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Traditional Indonesian rempah-rempah as a modern functional food and herbal medicine

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ABSTRACT

Rempah-rempah are endemic spices from Nusantara (Southeast Asia archipelago) that have been used traditionally as food flavoring for centuries. Traditionally, rempah-rempah has been processed in a variety of ways including boiled, fried, distilled, fermented, extracted, and crushed and mixed fresh with other foods. Foods flavored with rempah-rempah are served daily as beverages, hot drinks, snacks, and crackers. Nowadays, the consumption of synthetic ingredients was increased globally, but rempah-rempah was rarely used in food. In traditional medicine, various parts of rempah-rempah have been used in many countries for the treatment of a number of diseases. Unfortunately, information concerning the human health benefits of rempah-rempah is still limited. Therefore, a detailed ethnomedical, phytochemical review of the correlated chemical compounds of rempah-rempah was performed.

This review summarizes the most recent research regarding the phytopharmaceutical actions of rempah-rempah like immunomodulatory, antioxidant, analgesic, digestive, carminative, and antibacterial effects, as well as other physiological effects. Modern pharmacological studies and clinical studies performed note that rempah-rempah ameliorates potential disease threats. Such rempah-rempah include ginger (*Zingiber officinale*), Katuk (*Sauropus androgynus* (L.) Merr), andaliman (*Zanthoxylum acanthopodicum*), antarasa (*Litsea cubeba*), kecombang (*Nicolai speciosa* Horan), tapak liman (*Elephantropus scaber* L.), kedondong laut (*Polyscias obtusa*), mengkudu (*Morinda citrifolia*), kapulaga (*Amomum cardamomum*), lemongrass (*Cymbopogon fleuopsus*), sirsak (*Anona muricata*), and kunyit (*Curcuma* sp.). Due to its nutritional and medicinal values, rempah-rempah can be categorized as a functional food with natural ingredient that provide health benefit for some diseases. The resolution of various issues, such as packaging, canning, preserving, and marketing, is needed for future improvement of rempah-rempah as a traditional Indonesian flavor and functional food.

Keywords: Functional food, herbal medicine, rempah-rempah, spices, *Zingiber officinale*, *Sauropus androgynus*, *Zanthoxylum acanthopodicum*, *Litsea cubeba*, *Nicolai speciosa*, *Elephantropus scaber*, *Polyscias obtusa*, *Morinda citrifolia*, *Amomum cardamomum*, *Cymbopogon fleuopsus*, *Anona muricata*, *Curcuma* sp.

INTRODUCTION

Rempah-rempah, endemic to the Nusantara region (Southeast Asia archipelago), or specifically Indonesia, has long been very important both as a spice and as a commodity. For centuries, spices were used to preserve food in traditional communities. Sources of spices may include aromatic lichens; any part of a tree, woody shrub, or vine used for flavoring; or roots, flowers, seeds, or fruits of herbaceous plants such as saffron and ginger, the leaves of which are not used for flavoring and extracts or essential oils of any of these plants. Spices commonly found in Indonesia include galangal, pandan leaves, lemongrass, cloves, nutmeg, pepper, ginger, turmeric, and cinnamon. Spices are mainly applied as food additives at the industrial level and commonly used for their taste and flavour.

Spices typically contain a mixture of different phytochemicals, known as secondary metabolites that may act as an immunomodulatory, antioxidant, analgesic, digestive, carminative, and antibacterial, as well as other physiological effects [1, 2]. The phytochemical compounds include flavonoids, phenols and phenolic glycosides, saponins and cyanogenic glycosides, stilbenes, tannins, nitrogen compounds (alkaloids, amines, betalains), terpenoids and other metabolites. Spices as herbal medicine commonly have many phytochemical compounds that work together individually or synergistically to produce a combined effect. Nowadays, there may be some benefits of the medicinal use of the crude extract of spice as opposed to an isolated single compound. The scientific literature has evaluated the efficacy of some spices and herbs acting as medicinal plants, which are believed to have important contributions in health maintenance. However, there is still a limited number of comprehensive compilations of promising functional foods and herbal medicines from traditional Indonesian rempah-rempah. The main aim of the present review is to highlight the potential of rempah-rempah from Indonesia, which has phytopharmaceutical effects to treat some infectious and chronic diseases. This review might also provide a starting point for future studies to isolation, purification and characterization of bioactive compound in rempah-rempah.

RETRIEVAL OF PUBLISHED STUDIES

A systematic review of published studies concerning the potential of rempah-rempah for the treatment of diseases was conducted electronically using PubMed and Google Scholar. Both review and research papers were included. Eligible articles provided reasonable scientific evidence on the benefits of rempah-rempah for human health. Articles not available in English were excluded. Keywords for the search included herbal medicine, rempah-rempah, spices, immunomodulatory, and functional food.

GINGER (*Zingiber officinale*)

Ginger is a flowering plant in which the rhizome is used both as a cooking spice and in traditional medicine. In Indonesia, a beverage called wedang jahe is made from fresh ginger and palm sugar along with hot water. It is commonly used as a herbal remedy for cough and sore throats. There are three kinds of ginger: small red ginger (*Zingiber officinale* var. *rubrum*),

small white ginger (*Zingiber officinale* var. *amarum*), and big white ginger (*Zingiber officinale* var. *officinale*). The morphologies of both types are shown in Figure 1. The ginger rhizome commonly consists of two types of compounds:essential oils (volatile oil) and gingerols (nonvolatile). The pungency of ginger is caused by phenolic compounds in the rhizomes; 6-, 8-, and 10-gingerol are mostly found in fresh ginger [3]. This compound can undergo dehydration and convert to 6-, 8-, and 10-shogaol. Ginger oil is characterized by a high proportion of sesquiterpene hydrocarbons and small amounts of monoterpene hydrocarbons and oxygenated compounds [4]. The effects of ginger are described in Table 1.

