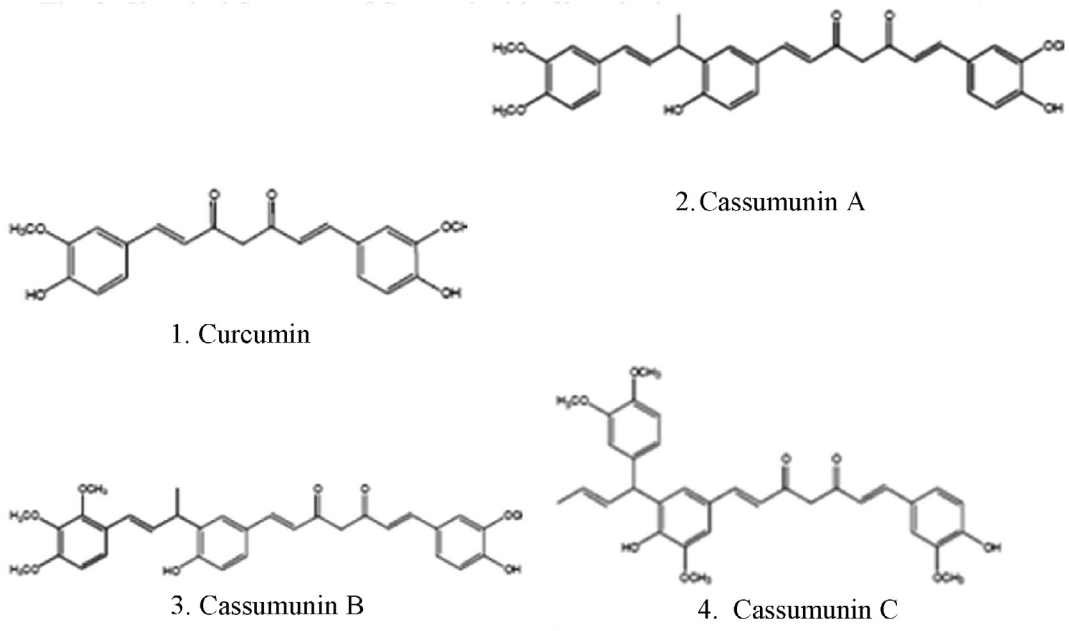


Fig. 3. Chemical structure of curcuminoid of bangle rhizome (*Zingiber montanum*).

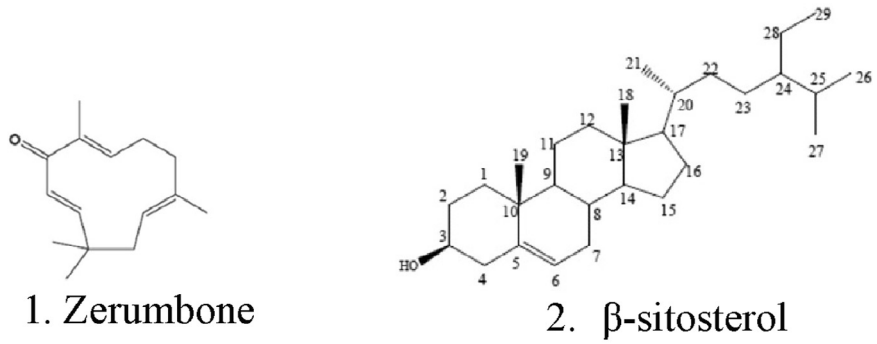


Fig. 4. Chemical structure of zerumbone and β-sitosterol of bangle rhizome (*Zingiber montanum*).

