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Review Article

REVIEW OF TRADITIONAL USE, PHARMACOLOGICAL EFFECTS, AND TOXICITY OF MEDICINAL PLANTS FOR WOMEN'S HEALTH IN INDONESIA

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ABSTRACT

The aim of this review is to provide inspiration for research in traditional use, pharmacological effects, and toxicity of medicinal plants for women's health in Indonesia. *Punica granatum* L., *Coriandrum sativum* L., *Elephantopus scaber* L., *Foeniculum vulgare* M., *Kaempferia galanga* L., and *Nigella sativa* L. are herbs often used as medicinal plants for women's health care such as pregnancy's disorders, leucorrhea, menstrual disorders, aphrodisiac, natural contraception, care during childbirth, lactagogue, and body and skin beauty care. The medicinal plants are often consumed directly or mixed in *jamu*/herbal medicine. Many research reported regarding the pharmacological effect and toxicity test of medicinal plants. This review will show the traditional use, pharmacological effect, and toxicity of *P. granatum, C. sativum*, *E. scaber, F. vulgare*, *K. galanga*, *and N. sativa.*

Keywords: *Punica granatum, Coriandrum sativum, Elephantopus scaber, Foeniculum vulgare, Kaempferia galanga, Nigella sativa.*

INTRODUCTION

The using of medicinal plants had been known since ancient time to prevent and maintain health. In Indonesia, 89.753 of 294.962 (30.4%) patriarch use traditional health service. The use and knowledge about medicinal plants in Indonesia vary in many aspects like the medicinal plants use for handling women's health and treatment.

Medicinal plants are used for women to cure the problem in pregnancy period, leucorrhea, menstrual disorders, aphrodisiac, natural contraception, care during childbirth, and *galactagogue* [1-4].

Pomegranate (*Punica granatum*), coriander (*Coriandrum sativum*), liman (*Elephantopus scaber*), fennel (*Foeniculum vulgare*), kaempferia (*Kaempferia galanga*), and black cumin (*Nigella sativa*) are herbs that often used as medicinal plants in traditional medicines for handling women's health and treatment. The medicinal plants are often consumed directly or mixed in *jamu*/herbal medicine [3,4]. Many research showed the pharmacological effect and toxicity test of medicinal plants [1,2].

This review will show the traditional use pharmacological effect, and toxicity of pomegranate (*P. granatum*), coriander (*C. sativum*), liman (*E. scaber*), fennel (*F. vulgare*), kaempferia (*K. galanga*), and black cumin (*N. sativa*).

METHODS

This review was performed by analyzing sources from books and articles that contain the use of pomegranate (*P. granatum*), coriander (*C. sativum*), liman (*E. scaber*), fennel (*F. vulgare*), kaempferia (*K. galanga*), and black cumin (*N. sativa*).

The articles choosing based on: (1) article shows the traditional use of medicinal plants, (2) article reported the testing of extract, fraction, or pure compound of plants in animals.

RESULTS

C. sativum L.

Scientific classification of *C. sativum*: Division - *Magnoliophyta,* Class - *Magnoliopsida,* Sub-class - *Rosidae,* Order - *Apiales,* Family - *Apiaceae,* Genus - *Coriandrum,* and Species - *C. sativum* L. [5].

Traditional use

Coriander seed was used for weak deterrent during childbirth, medicine after 5 months pregnancy, hemorrhoid [4], nausea, irregular menstruation, cold, stomach ulcer, poor digestion, headache [6], and stomachache [7] (Table 1).

Elephantopus scaber L.

Scientific classification [5] *E. scaber*: Division - *Magnoliophyta,* Class - *Magnoliopsida,* Sub-class - *Asteridae,* Order - *Asterales,* Family - *Asteraceae,* Genus - *Elephantopus,* Species - *E. scaber* L.

Traditional use

E. scaber was used for facilitating the birth process, anemia, inflammation of the uterus, leucorrhea, treatment for after birth [20], asthma, pain-reducing, aphrodisiac, diarrhea, cough, sprue, and cold [21] (Table 2).

Foeniculum vulgare M.

Scientific classification [5] of *F. vulgare*: Division - *Magnoliophyta,* Class - *Magnoliopsida,* Sub-class - *Rosidae,* Order - *Apiales,* Family - *Apiaceae,* Genus - *Foeniculum,* Species - *F. vulgare* Mill.