Ginger plays a vital role in the prevention of some disease (Table 1). Ginger and its constituents perform anti-cancer activities through activation of the suppressor gene and modulation apoptosis [5, 6]. Ginger also performs an anti-inflammatory effect by inhibition of cyclooxygenase (COX) and down-regulating the induction of inflammatory genes [8]. Ginger rhizome contains several constituents, such as gingerol and shagelol, that have an anti-microbial and antifungal effect. Earlier studies have shown that ginger has an antimicrobial effect against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. [6]-gingerol and [12]-gingerol from ginger has been found as an effective constituent to inhibit the periodontal bacteria and M. tuberculosis *in vitro* [8, 9]. Ginger also acts as an antioxidant via neutralization of free radicals and oxidative stress. An important finding showed that combining ginger with pumpkin seeds has the most potent protective effect on male reproductive system [5]. Recently, ginger also can be considered as an anti-obesity agent in an obese animal model through increasing thermogenesis and lipolysis, inhibition of intestinal fat absorption and controlling appetite [6].

Nowadays, ginger has been widely used as a popular functional food in Indonesia. Ginger rhizome is eaten raw or cooked as vegetables and used as spices and condiments in food preparation. Ginger can be combined with other rempah-rempah such as cinnamon to treat diabetes related to obesity and hypertension. The mode of administration of ginger is usually orally diluted with water. The administration of ginger should be 4 grams per day for adults. Oral ginger is thought to be safe and is probably effective in the treatment of pregnancy-induced nausea and vomiting. Ginger can be categorized as a functional food and health promoter based on its nutrition value.

A **B** **C**

Figure 1. The morphology of (A) small red ginger (*Zingiber officinale* var. *sunti*) (B) small white ginger (*Zingiber officinale* var. *amarum*) and (C) big white ginger (*Zingiber officinale* var. *officinale*).

Table 1. The pharmacological effect of ginger constituent

Biological effect	Type of study	Constituent	Primary outcomes	Dose	Results
Anti-cancer activity	In vitro	[6]-gingerol	Anti-apoptotic effects in human epidermoid carcinoma A431 cells	250, 300 and 350 μM for 48 h	Deregulation of Bax/Bcl-2 ratio, up-regulation of Cytochrome-c and Apaf-1 in triggering of Caspase cascade [5,6].
	In vivo	[6]-gingerol	Delay in the onset of mouse skin tumorigenesis	2.5 μM/animal for 32 weeks	Sub-G1 phase was significantly elevated, a release of Cytochrome c, Caspases activation, Increase in Apaf-1 as the mechanism of apoptosis induction [5].
Anti-coagulant activity	In vitro	[8]-Gingerol, [8]-shogaol, [8]-paradol and gingerol analogues	An anti-platelet effect in human blood	0.01 to 10 μM	Paradol is the most potent anti-platelet agent and COX-1 inhibitor [7].
Anti-emetic activity	Clinical trial	Ginger crude extract	Decreasing the severity of nausea and vomiting of pregnancy	oral ginger 1 g per day	The number of vomiting episodes also decreased and improvement in nausea symptoms [4].
Anti-inflammatory effect	In vivo	Ginger crude extract	Reduced the elevated expression of NF-κB and TNF-α in rats with liver cancer	100mg/kg	Inactivating NFκB through the suppression of the pro-inflammatory TNF-α [8].
The protective effect on reproductive	In vivo	Combined ginger and pumpkin seed extract	Changes on sperm characteristics, epididymal histology and biochemical parameters of cyclophosphamide -treated rats.	300 and 600 mg/kg	Epididymal epithelium and fibromuscular thickness were also improved, increasing the total antioxidant capacity (TAC), motile spermatozoa were increased [5,6].
Antioxidant effects	In vitro	[6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol.	Scavenging of DPPH, superoxide and hydroxyl radicals, inhibition of ROS, inhibition of LPS induced nitrite and prostaglandin E2 production in RAW 264.7 cells.	10 μM	6-Shogaol has exhibited the most potent antioxidant and anti-inflammatory properties [9].
Anti-microbial activity	In vitro	Ethanolic extract	Inhibit the *Staphylococcus aureus* and *Pseudomonas aeruginosa* growth.	0.8gml-1.	Ginger performed the widest zone of inhibition and produced more inhibitory effect against *Staphylococcus aureus* and *Pseudomonas aeruginosa* compared to onions [8,9].

KATUK (*Sauropus androgunus* L. Merr)

Sauropus androgynus L. Merr (SA) is one of the most famous herbs in Indonesia and traditionally consumed to increasing breast milk production during lactation. This plant belongs to the Euphorbiaceae family and is widely used in traditional medicine [10]. SA contain some compound such as sterols, saponins, alkaloids, terpenoids, phenols, tannins, flavonoids, and catechol, as well as other compounds [11,12]. Clinical studies proved that SA leaves possesses a high potential for lowering glucose level in human blood, which could contribute to reducing diabetes [13]. Furthermore, the leaves and sticks of this plant had been used as a health food for lowering body weight gain [14].

In Indonesia, the leaves of SA are traditionally used to induce breast milk production [11, 12]. A study was conducted to verify this effect on breast milk production (Table 2). The study found that SA has a beneficial effect on breast milk production by increasing prolactin and oxytocin hormone in the bloodstream. The increase of both genes might be due to papaverine compound in SA which can dilate the blood vessels and result in the smoother circulation of both hormones. The other compound of SA that might have an effect as breast milk inducer is sterol. Sterol compound induces the signal transduction of oxytocin hormone and the glucose metabolism for lactose synthesis [15]. The phytochemical compounds in this plant also provide its antioxidant effect, antimicrobial effect against some pathogenic bacteria, and anti-inflammatory effects on some inflammatory disease [12, 16, 17].

The strong effects of this plant were increased when combined with other plants, such as Tapak Liman (*E. scaber*/ES), as a food supplement in pregnant mice [2]. SA if combined with ES could act synergistically to increase prolactin hormone and erythrocytes during pregnancy. Author has been proved this effect on previous research by fed combined SA and ES in pregnant mice infected with *Salmonella*. SA acts as a secondary messenger in cell signal transduction of hormones and growth factors. Increasing prolactin indirectly increases the number of erythrocytes [1,2]. In Indonesia, this plant is also used in traditional medicine to treat urinary tract and fever. The leaves and succulent young tips of the plant are often eaten in the salad; the flowers are also eaten (Figure 2). The leaves of SA are generally not toxic in the human body if consumed moderately. Thus, according to its detailed effect, SA can be categorized as a medicinal and functional food that have prospective value in the several disease treatment.