In Indonesia, pure bangle essential oil is sold online and in drugstores under the name Minyak atsiri bangle murni (means = Pure bangle essential oil), and Pavettia minyak bangle/plai oil, this oil is used for jaundice, fever, headache, cough with phlegm, stomach pain, colds, constipation, intestinal worms, rheumatism, postpartum abdominal shrinkage & to treat obesity. And a mixture of Bangle oil and *Acorus calamus* oil (85% oil of bangle + 15% oil of *Acorus calamus*) with the name Dlingo, this oil is used to relieve seizures, relieve headaches, reduce pain, reduce fever, overcome colds, and to calm the mind. While the capsules are also sold online under the name Bangle with a dosage of 500 mg per capsule and taken 1–2 times a day, most consumers buy to lose weight, increase endurance, and prevent allergies through breathing. While in Thailand, it is also sold in various places under the name Phlai (plai) oil, phlai capsule, and plai cream (Kaewchoothong, 2009).

3.3. Phytochemistry of Zingiber montanum J.König (Bangle)

Based on the results of research by Majaw and Moirangthem (2009), Bangle rhizome extract contains chemical compounds: Phlobatnins, Flavonoids, Alkaloids, Saponins, Tannins, Terpenoids, Steroids, and Gylcoside (Majaw and Moirangthem, 2009).

While the main content of bangle rhizome extract is phenylbutanoid, according to Thai herbal pharmacopoeia, it contains a total phenylbutanoid content of not <45% w/w (Kaewchoothong, 2009). The yield of bangle rhizome essential oil distillation has a yield between 0.857 and 1.373% (Sukatta et al., 2009)and the main content of bangle essential oil is Terpinen-4-ol, which is around 32 vol % (Pithayanukul and Tubprasert, 2007), the chemical structure of the main important bangle chemical compounds is shown in Fig. 2, Fig. 3 and Fig. 4 below:

4. Pharmacological properties of bangle (Zingiber montanum J. König)

Until now, because there is no vaccine and the right drug to treat COVID-19, the way taken to prevent COVID-19 outbreaks is by implementing health protocols and increasing antibodies. Meanwhile, to treat COVID-19 patients, the focus point is to overcome the symptoms of a cytokine storm in the form of ARDS caused by SARS-CoV-2, increase endurance by giving immunomodulatory drugs and antiviral drugs to prevent SARS-CoV-2 to do replication (WHO, 2020b). In the below, we will discuss the role of bangle rhizome extract in helping to prevent and reduce symptoms of COVID-19 based on its pharmacological properties.

4.1. Efficacy of bangle for treating acute respiratory distress syndrome (ARDS)

Various ways to deal with ARDS caused by COVID-19 must be pursued. According to Hu, W.-C. (2020), interleukin-10 (IL-10) can be used as a therapeutic agent for COVID-19, because IL-10 has several advantages for treating ARDS. First, IL-10 is a cytokine that has antiviral activity. Second, IL-10 has activity in modulating immunity to suppress the pro-inflammatory cytokines ARDS associated with COVID-19 caused by coronavirus infection and uncontrolled innate immunity with cytokine storms. Third, IL-10 is an anti-fibrotic agent that works to reduce pulmonary fibrosis (Hu, 2020).

Based on the research results of Nurkhasanah, et al. (2019). Ethyl Acetate Rhizome extract of Bangle (*Zingiber Cassumunar* Roxb.) has activity to increase Interleukin-10 (Nurkhasanah et al., 2019).

4.2. Efficacy of bangle rhizome extract and its constituents for asthma, allergies, and pneumonia

According to Jitapunkul et al. (2018), herbal pharmacopoeia of Thailand showed that about 50% of Thai recipes for asthma disease contain bangle rhizome extract. (Jitapunkul et al., 2018), likewise in Indonesia and Malaysia, a lot of people use it to treat asthma (Iswantini et al., 2011; Jantan et al., 2008; Kaewchoothong, 2009; Lim, 2016).

Based on the research results of Limvuttegrijerat et al. (2014) showed that the ethanol extract of bangle rhizome has anti-asthma and anti-allergic properties, where the ethanol extract of bangle rhizome has activity by suppressing phorbol12-miristate13-acetate (PMA) induced MUC2 and MUC5AC gene expression in human airway epithelial cells via inhibition of extracellular signal-regulated kinase mitogen-activated protein kinase (ERK MAPK)-dependent pathway (Limvuttegrijerat et al., 2014).