Traditional use

Fennel can be used as leucorrhea medicine, preventive medicine difficult to get out of the placenta, the drug after 5 months of pregnancy, miscarriage drug [4], irregular menstruation, cough, flatulence, and sprue medicine [6], menstrual pain, lack of breast milk, laxative medicine kidney stones, abdominal pain, flatulence, stomach fullness, nausea, vomiting, diarrhea, jaundice, lack of appetite, coughing with phlegm, shortness of breath (asthma), protein in the urine (proteinuria), insomnia, orchidoptosis, hernia inguinalis, epididimis, hydrocele testis, and rheumatic gout [20] (Table 3).

P. granatum L.

Scientific classification [5] of *P. granatum*: Division - *Magnoliophyta,* Class - *Magnoliopsida,* Sub-class - *Rosidae,* Order - *Myrtales,* Family - *Punicaceae,* Genus - *Punica,* Species - *P. granatum* L.

Traditional use

Pomegranate can be used for leucorrhea, antiobesity, stomachache, frequent urination, high blood pressure, cough, and diarrhea [21] (Table 4).

Table 1: Pharmacological effect and toxicity of coriander (*Coriandrum sativum* L.)

Tested sample	Effect	Source
Methanol extract of coriander seed	Coriander seed extract significantly increased the excretion of cholesterol and phospholipid, so it was effective for hyperlipidemia and atherosclerosis treatment	[8]
Methanol and ethanol extract of coriander seed	Methanol extract of coriander seed was effective to be used as bactericidal for *Escherichia coli* and *Lactococcus lactis*	[9]
Ethyl acetate extract of coriander root	Showed high antiproliferative activity in MCF-7 cells, and showed the potential for preventing diseases which associated with oxidative stress	[10]
Water extract of coriander seed	Contained many phenolic compounds and have antioxidant activity thus effective as hepatoprotector	[11]
Hydro-methanolic extract of coriander seed	Prevent atherosclerosis in mice	[12]
Methanol extract of coriander leaf	Significantly decreased blood sugar and reduce lipid parameters such as total cholesterol, LDL, HDL, VLDL, and TG	[13]
Ethanol extract of coriander leaf	*In vitro* showed significant activity as antioxidant and anticancer activity in colon	[14]
Methanol extract of coriander seed	Significantly decreased total cholesterol, TG, LDL, VLDL in rat, but increased HDL	[15]
Essential oil from coriander seed extract	Coriandrum extract has toxic activity against larvae of *Aedes albopictus* Skuse with 421 µg/ml LC_{50} and LC_{90} 531.7 µg/ml	[16]
6% oil coriander seed in *Unguentum leniens*	Effective and well-tolerated in interdigital tinea pedis treatment	[17]
Methanol extract of coriander seed	The toxicity test • LD_{50} more than 5000 mg/kg bw • There is significant reduction in body weight and fat plasma • No change in the profile of hematology, organ weight, histology, and plasma markers of vital organs	[18]
Water extract of coriander seed	Antifertility activity • At doses of 250 and 500 mg/kg bw resulted in anti-implantation effect but did not show a complete infertility • There is no significant change in weight and length of fetuses born • There were no organ abnormalities • Significantly reduced progesterone level on day 5 of pregnancy, which may be the cause of anti-implantation effect	[19]

MCF: Michigan Cancer Foundation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, TG: Total glyceride, LC: Lethal concentration, LD: Lethal dose

Table 2: Pharmacology effects and toxicity of liman (*Elephantopus scaber* L.)