Figure 2. The morphology of *Sauropus androgynus* L. Merr.

Table 2. Pharmacological effects of *Sauropus androgynus* L. Merr.

Biological effect	Type of study	Constituent	Primary outcomes	Dose	Results
Anti-diabetes activity	Clinical	Aqueous leaf extract	Lowest fasting blood glucose levels in human	10 grams in 100 ml of water	The glycemic index (GI) score was significantly lower than glucose control [13].
Anti-obesity activity	In vivo	SA isolated GGK (3-O-b-D-Glucosyl-(1→6)-b-D-glucosyl-kaempferol)	Body weight reduction in Wistar male rats	60 mg per kg dose of GGK mg/kg	A decrease in food intake of rats (15%) and a reduction in body weight. No histopathological changes [14].
Lactation inducer	In vivo	Young and mature leaves extract	Increasing expression of oxytocin and prolactin in lactation mice	173.6 mg/kg for 12 days	Mature SA leaf extracts significantly increased the expressions of both genes than young leaf [15].
Anti-inflammatory and analgesic activity	In vivo	Ethanolic and Aqueous leaves extract	Led to anti-inflammatory and analgesic activity in carrageenan-induced rat paw edema.	100, 200 and 400 mg/kg body weight	Ethanolic extract was found to possess potent anti-inflammatory effect than aqueous extract [16].
Anti-microbial activity	In vitro	Methanol, ethanol and aqueous extracts	Produced higher antibacterial effects some pathogenic bacteria [12].	100 µl	Methanol extract showed more antibacterial activity than aqueous extract against *Salmonella typhimurium* and *Klebsiella pneumoniae* [12].
Improve hormonal and immune system in pregnant mice	In vivo	Combined SA and ES	Support pregnancy in typhoid pregnant BALB/c mice	Ratio ES and SA: 100:0 (T3), 75:25 (T4), 50:50 (T5), 25:75 (T6) and 0:100 % (T7).	ES and SA significantly increased the levels of prolactin and erythrocytes in T7 dose [1,2].
Antioxidant effects	In vitro	Ethanolic leaves extract	Free radical scavenging	ranging from 20 to 200 µg /ml	Ethanolic and aqueous extract of SA has possessed the inhibition of DPPH radical. GC/MS analysis of SA revealed the existence of Phytol and Squalene,

ANDALIMAN (*Zanthoxylum acanthopodicum*)

Andaliman (*Zanthoxylum acanthopodicum*) is a member of the Rutaceae family and is endemic plant on Sumatera Island, Indonesia. The fruit of Andaliman is the most popular spice for

cuisine in the Batak tribe [18, 19]. The leaves of the plant are edible as vegetables and condiment in food ingredient. In Indonesia, the plant also traditionally used to treat diarrhea, toothache, and stomachache. Andaliman has a specific and strong citrus aroma which makes it unique. The major volatile compounds in the fruits of Andaliman's include geranyl acetate (32.04%) and limonene (15.80%), and the other were citronella, β-citronellol, neral, geraniol, citronellyl acetate, α-pinene, α-Myrcene, and linalool [19,20].

A study by Wijaya showed that the crude extract of Andaliman has potential biological activity as an antioxidant and antimicrobial agent [22]. Some of the bioactive compounds in the Andaliman extract have been identified and include alkaloids, flavonoids, triterpenoids, steroids, and dan saponin. These compounds have potential action in the treatment of various diseases. Some studies have revealed that terpenoids in Andaliman exhibit antioxidant, antimicrobial, and immunostimulatory activity [23, 24, 25]. The ethanolic extract of this plant also has the highest phenolic compound and showed the highest scavenging activity compared to hexane and acetone extract [23].

Another study showed that Andaliman could also be used to overcome aging and acne in 12 female volunteers aged 20–30 years old. Andaliman ethanolic extract in the form of a peel-off gel mask (AEE PGM) on human skin was effective as an anti-aging and anti-acne agent. AEE PGM could exhibit skin moisture, skin evenness, small pore size, and resulted in a decline in the number of black spots and wrinkles. Furthermore, AEE PGM also showed acne healing activity after 4 weeks of treatment. This activity may be influenced by the flavonoid compounds in Andaliman fruit, which have been shown to be effective as antibacterial and anti-inflammatory agents [26]. The results of various studies investigating the effects of Andaliman extracts are shown in Table 3.

Andaliman may be considered to be an importance rempah-rempah due to its benefits in health and food preparation. Further study is needed to support traditional claims of this plant. The essential oil of andaliman has been successfully determined as an antimicrobial agent against fungi and gram-positive bacteria. Due to antioxidant activity in the plant, andaliman could act as a natural preservative in food. Andaliman ethanol and hexane-ethanol extract performed the best protective effect in food system [24]. Andaliman has been suggested to contain potent materials for functional food, making it promising for pharmaceutical industries in the future.