On the other hand, Poachanukoon et al. (2015) investigated effects of bangle rhizome ethanol extract and its constituent (E)-4-(3′,4′-dimethoxyphenyl)but-3- en-1-ol (compound D) (Fig. 2.3) by using house dust mite (HDM) induced matrix metalloproteinase (MMP)-9 plays a role in asthma, the results showed that the ethanol extract of bangle rhizome and its constituent compound D inhibited the cleavage of pro-MMP-9 and MMP-9 production in PMA-induced airway epithelial cells (Poachanukoon et al., 2015).

Still related to asthma, Jitapunkul et al. (2018) conducted a study of compound D and DMPBD ((*E*)-1-(3,4-dimethoxyphenyl) butadiene), extracted from the rhizome bangle, by molecular docking and molecular dynamics (MD) simulations with simulate complex systems and analyze molecular interactions between these compounds and protein target, 5-lipoxygenase (5-LO) enzyme. The results of this study showed that Compound D and DMPBD molecules bind at the same binding site of its natural substrate (arachidonic acid) on 5-LO enzyme, which is similar to the binding of commercial asthma drug (Zileuton) (Jitapunkul et al., 2018).

Besides that, there was a clinical trial study conducted by Tuchinda et al. (1985) on children with asthma, reporting that giving rhizome extract at a dose of 260 mg orally to 5 boys and 3 girls with an age range of 9–13 years, where these children had never been given drugs previously. After a physical examination is carried out, which includes observing the ability of breathing, heart rate. Then every 30 min for 2 h compared to lung function between before and after drug administration. The results of this study indicate that 2 h after administration of bangle rhizome extract, the patient's physical health and lung function improved greatly, while the patient's heart rate and blood pressure were not affected due to the administration of bangle rhizome extract. The patient's condition. Whereas for long-term treatment of 8 male patients and 4 female patients with an age range of 9–14 years, 130 mg of bangle rhizome extract were given twice a day for 3 months. The results of the observation of all patients showed that their condition was greatly improved and that there were no complications and toxicities during the observation (Kaewchoothong et al., 2012; Tuchinda et al., 1985).

As is known between asthma and pneumonia are similar but different, asthma is an allergic disease, whereas pneumonia is an infectious disease. Generally, asthma occurs when the patient is exposed to allergens, and causes the bronchial tubes to narrow, whereas in pneumonia, the infection will attack the lung lobes. Bangle rhizome extract can relieve or cure asthma and pneumonia, because the work of bangle rhizome extract is anti-allergic, anti-inflammatory, analgesic, antipyretic, antimicrobial, antiviral, and immunomodulatory, as described below (Sutherland et al., 2008; Wong et al., 2001).

4.3. Efficacy of bangle as immunomodulator

Chairul et al. (2009) conducted immunomodulatory tests for 3 kinds of phenylbutenoid isolated from bangle rhizome, namely, {1} [(E) -4- (3′, 4′-dimethoxyphenyl) but-3-en-1-ol], {2} [(E) -4- (2′, 4′, 5′-trimethoxyphenyl) but-3-en-1-ol] and {3} [(E) -4- (3′, 4′, 1-trimethoxyphenyl) but-3-en-1-ol]. The experiment was carried out in vitro by stimulating mouse macrophage cells with these 3 kinds of phenylbutenoid compounds. Then the activity and capacity of the macrophage cells were measured by ingesting *Staphilococcus epidermidis* and compared with normal controls, and positive controls. The results showed that 3 kinds of phenylbutenoid compounds had immunomodulatory effects and compound number {1} was the best, followed by compound number {2} and then compound number {3} (Chairul, Praptiwi, 2009).

Then Adhila et al. (2019) also conducted research using bangle rhizome extract with concentrations of 25, 50, and 100 ppm. Experiments were carried out with the macrophages and lymphocytes of male BALB/c mice. Observation of the research results was carried out with an ELISA reader used to measure the absorbance at a wavelength of 595 nm. The results showed that at a concentration of 100 ppm there was a significant difference compared to normal controls. The results of 3 kinds of phenylbutenoid compounds have immunomodulatory effects and the compounds [(E) -4- (3′, 4′-dimethoxyphenyl) but-3-en-1-ol] were the best. The immunomodulatory effect of this compound increases the activity and capacity of mouse macrophage cells in ingesting *Staphilococcus epidermidis* (Adhila et al., 2019).