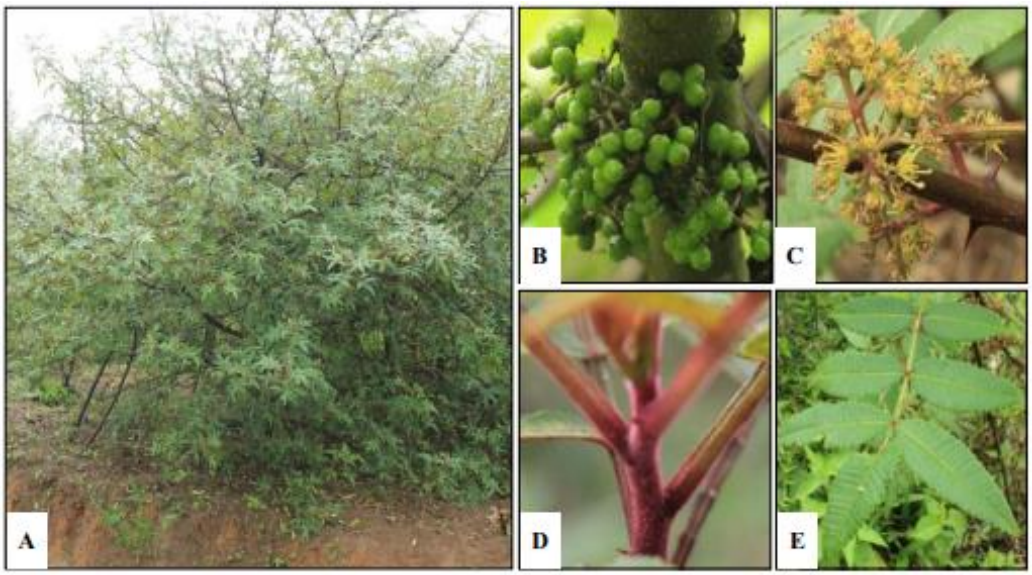

Figure 3. The morphology of Andaliman. (A) Habitat; (B) fruit; (C) flower; (D) young branches; and (E) leaves [23].

Table 3. Biological activity of Andaliman (*Zanthoxylum acanthopodicum*).

Biological effect	Type of study	Constituent	Research outcomes	Dose	Results
Anti-aging and antiacne	In vitro	Ethanol extract	Antibacterial activity against *P. acnes* was found at 300 mg/mL of Andaliman ethanol extract	300 mg.mL	*P. acnes* inhibition area: 15.95 ± 0.46 mm and S. aureus inhibitory area: 14.61 ± 0.53 mm [26].
Anti-microbial activity	In vitro	Ethyl-acetate and methanol extract	The comparison between two kind of Andaliman extract had antibacterial activity	-	Ethyle-acetate of Andaliman extract exhibited antibacterial activity against *Bacillus cereus* with MIC and MBC values of 0.2% and 0.8% [24].
Antioxidant activity	In vitro	Hexane, acetaone and ethanol extract	The phenolic compound of Andaliman showed an anti-oxidant effect	0,500,1000 and 1500 ppm	Andaliman ethanolic extract exhibited a singlet oxygen quenching effect in light-induced lipid oxidation. Andaliman hexane and acetone extracts had a stronger lipid peroxidation effect than the antioxidative effect of phenolic substances [25].
Locomotor activity	In vivo	Essential oils of Andaliman	Enhancing the locomotor activity of mice in a whell cage.	0.1, 0.3, 0.5 ml/cage	GC-MS analysis showed 29 chemical component was identified and geranyl acetate was major compound. The essential oil of the plant performed an increasing locomotor activity at dose 0.3 mL and 0.5 mL [27].
Antioxidant and cytotoxic activity in breast cancer	In vitro	Petroleum extract of andaliman fruit	Free radical scavenging activity and inhibition of the growth of breast cancer T47D cells.	100 µl	Cytotoxic activity had an IC_{50} of 149.4 µg/ml [28].
Anti-migration activity	In vitro	Ethylacetate fraction of fruit powder	Inhibition of the cell cycle of 4T1 breast cancer cell line.	10 µg/mL	Andaliman has antimigration activity through inhibition of cell cycle on G2/M phase, wound healing assay, the proliferation of cells, and expression of Cox-2 and VEGFR-2 [29].
Anti-inflammatory activity	In vitro	Ethanol extract of andaliman fruit	Inhibit inflammatory marker (TNF-α, IL-6, COX-2 and iNOS) in LPS-induced macrophage.	1-50 µg/ml	Decreasing the expression of TNF-α and COX-2 protein and MMP-9 activity at dose-dependently. Blocking mRNA expression of TNF-α, IL-6, COX-2, iNOS and MMP-9 [25].

ATTARASA (*Litsea cubeba* Pers)

Attarasa is an aromatic plant in Indonesia, which belongs to the Lauraceae family, and it is traditionally used as cough medicine and spice. Attarasa contains high essential oil content such as monoterpene hydrocarbon, oxygenated monoterpenes, sesquiterpene hydrocarbon, and oxygenated monoterpenes. GC/MS analysis of attarasa showed that aldehydes (citral, citral isomer, citronellal and citronellal isomer) were mostly found of attarasa oil. The antibacterial properties of Attarasa are closely related to the presence of aldehydes which mostly found in whole plant [28]. The essential oil from Attarasa has some biological activity (Table 4) including antioxidant, antimicrobial, and anticancer effects [30, 31]. Attarasa has the highest phenolic and flavonoid compound that has been known as strong chain antioxidant [31].

Ethanolic extract of Attarasa bark at a dose of 300 mg/kg body weight decreased the level of nitric oxide in the blood serum of mice infected with doxorubicin. The bark extract of this plant also reduced damage to heart muscle tissue [32]. Interestingly, attarasa could act as an immunostimulatory agent in fish breeding. A study by Van et al. [34] revealed that Attarasa leaves powder supplementation diets to enhance the nonspecific immunity (lysozyme, haemolytic and bacterial activities of plasma) in common carp (*Cyprinus carpio*) infected with *Aeromonas hydrophilla*. Furthermore, supplementation fed with Attarasa increased the resistance against bacterial infection. The use of attarasa leaves powder in the feed is efficient, making it an ecological way to improve the sustainability of aquaculture by reducing the use of antibiotics [34, 35]. These studies suggest that Attarasa may have a potential application in the antimicrobial industry. Its application in aquaculture may be a further opportunity giving an added value to the local biodiversity as this plant is easily grown in Indonesia.

The use of attarasa is also benefited for food preservation by exhibit antimicrobial activity. The making of edible film and coating with essential oil of attarasa in food packaging and preservation has been reported by Zuhra et al. [36]. The study revealed that incorporation attarasa oil increased the thickness, tensile strength and elongation of edible film from breadfruit (*Artocarpus artilis*). Enhancing the ability of edible film could inhibit the growth of microbes. Due to its beneficial as an antibacterial and antioxidant agent, the essential oil of attarasa has been widely used in cosmetic, sanitary, agricultural, and food industries.

Figure 4. The morphology of Attarasa (*Litsea cubeba* Pers).

Table 4. The biological activity of Attarasa (*Litsea cubeba* Pers)

Biological effect	Type of study	Constituent	Research outcomes	Dose	Results
Anti-bacterial and kinetic activity	In vitro	Attarasa oil	Increasing of antibacterial activity against 10^6 CFU/mL *E. coli.*	0%, 0.0156%, 0.0313%, 0.0625%, 0.125%, and 0.25%	Attarasa oil penetrated and destroyed the outer and inner membrane of *E. coli*, thus led to cell death [33].
Biological response of common carp	In vivo	Attarasa leaves powder	Attarase increased nonspecific immunity of carp (*Cyprinus carpio*) infected with *Aeromonas hydrophila*	2%, 4%, and 8% for 21 days	Plasma lysozyme and haemolysis was increase, the high dose performed a high antibacterial activity [34].
Anti-microbial synergy in aquaculture	In vitro	Attarasa essential oil (EO)	Synergistically antimicrobial effect of EO and antibiotic enhance the efficacy, reduce toxicity, decrease side effect and lowering the use of the antibiotic.	ranging from 0.195 µL/mL to 50 µL/mL	There was an antimicrobial synergy of *Litsea cubeba* essential oil and antibiotic that often used in the treatment of bacterial activity in aquaculture. *Litsea cubeba* and the antibiotic enhanced efficacy and reduced toxicity and side effects of bacteria in aquaculture [35].

KECOMBRANG (*Nicolaia speciosa* Horan)

Kecombrang (*Nicolaia speciosa* Horan) is a spice often used as food flavoring as well as in Indonesian traditional medicine. The flower and stem of this plant are commonly used as a potent antimicrobial agent. The bioactive compound contained in Kecombrang are polyphenol, flavonoid, alkaloid, terpenoid, steroid, saponin, and glycoside for making the preservative formula [37]. The possible formula of kecombrang, which can be used for preservative foods, can be seen at Table 5. Kecombrang also has potential as a natural antioxidant due to the higher content of phenolic compound. Thus, this plant can be considered to protect the male reproductive organ. A study by Haw et al. [38] revealed that kecombrang has a beneficial effect against oxidative stress in testicular tissue induced by lead. 1,7-bis(4-hydroxyphenyl)-2,4,6-heptatrienone and 16-hydroxylabda-8(17),11,13-trien-15,16-olide are the two main bioactive compounds which mainly act as anti-oxidant properties [39].

The highest microbial activity against *E. coli* and *B. cereus* was observed following the addition of kecombrang flower and its dried powder [35]. Other parts of this plant also exhibit antibacterial activity, such as the fruit. Ethanolic extract of the kecombrang fruit contains bioactive compounds that exhibit antimicrobial effects against *E. coli*, *B. cereus*, and *Pseudomonas aeruginosa*. Damage of microbial cells from the ethanolic extracts of kecombrang fruit has been demonstrated using the leakage of bacterial cells test [40].

The essential oil of Kecombrang is rarely used to the antibacterial agent because the volatile compound is easily oxidized and undispersed in dry ingredient. By microencapsulation technique, the essential oil of Kecombrang can be protected from environment factor and

become solid particles. A study proved the effectiveness of microencapsulation kecombrang flower extract as an antibacterial against *E. coli* [37, 40]. Thus, Kecombrang may be considered as a nutritious or functional food to preserve food because of their ability to inhibit gram-positive and negative bacteria and also fungi.

Figure 5. The morphology of Kecombrang (*Nicolaia speciosa* Horan).

Table 5. The biological activity of Kecombrang (*Nicolaia speciosa* Horan)

Biological effect	Type of study	Constituent	Research outcomes	Dose	Results
Antimicrobial activity	In vitro	Kecombrang flower: ethyl acetate and ethanol acetate extract	Microcapsule provides the best antibacterial activity against *E. coli* and *B. cereus* growth	0, 15 and 30 %	Microcapsules had inhibition zone (12.00 – 13.42 mm) to *B. cereus* and (12.00 – 13.70 mm) to *E. coli* at dose dependent manner [40].
	In vitro	Kecombrang fruit powder: hexane, ethyl acetate and ethanol extract,	Antibacterial activity against *E.coli*, *B. cereus* and *P. aeruginosa*	5, 10,15,20,25, 30, 40, 50 mg/ml	Ethanolic extract of Kecombrang has the strongest inhibitory effect against bacteria ranging from 20 mg/mL to 32 mg/mL [37].
Antioxidant activity	In vivo	Ethanol flower extract	Increasing of free radical scavenging and antioxidant properties in rat with lead treatment.	50, 100 and 200 mg/kg	Reduction of lipid hydroperoxides (LPO) and protein-carbonyl-contents (PCC). A significant increase in total antioxidants and antioxidant enzyme levels [41].
Protective effect in male reproduction	In vivo	Flower crude extract	Inhibit functional damage in rat testis induced with acetate.	100 mg/kg	Improving the testis histological changes. Reduction on testis PCC activity. Increasing of SOD and GPx and testosterone level in testis [38].

TAPAK LIMAN (*Elephantropus scaber*)

Tapak liman (*Elephantropus scaber*) belongs to the Asteraceae family, which is widely used in traditional medicine for various health-related issues. The whole of this plant is commonly used in many countries as an anti-inflammatory, antipyretic, antibiotic, anti-cough, and diuretic agent [42]. This plant is a rich source of sesquiterpene lactones and other biological compounds, such as triterpenoids, steroids, glylcosides, flavonoids, phenolic compounds, long chain hydrocarbons, and essential oils [43]. Sesquiterpene lactones of this plant; i.e., deoxyelephantopin, isodeoxyelephantopin, scabertopin, and isoscabertopin, exhibit anticancer activity. Many other biological actions, such as antimicrobial, hepatoprotective, antioxidant, anti-diabetic, anti-inflammatory, antiparasitic, and wound healing effects have been described in various studies [42-53]. Details of the biological activity of this plant are described in Table 6.

Figure 6. The morphology of Tapak liman (*Elephantropus scaber*).