A more recent study was conducted by Mahfudh et al. (2020) for the efficacy of bangle as an immunomodulator. The study was conducted in vitro using macrophage cells of male Balb/C mice. Immunomodulatory properties were observed through the secretion of Reactive Oxygen Intermediate (ROI), Nitric Oxide (NO), and interleukin (IL-10 and IL-14) expression levels. Macrophage cells were taken from mice and used to test the immunomodulatory efficacy of the test preparation group and the control group. The bangle was macerated in 96% ethanol and dried by a vacuum evaporator. Bangle extract administration at doses of 25, 50, and 100 ppm were tested on mice macrophage cells and compared with normal controls. The results of the research statistical test showed that the doses of 25 and 50 ppm caused an increase in ROI and decreased NO levels, which were significantly different compared to the control group ($p < 0.05$). The results of this study also showed an increase in IL-10 and IL-14 expression, which was significantly different ($p < 0.05$) compared to the control group (Mahfudh et al., 2020).

4.4. Efficacy of bangle as anti-inflammatory, analgesic, and anti-pyretic

Ozaki et al. (1991) conducted anti-inflammatory and analgesic research from on the isolation of bangle rhizomes, namely, the compound (E) -1- (3,4-dimethoxyphenyl) but-1-ene, (E) -1- (3,4 -dimethoxyphenyl) butadiene (Fig. 2.6) and zerumbone (Fig. 4.1) from bangle rhizomes. The anti-inflammatory and analgesic tests of this compound were carried out on rats. The anti-inflammatory test was carried out on edema rats induced with carrageenan, while for the analgesic test the rats were induced with acetic acid. The test preparation was administered by 0.016 g/kg orally. The results of this experiment showed that the compound (E) -1- (3,4-dimethoxyphenyl) but-1-ene (Fig. 2.6) was the best with anti-inflammatory and analgesic effects (Ozaki et al., 1991).

In addition, Chongmelaxme et al. (2017) conducted a clinical trial using 14% bangle cream on 178 patients who were given bangle cream and 177 patients as controls. Cream administration was carried out for a range of 7 days to 2 months. The results of this comprehensive test showed that the 14% bangle cream has powerful benefits in reducing muscle pain and ankle sprains (Chongmelaxme et al., 2017).

Previous research also showed that cassumunarin A, B, and C were isolated from Bangle rhizome. The anti-inflammatory effect of these compounds was compared with curcumin and measured by inhibition of edema formation in rats ear induced by 12-O-tetradecanoylphorbol-I 3-acetate. The results of this experiment showed that the antiinflammatory effect of cassumunarin was stronger than the curcumin of *Zingiber officinale* (Masuda and Jitoe, 1994).

In addition, the bangle rhizome extract contains steroids, namely β-sitosterol (Majaw and Moirangthem, 2009). As it is known that the steroid group is an excellent antiinflammatory compound, it is possible that the antiinflammatory activity of bangle rhizome extract comes from this steroid or its synergy with cassumunarin or its synergy with other chemical compounds present in bangle rhizome extract. The main problem in COVID-19 patients is the occurrence of inflammation, especially in the lungs, besides that there is also fever and pain in the body, with antiinflammatory, anti-pyretic and analgesic effects of bangle rhizome extract, this extract will really help relieve symptoms caused by COVID-19.

4.5. Bangle efficacy as an anti-virus

Based on the results of the research conducted by Klaywong et al. (2014), Rhizome extract is one of the 4 plants that can reduce more than 50% of the infectivity of the bird flu virus (H5N1). The results of this experiment showed that the bangle rhizome extract was able to inhibit the relationship between nonstructural protein-1 RNA binding domain (RBD) and double-stranded RNA (ds) in the electrophoretic mobility shift test (Klaywong et al., 2014).