The interesting role of this plant that is considered as herbal medicine is anticancer activity against some cancer cell line. Recent studies have indicated the potential effect of *E. scaber* against human colorectal cancer cell line HCT116. The study compared two active compounds from ethyl acetate fraction of *E. scaber* which have a strongest anticancer activity. Two anticancer compounds that were used in this research were deoxyelephantopin (DET) and isodeoxyelephantopin (isoDET) which is a sesquiterpene lactones compound. The results revealed that DET is the strongest anticancer agent for colorectal carcinoma as it induces apoptosis and cell cycle arrest, regulation of p53, cyclins and cyclin-dependent kinases proteins in HCT116 cells [44]. The other compound of *E. scaber* such as lupeol (triterpenoid) also has anticancer activity against MCF-7 cell line by downregulating Bcl-2 and Bcl-xl protein expression and thus lead to cell apoptosis. Another study also performed the effectivity of *E. scaber* against breast cancer (T47D) cells by enhancing cytotoxic activity and cell cycle arrest [45]. There are many evident that the compound of *E. scaber* is a potential agent against other cancer such as human prostate, skin, liver and gastric cancer [42]. From these results, *E. scaber* is potent herbal medicine for treating some cancer cell and also for some disease as shown in Table 6.

Table 6. The biological activity of *Elephantropus scaber*

Biological effect	Type of study	Constituent	Primary outcome	Dose	Results
Anti-tumor and anti-cancer activity	In vitro	Deoxyelephantopin (DET)	Inhibition of HCT116 Human Colorectal Carcinoma cell growth inducing apoptosis and cell cycle arrest	0.75 µg/mL, 1.5 µg/mL and 3.0 µg/mL	DET is the strongest anticancer agent for colorectal carcinoma by inducing apoptosis and cell cycle arrest at S phase following the upregulation of p21 and p53 expression, activating the caspase-3 and PARP cleavage and downregulating cyclin D1, A2, B1, E2, CDK4 and CDK2 protein expression [44].
	In vitro	Crude extract and the fraction (petroleum ether, chloroform, methanol)	Inhibit the growth of breast cancer cell line (T47D)	2000; 1500; 1000; 800; 400; 200; 100; 50; 25; 12.5; 6:25; and 3.125 µg/mL	Crude and the fraction extract have cytotoxic activity with IC_{50} were 58.36±2.38, 132.17±9.69, 7.08±2.11, and 572.89±69.23 µg/mL respectively. Inhibition of the cell cycle in sub G1 phase [45].
	In vitro	Lupeol (triterpenoid)	anticancer efficacy of the Lupeol agains MCF-7 cells	10, 20, 30, 40 and 80 µM	Downregulate the expression of Bcl-2 and Bcl-xL anti-apoptotic protein [47].
Anti-diabetic activity	In vivo	Crude extract and acetone fraction	Reduction of serum glucose level and Increasing of insulin in streptozotocin-diabetic rat.	150 mg/kg	The crude extract of *E. scaber* decreased serum glucose levels and increased the lowered insulin concentrations [48].
Antibacterial activity	In vitro	Methanol leaves extract	Exhibited anti-bacterial activity against *Staphylococcus aureus, Bacillus subtilis, Proteus vulgaris, E. Coli, and Pseudomonas aeruginosa*	100 µg/disc	The methanol extract of tapak liman has a significant antibacterial activity compared to chloramphenicol (30 µg/disc) [49]
Anti-parasitic activity	In vitro	Leaf and root extract	*E. scaber* exhibited anti-plasmodial activity against *P. falciparum*	10 µg/ml	Performed antiplasmodial activities against the blood stage chloroquine-resistant *P. falciparum* (EC50 < 10 µg/ml) with negligible toxicity effect [50].
Memory enhancer	In vivo	Ethanol leaves extract	Enhancing memory in Swiss albino aged mice.	150, 300, and 600 mg/kg	Increasing anticholinesterase and caspase activity in the mouse brain [51].
Protective effect in pregnancy	In vivo	Combined *E. scaber* and *P. obtusa* ethanol leaf extract	Support pregnancy in typhoid pregnant BALB/c mice	Ratio ES and PO: 100:0 (T3), 75:25 (T4), 50:50 (T5), 25:75 (T6) and 0:100 % (T7).	Synergistic modulation of immune system activation in pregnant typhoid mice by increasing the levels of CD4+, CD8+, and TER119+ cells [52].
Hepatoprotective activity	In vitro	Waterleaf extract	Reduced inflammation in BV-2 microglial cells with LPS iduction	1, 5, and 10 µg/ml	ES reduced LPS-induced nitric oxide (NO), interleukin (IL)-1, IL-6, ROS, and prostaglandin production [53].
	In vivo	Waterleaf extract	Inhibition of acute liver injury in Sprague-Dawley rat	10 mg/kg or 30 mg/kg	Water extract of *E. scaber* exhibited a hepatoprotective effect on SD rats (lipopolysaccharide-induced liver damage) by inhibiting p38 MAP kinase and COX-2 expression and decreasing serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in LPS-treated rats [53].

KEDONDONG LAUT (*Polyscias obtusa*)

Polyscias obtusa, which is known as Kedondong Laut, is a shrub plant found mostly in Indonesia, especially in Papua Island, and other tropical countries. This plant is generally used both as a vegetable and in traditional herbal medicine as an analgesic, febrifuge, and urine expedite. The leaf extract of *P. obtusa* contains flavonoids, steroids, triterpenoids, saponins, tannins, vanillate acid, and panaxadiol. Saponins in *P. obtusa* function as immunostimulatory agents, while flavonoids function as antioxidants and immunomodulatory agents [1]. The flavonoids in *P. obtusa* are able to scavenge free radicals directly by hydrogen atom donation [54].

This plant has a protective effect against *S. typhimurium* during pregnancy. Asfi and Djati [55] demonstrated that the ethanolic extracts of *P. obtusa* and *E. scaber* leaves could return the level of naïve T cells ($CD4^+$ $CD62L^+$) to normal following *Salmonella typhi* infection. The combination of these two plants influenced the proliferation of T cells. In addition, *P. obtusa* exhibited an immunomodulating effect. Fadhilah et al. [56] demonstrated that *P. obtusa* could increase $B220^+$ and TER-119, a marker of hematopoietic cells. Furthermore, the simplicia of *P. obtusa* leaves could act as an immunostimulatory agent in broiler feed with *S. typhimurium* infection. The administration of *P. obtusa* leaves significantly increased the level of $CD4^+$, $CD8^+$, and $B220^+$ cells in Broiler with *S. typhi* infection. This research strengthens the role of *P. obtusa* as an immunostimulatory agent, which is a result of the bioactive compounds present in the extract [57].