Whether bangle rhizome extract can fight SARS-COV-2 which causes COVID-19, research is needed for this.

4.6. Efficacy as anti-microbial, anti-fungal, and anti-diarrhea

Bangle rhizome contains essential oils. The results showed that the essential oil from bangle had antimicrobial activity. As according to the research of Panphut et al. (2018) essential oils from the Zingiberaceae family, namely: *Z. cassumunar* (bangle), *Curcuma aromatica, C. comosa*, *C. longa*, and *C. zedoaria* with the broth microdilution method and agar disc diffusion assay. The results of this study showed that all essential oils of the Zingiberaceae family are bioactive against all gram-positive and gram-negative bacteria, namely: Bacillus subtilis (ATCC6633), Enterococcus faecalis (ATCC2921), Escherichia coli (ATCC25922), Klebsiella pneumoniae (TISTR1843), Pseudomonas aeruginosa (ATCC741), Staphylococcus aureus (ATCC25923); Salmonella typhi (clinical isolate), Vibrio parahaemolyticus (5HP) and yeast of Candida albicans (ATCC90020) (Panphut et al., 2018).

Meanwhile, Pithayanukul and Tubprasert (2007) tested this essential oil against bacteria: *Escherichia coli*, *Propionibacterium acnes, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus, Staphylococcus pyrogenes, Staphylococcus epidermidis, Candida albicans, Cryptococcus neoformans, Epidermophyton occosum, Microsporum gypseum, Trichophyton mentagrophytes,* and *Trichophyton rubrum*. The test was carried out by measuring the average diameter of the inhibition zone with the disc diffusion screening method using bangle essential oil with a concentration of 6.25–50 vol%, whereas the minimum bactericidal concentration (MBC) was determined by broth microdilution method using bangle essential oil with a concentration of 0.62–2.5 vol%, and 52–79 mg/mL for 5 wt% Plai oil gel, while for the minimum fungicide concentration (MFC) 0.31–1.25 vol% and 13.8–39.5 mg/mL for 5% Plai oil gel. The results showed that dermatophytes were the most sensitive, followed by yeast and then bacteria. The results showed that bangle essential oil had antimicrobial activity against various gram-positive and gram-negative bacteria, dermatophytes and yeast. Dermatophytes were the most sensitive followed by yeast and then bacteria. The average diameter of the inhibition zone and the ability to kill microrganisms increase with increasing oil concentration (Pithayanukul and Tubprasert, 2007).

Then research on Antifungal Activity was carried out by Jantan et al. (2008) using 9 types of essential oils of the Zingiberaceae family of rhizomes, and one of them was Bangle essential oil, while the other plants are: *A. galanga* Swartz, *B. pandurata* Roxb, *C. aeruginosa* Roxb, C mango Valeton & van Zyp, C. xanthorrhiza Roxb, K galanga Linn, Z. officinale Rosc, and *Z. zerumbet* Smith. Experiments were carried out on 3 fibrous fungi, namely: *A. niger, A. fumigatus* and *Mucor sp,* 5 against dermatophytes, namely: *E. floccosum, M. canis, M. nanum T. mentagrophytes*, and *T. rubrum,* and 5 against yeast strains, namely: *S. cerevisiae, C. neoformans, C albicans, Ca. tropicalis* and *T. glabrata*. The antifungal activity test was carried out using the broth microdilution method and the gel disc diffusion method. The results showed that bangle and *Z. officinale* essential oil gave the highest activity against yeast (11.7–15.7 mm), while B. pandurata essential oil was effective against all fungi (Jantan et al., 2008).

Because bangle rhizome extract has antibacterial, antifungal and anti-allergic activity as described below. Because generally, diarrhea is caused by bacteria, fungi and allergens, so it is logical that rhizome extract has long been believed and used to cure diarrhea, pneumonia, and other infectious diseases.

4.7. Efficacy as anti-malarial

Andika (2018), at the Faculty of Medicine, University of Jember, Indonesia, conducted a study on the anti-malarial efficacy of the bangle rhizome alcohol extract against mice induced by *Plasmodium berghei*. The experimental animals used were 25 balb/c mice which were divided into 5 groups. The research was conducted on mice induced by *Plasmodium berghei*. The anti-malarial effect of test preparations was compared with negative controls. The administration doses of the test preparation were 18.08 mg, 9.04 mg, 4.52 mg, and 2.26 mg/20 g BW. An indicator of antimalarial activity was shown by the difference in the percentage of inhibition obtained from measuring the degree of parasitemia for five days, from D0 to D4. The results of statistical tests using the Saphiro-Wilk and Pearson methods showed that this in vivo study had activity as an antimalarial therapy by suppressing the increase in the degree of parasitemia and an IC50 value of 6.09 mg/20 g BW

which was able to inhibit the growth of *Plasmodium berghei* by 50% (Andika, 2018).

Chloroquine and hydroxychloroquine have been used to treat COVID-19, because the in vitro effect of these anti-malarial drugs inhibits the replication of SARS-CoV-2, but their side effects cause severe arrhythmias and can lead to sudden death. How does bangle rhizome extract work as anti-malarial and anti-viral, whether it also inhibits viral replication, further research is needed for this matter (Cortegiani et al., 2020).

4.8. Efficacy as an antioxidant

Cassumunarins A, B, and C were isolated from bangle rhizome and their structures were determined by spectroscopic analysis. The anti-oxidant effect of these compounds were compared to curcumin. For antioxidant observation, the autoxidation activity test of linoleic acid was carried out in a buffer-ethanol system. The antiinflammatory effect of antioxidants was measured by inhibition of edema formation in mice ears induced by 12-O-tetradecanoylphorbol-I 3-acetate. The results showed that the antiinflammatory and antioxidant effects of Cassumunarins A, B, and C compounds were greater than curcumin (Masuda and Jitoe, 1994).

4.9. Efficacy as an anti-ulcer

Zerumbone (Fig. 4.1) isolated from bangle rhizome was determined for its antiulcer activity in Swiss albino mice by inhibiting it with 1 N HCl, 95% ethanol, and indomethacin-induced gastric lesions. The administration of doses for Zerumbone and indomethacin for mice were 20 mg/kg and 40 mg/kg, respectively, for Zerumbone obtained 45.77% and 92.25% inhibition, while for indomethacin 64.76% and 72.38%. The results of this study indicate that Zerumbone has a strong cytoprotective effect against necrotizing agents (HCl) and nonsteroidal anti-inflammatory drugs (indomethacin) induced by gastric ulcers. The results of this study also showed a moderate cytoprotective effect against gastric lesions induced by harmful agents (EtOH) (Al-amin et al., 2012).

4.10. Efficacy as anti-obesity and anti-hypertension

According to the research by Hasimun et al. (2019) regarding the efficacy of bangle extract as an anti-hyperlipidemic agent and its effect on the HMG-CoA reductase enzyme in the liver. Where the experiment was carried out on 30 Wistar white rats. The animals were divided into 6 groups, namely groups: Normal control was not given anything, except eating and drinking, negative control was given drug carrier solution, positive control was given simvastatin 0.9 mg/kg BW, and 3 groups of test preparations were given doses 30, 50, and 100 mg/kg BW, respectively. All groups of tested animals were given 25% fructose in water for 21 days, except for group 2. On day 22, total cholesterol, HDL, LDL, and triglycerides were measured in the blood of the tested animals. After the rats were sacrificed, the enzyme HMG CoA reductase was isolated from the rat liver and its activity was tested. The results showed that all given doses of bangle extract, namely, doses of 30, 50, and 100 mg/kg BW, had activity to reduce the levels of total cholesterol, triglycerides, LDL, and increase HDL compared to the control group. And it can inhibit the activity of the HMG CoA reductase enzyme for 11, 20, and 47%, respectively. The conclusion of this study showed that bangle extract has anti-obesity properties because bangle extract has anti-hyperlipidemic activity by inhibiting the activity of the HMG CoA reductase enzyme (Hasimun et al., 2019).