Figure 7. The morphology of *Polyscias obtusa*.

MENGKUDU (*Morinda citrifolia*)

Mengkudu (*Morinda citrifolia*) belongs to the Rubiaceae family and the Rubioideae subfamily and is commercially known as ”Noni”. This plant is traditionally used medicinally to prevent and cure disease. Mengkudu fruit, leaves, flowers, stems, bark, and root are often used to prepare traditional medicine. The phytochemical properties of *M. citrifolia* are due to phenolic compounds (antraquinones), organic acids (caprylic acids), and alkaloids (xeronine). Moreover, several studies have shown that *M. citrifolia* exhibits therapeutic properties, such as analgesic and anti-inflammatory effects [58]. Mengkudu alcohol extract has an anti-inflammatory activity through inhibition of MMP-9 release from human monocytes after LPS stimulation [59]. Details of the biological effects of this plant are described in Table 8. Different parts of this plant have been investigated with respect to their health effects. Several studies, both *in vivo* and *in vitro*, have indicated that this plant is useful in the alternative treatment of several diseases, including diabetes, high blood pressure, cardiovascular disease, and various cancers. This effect was attributed to the presence of 6-o(beta-glucopyranosyl)-1-o-octanoyl-beta-D-glucopyranose and asperulosidic acid in mengkudu [60].

Table 7. The biological activity of Kedongdong Laut (*Polyscias obtusa*)

Biological effect	Type of study	Constituent	Research outcomes	Dose	Results
Immunomodulatory activity	In vivo	Combined ethanol leaves extract of *P. obtusa* and *E. scaber*	Support the pregnancy of mice infected with *Salmonella typhi*	Ratio dose combination: 0%, 100% and 50%: 50%	The number of naive T cells was significantly increase. The level of activated CD4 T cells was decreased [55]
Pregnancy Supporting	In vivo	Combined ethanol extract of *P. obtusa* and *E. scaber*	Enhancing the level of B220 cells and erythrocytes in pregnant mice with *Salmonella thypimurium*	Ratio dose combination: 0%, 100% and 50%: 50%	The number of TER119 and B220 cell was increased after treatment with combined extract [56]
Antibacterial and Immunostimulatory activity	In vivo	Simplicia leaves	Enhancing the activation of lymphocyte during Salmonella infection in broiler chicken.	0%, 0.08%, 0.16%, 0,26%	Feeding with Simplicia *P. obtusa* increase the level of CD4 and CD8 T cells after infection with Salmonella in broiler chicken [57]

Figure 8. The morphology of Mengkudu (*Morinda citrifolia*).

Sereh or lemongrass (*Cymbopogon flexuosus*) is a tropical plant that has been used in the treatment of various diseases. Lemongrass produces an essential oil that is highly aromatic. This plant is often used in the food industry as a flavoring. The dried leaves of this plant are used for an aromatic herbal tea and are useful for fevers. *C. flexuosus* contains bioactive compound such as monoterpenes, aldehydes, alcohols, esters, and various trace components. Lemongrass essential oil has been used as a treatment for several health issues because of its powerful antioxidant effect. The essential oil of lemongrass is effective for scavenging free radical such as DPPH, NO and reducing the β-carotene bleaching method [67]. Recent studies have revealed that this plant exhibits biological activity, including antimicrobial, antioxidant, antifungal, and anti-inflammatory effects in several diseases [68]. Studies regarding the use of this plant are described in Table 9. Lemongrass also exhibited anti-inflammatory activity in human skin cells, making it a good therapeutic agent for treating inflammation of the skin [69].

Table 8. The biological activity of *Morinda citrifolia*.

Study	Type of study	Constituent	Primary outcome	Dose	Results
Anti-diabetic and anti-hyperlipidemia effects	In vivo	Combined aqueous fruit extract of *M. Citrifolia* and *Coccinia indica*	Blood glucose of diabetic rats returned to the normal level	300 mg/kg	A significant increase in insulin, blood glucose return to normal, and improving HDL-cholesterol level [61].
Anti-diabetic activity	Clinical	Noni Fruit Juice	Blood sugar level and other serum returned to normal in patients with diabetes type 2	2 ml/kg BW per day	Reducing the elevated blood sugar to the normal level, decreasing the sensitive CRP value and increasing level of C-peptide [62]
Anti-bacterial activity	In vitro	Water (WE), petroleum ether (PEE), ethyl acetate (EAE), chloroform (CE), and n-butanol (BE) extract	Performing the anti-bacterial activity against bacterial tested	20 µl	*M. citrifolia* leaves possessed antibacterial effects against *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, and *Staphylococcus aureus*. N-butanol extract (BE) produced the best antibacterial activity [63].
Anti-cancer effect	In vitro	Two glycosides: 6-O-(β-D-glucopyranosyl)-1-O-octanoyl-β-D-glucopyranose and asperulosidic acid from noni fruit juice	chemopreventive effects by inhibiting the growth of mouse epidermal cells.	10–150 µm	Both compounds suppressed TPA or EGF-induced cell transformation and AP-1 activity [64,65].
Antioxidant activity	In vitro	Ethanol extract of the fruit	Antioxidant activity against the free radicals and prevents oxidative damage	10-50 µg/ml	50% ethanolic extract of Morinda citrifolia fruit extract exhibits high antioxidant activity [66].

Figure 9. The morphology of Sereh or lemongrass (*Cymbopogon flexuosus*).