Previous research was conducted by Iswantini et al. (2011). Their research compared the antiobesity properties of 3 types of plant extracts and their mixtures, namely, *Zingiber cassumunar* rhizome extract, *Guazuma ulmifolia* rhizome extract, and *Guazuma paniculata* leaf extract. The plant extracts tested were extracted using water, 70% ethanol, and saponins. The antiobesity test was carried out based on the in vitro inhibitory activity of the extract on pancreatic lipase activity. The results of this study showed that the ethanol extract of bangle rhizome with a concentration of 100 ppm had the highest inhibitory effect on pancreatic lipase activity, namely, 29.17%, followed by aqueous extract of *Murraya paniculata* leaves with a concentration of 100 ppm, namely, 25.66%, ethanol extract of *Guazuma ulmifolia* leaves. With a concentration of 60 ppm, namely, 25.13%, and a mixture of the ethanol extract of bangle, *Guazuma ulmifolia*, and *Guazuma paniculata* with a ratio of 25 : 25 : 25, namely, 21.58%. This inhibitory effect was higher than the inhibitory effect of the positive control (100 ppm Xenical®/orlistat), which was 17.53%. The results of this study showed that bangle rhizome extract has a strong potential as antiobesity (Iswantini et al., 2011).

4.11. Efficacy for depression and neurodegenerative diseases

Matsui et al. (2012) in Japan, had carried out isolation from bangle rhizome originating from Indonesia, to obtain trans-3- (3', 4′-dimethoxyphenyl) -4 - ((E) -3′′compounds, 4′′-dimethoxystyryl] cyclohex-1-ene (Comp.1) and cis-3-(3′,4′-dimethoxyphenyl) -4 - ((E) -3′′, 4′′- dimethoxystyryl] cyclohex- 1-ene (Comp.2). These compounds were tested for their neurotropic effects in vitro and in vivo. The results of this study showed that (Comp.1) and (Comp.2) have neurotrophic properties characterized by neuritogenesis, neurite development, and increased neuron survival in cultured neurons. Likewise, for chronic medicine, these two compounds increase hippocampal neurogenesis in olfactory bulbectomy rats. Therefore, bangle rhizome extract has therapeutic potential for depression and neurodegenerative diseases such as Alzheimer's disease (Matsui et al., 2012).

In addition, Okonogi and Chaiyana (2012) have also conducted research on the efficacy of the volatile oil from bangle rhizome as anti-cholinesterase using a microemulsion technique. The acetylcholinesterase and butyrylcholinesterase efficacy tests were performed using Ellman colorimetry. The results showed that the volatile oil of bangle rhizome had inhibitory activity against acetylcholinesterase and butyrylcholinesterase, where the microemulsion formulation of bangle essential oil with alkyl chain length and the number of co-surfactant hydroxyl groups had a exellent effect on the pseudoternary phase diagram. The results of this essential oil microemulsion formulation showed that the anticholinesterase activity and butyrylcholinesterase activity of the microemulsion were much greater than the original Bangle essential oil, which was 20 times higher against acetylcholinesterase and 25 times higher against butylylcholinesterase. The results of this study showed that the microemulsion formulation of bangle essential oil has great potential to cure Alzheimer's disease (Okonogi and Chaiyana, 2012).

5. Discussion

As many have reported at this time, that COVID-19 has common symptoms and some with rare symptoms, when combined, the symptoms of COVID-19 include: fever, dry cough, sore throat, headache, difficulty breathing, fatigue, chills, runny nose, loss of taste/smell, nausea, phlegm, muscular and joint pain, diarrhea, and others (Dhama et al., 2020; Frohman et al., 2020; Magro, 2020; Prasad and Yadav, 2020; Pre-proofs et al., 2020). If we observe about the efficacy of bangle as shown in the Pharmacological properties of bangle listed above, and shown in Fig. 5, that the

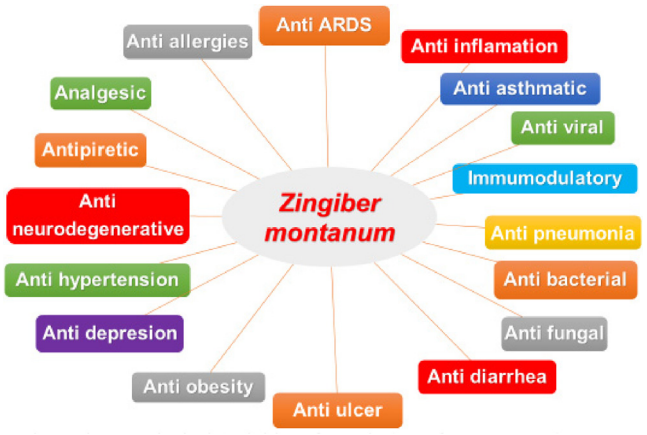


Fig. 5. Pharmacological activities of bangle (*Zingiber montanum*).

bangle rhizome has activity as anti-fever, anti-dry cough, anti-sore throat, anti-headache, anti-difficulty breathing, anti-fatigue, anti-chills, anti-runny nose, anti-loss of taste/smell, anti-nausea, anti-phlegm, anti-muscular and joint pain and anti-diarrhea.

On the other hand, there are those who make classifications for COVID-19, based on the patient's condition, there are various ways to determine the classification of COVID-19, but the most common ones are Mild, moderate, and severe-critical (Jaiswal et al., 2020; Li et al., 2020; Y. Liu et al., 2020; WHO, 2020a) Based on this classification, research is needed, whether the use of bangle extract can be useful for all types in reducing the symptoms of COVID-19.

As explained above, that bangle rhizome extract is powerful enough to treat asthma, while the symptoms of asthma, pneumonia and COVID-19 have many similarities (Bauer et al., 2000; M. Adcock et al., 2006; Novak, 2020). According to the research results of Wong et al. (2001) in patients with asthma there is an increase in proinflammatory cytokines (IL-6, IL-12, IL-17, and IL-18) and Th cytokines(IFN-g, IL-4, IL-10 and IL-13) (Wong et al., 2001). Inflammation of the lower airways is a key feature of many lung diseases, including asthma, pneumonia, and COVID-19. The difference is in the specific characteristics of the inflammatory response and the site of inflammation from one disease to another (Endeman et al., 2011; S. Liu and Zhi, 2020).

This disease invariably involves recruitment and activation of inflammatory cells and changes in pulmonary structural cells. The inflammatory response in disease is generally associated with increased cytokines, chemokines, and the expression of a cascade of growth factor proteins, enzymes, adhesion molecules, and receptors. Generally, the increased expression of these disease proteins is the result of increased gene transcription: these genes are not expressed in normal cells but they are induced in the inflammatory process. Many research results showed that the role of viral infections is not only as a causative agent for pneumonia but also asthma and COVID-19 (Endeman et al., 2011; Liu & Zhi, 2020).

According to research conducted by Nurkhasanah et al. (2019). Rhizome extract of bangle has activity to increase IL-10 in blood (Nurkhasanah et al., 2019). In this regard, Cytokine L-10 plays an important role in maintaining the integrity and homeostasis of the epithelial layer of tissue. IL-10 can increase the innate immune response of the epithelial tissue to limit the damage caused by viral and bacterial infections. IL-10 can also facilitate the process of tissue healing in wounds caused by infection or inflammation. Then IL-10 can also suppress the pro-inflammatory response and limit unnecessary tissue disruption caused by inflammation. Thus the increase in IL-10 triggered by rhizome extract from bangle is very useful in treating acute respiratory distress syndrome (ARDS) that occurs in COVID-19 (Hu, 2020; Ouyang et al., 2011; Sabat, 2010).

6. Conclusion

Based on the description above, it can be postulated that drinking bangle rhizome extract can increase antibodies to prevent Covid-19 and can also reduce symptoms caused by Covid-19.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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