Table 9. The biological activity of *Cymbopogon flexuosus*

Study	Type of study	Constituent	Research outcomes	Dose	Results
Anti-inflammatory activity	In vitro	Citral	The essential oil of *Cymbopogon flexuosus* inhibited the skin inflammatory response in mice	-	Inhibition the production of VCAM-1, IP-10, M-CSF, I-TAC and monokine, as an inflammatory marker [68].
Antioxidant activity	In vitro	Essential oil	Lemongrass exhibited a protective effect against oxidative stress and DNA damage in human embryonic lung fibroblasts	0.5 %, 1%, 2.5 %	Citral is the main compound in the essential oil of lemongrass. Decreasing of MDA and leading to enhanced levels of SOD and CAT activities [70].
Anticancer activity	In vivo	Essential oil	Inhibited the various cancer growth through cell death mechanism.	4.2 to 79 micron/ml	Essential oil from *C. flexuosus* exhibited anticancer activity. Morphological studies of Sarcoma-180 solid tumor cells from animals treated with the essential oil of *C. flexuosus* revealed condensation and fragmentation of nuclei, which is typical of apoptosis. This plant oil also caused a loss of tumor cell viability by enhancing apoptosis [69, 70].
Antibacterial activity	In vivo	Essential oil of lemongrass and citral	Necrotic and DNA shrinkage of *A. baumannii* was observed	-	The essential oil of lemongrass and citral effectively inhibited and killed multi-drug resistant (MDR) *Acinetobacter baumannii* strains, indicating lemongrass may be a possible alternative antibiotic for treating both MDR Gram-negative and -positive bacteria [70].

SIRSAK (*Anona muricata* L.)

Sirsak (*Anona muricata*) is a part of the Annonaceae family and can be found in tropical and sub-tropical countries [71]. This plant is evergreen, terrestrial, 5–8 m in height, and has a large canopy (Figure 10). The extract of this plant consists of various secondary metabolites, such as alkaloids, saponins, terpenoids, flavonoids, and coumarins [72]. This plant is also a rich source of annonaceous acetogenin compounds (AGEs). AGEs have been reported to exhibit significant anti-proliferative effects in various cancer cell lines an antidiabetic [69, 79]. Several parts of this plant are used in traditional medicine for the treatment of various diseases. The leaf extract of *A. muricata* is often used to prevent headaches, cystitis, insomnia, and cancer. The fruits are traditionally used to treat arthritis and fever [73, 74], while the seeds are used to treat parasitic infection [77]. Several studies have been conducted to examine the efficacy of this plant against various diseases (Table 10). *A. muricata* has been used widely as a curative agent and this plant is considered an alternative candidate for herbal medicine [78].

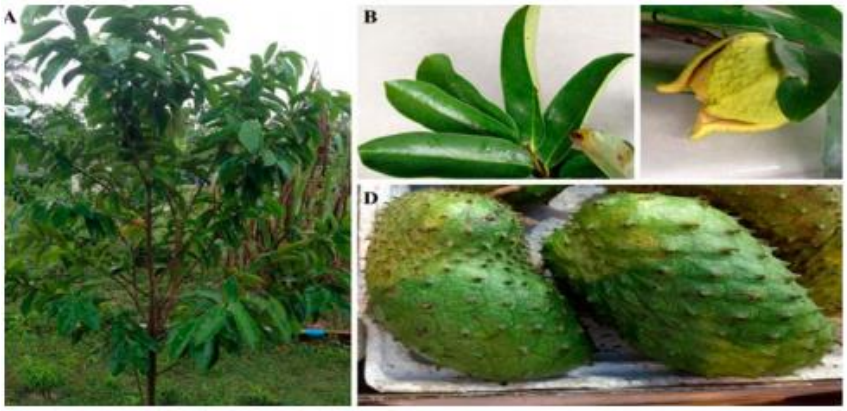

Figure 10. (A) The morphology of *Anona muricata* L. (B) Leaves; (C) flower; and (D) fruit [71].

Table 10. The biological activity of *Anona muricata*.

Study	Type of study	Constituent	Research outcomes	Dose	Results
Anticancer activity	In vivo	Ethanol extract	Chemopreventive effect of an ethanolic extract of Annona muricata leaves on DMBA-induced cell proliferation in the breast tissues of female albino mice.	50, 100, 200 mg/ml/day of extract	Ethanolic extract of *A. muricata* leaves prevented DMBA-induced DNA damage in breast tissue of mice [71]. The leaves boiled in water inhibited metastatic breast cancer [72]. Ethanolic extract of *A. muricata* leaves induced apoptosis of K562 chronic myeloid leukaemia cells [73] and reduced ACF formation in DMH-induced colon cancer [74].
	In vitro	leaves ethyl acetate extract	Induce the apoptosis in A549 cells	1.56, 3.12, 6.25, 12.5, 25, 50 and 100 µg/mL	Inhibit the proliferation of A549 cells, leading to apoptosis and cell cycle arrest at G1 [75].
Anti-diabetic	In vivo	Leaf aqueous extract	Antidiabetic effect on hepatic tissues subjected to STZ-induced oxidative stress.	100 mg/kg/day	The significant decrease in blood glucose, ROS, TBARS, TC,TG, and LDL. Increasing enzymatic activity / insulin [76].

CONCLUSIONS

Rempah-rempah, or spices, are powerful functional food with various health applications. The most famous *rempah-rempah* that have been used to treat various diseases include gingers (*Zingiberaceae*), katuk (*Sauropus androgynus* (L.) Merr), andaliman (*Zanthoxylum acanthopodicum*), antarasa (*Litsea cubeba*), Kecombang (*Nicolai speciosa* Horan), tapak liman (*Elephantropus scaber*), kedondong laut (*Polyscias obtusa*), mengkudu (*Morinda citrifolia*), sereh (*Cymbopogon fleuopsus*), and sirsak (*Anona muricata*). The resolution of various issues, such as packaging, canning, preserving, and marketing, is needed for future improvement of rempah-rempah as a traditional Indonesian flavor and functional food.

List of Abbreviations: COX, cyclooxygenase; SA, *Sauropus androgynus* L. Merr; AEE PGM, peel-off gel mask; EO, essential oil; DET, deoxyelephantopin; isoDET, isodeoxyelephantopin; NO, nitric oxide; IL, interleukin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WE, water; PEE, petroleum ether; EAE, ethyl acetate; CE, chloroform; BE, n-butanol extract; MDR, multi-drug resistant; AGEs, annonaceous acetogenin compounds

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