Tested sample	Effect	Source
Ethanol extract of liman leaves	Has hepatoprotection activity in mice with alcohol-induced liver damage	[22]
Water extract of liman leaves	Has anti-inflammatory and hepatoprotective effect by inhibiting the p38 mitogen-activated signaling protein and COX-2 in Sprague-Dawley rats	[23]
Liman's DET	DET (2 mg/ml) suppresses the growth of mammary adenocarcinoma in rats	[24]
Liman's DET and iso-DET	Reduced the L929 tumor cell viability (IC_{50} of 2.7 mg/ml and 3.3 mg/ml) and *in vivo* showed significant effect as anti-tumor to tumor cells DLA	[25]
Ethanol extract of liman leaves	Significantly ($p<0.001$) decreased bronchospasm-induced by histamine and acetylcholine and prevent degeneration of mast cells in Guinea pig	[26]
Etil asetat extract of liman leaves	Liman leaves extract with a concentration of 4 mg/ml have antimicrobial effect, which indicated the presence of microbial growth inhibition on the isolation of bacteria ATCC	[27]
Liman's DET	Effective as wound healing ($p<0.01$) by reducing chronic inflammatory cell, reduced edema, and improved collagenase	[28]
Acetone extract of liman leaves	Acetone extract of liman leaves reduced the blood glucose levels in streptozotocin-induced diabetic rats	[29]
Ethanolic extract of liman leaves	Acute toxicity test showed that liman leaves did not cause death and abnormalities at dose of 5000 mg/kg bw	[30]
Ethanolic extract of liman leaves	Oral administration of the ethanolic extract produced no abnormality or gross lesion in necropsy; no significant difference in body weight	[31]

COX: Cyclooxygenase, DET: Deoxyelephantopin, ATCC: American Type Culture Collection, DLA: Dalton's Lymphoma Ascites

***Kaempferia galanga* L.**

Scientific classification [5] of kaempferia (*K. galanga*): Division - *Magnoliophyta,* Class - *Liliopsida,* Sub-class - *Zingiberidae,* Order - *Zingiberales,* Family - *Zingiberaceae,* Genus - *Kaempferia,* Species - *K. galanga* L.

Traditional use

Kaempferia had medical efficacy for pregnant after 5 months, for women which weak after giving birth, cough, shortness of breath, flatulence, nausea, cold, sore, compress swelling/inflammation, tetanus, appetite enhancer, ulcers medicine, antihypertension, rheumatism, and asthma [4,6,58].

Research of pharmacological effect and toxicity of kaempferia could be seen in Table 5.

***Nigella sativa* L.**

Classification of *N. sativa*: Division - *Magnoliophyta,* Class - *Magnoliopsida,* Sub-class - *Magnoliidae,* Order - *Ranunculales,* Family - *Ranunculaceae,* Genus - *Nigela,* Species - *N. sativa* L. [5].

Traditional use

Traditional use has medical efficacy for pregnancy after entering 5 months, nausea, abdominal pain, menstrual disorders, leucorrhea, fever, palpitations, and anthelmintic [4,6].

Table 3: Pharmacological effect and toxicity of fennel (*Foeniculum vulgare*)

Tested sample	Effect	Source
Fennel fruit powder	Significantly ($p<0.001$) increased in serum prolactin levels in breastfeeding mothers	[32]
Ethanol extract of fennel fruit	Antidepressant activity in albino rats	[33]
Methanol extract of fennel fruit	Antioxidant and antidepressant effect by inhibiting monoamine oxidase	[34]
Ethanol extract of fennel fruit	Analgesic and anti-inflammatory activity of both the central and peripheral mechanism	[35]
Essential oil of fennel fruit	Inhibit the activity of the bacteria *Staphylococcus aureus, Bacillus megaterium*, and *Escherichia coli*	[36]
Methanol extract of fennel fruit	Hepatoprotective activity in Wistar albino rats with paracetamol-induced hepatotoxicity	[37]
Water extract of fennel fruit	Funnel water extract 500 mg/kg bw on mice showed significant result as protector for gastric mucosa from damage	[38]
Ethanol extract of fennel fruit	• Funnel water extract 500 mg/kg bw had an analgesic effect, diuretic, antipyretic, and increase the secretion of bile • Extracts also had antimicrobial effects by inhibiting the growth of *Staphylococcus aureus* and *Bacillus subtilis* • The toxicity test: Extract 3 g/kg bw caused piloerection, suppress locomotor activity and no mortality	[39]
Essential oil fennel fruit	• Essential oil of fennel fruit reduced the intensity of oxytocin and PGE2 which induced contraction significantly • LD_{50} in rat 1326 mg/kg bw	[40]
Anethole compound from fennel fruit	LD_{50} anethole in rat was 2090 mg/kg bw orally. Repeated doses of one-third the LD_{50} of anethole (695 mg/kg bw) caused mild liver lesion	[41]

PGE2: Prostaglandin E2, LD: Lethal dose

Table 4: Pharmacology effects and toxicity of pomegranate (*Punica granatum* L.)

Tested sample	Effects	Source
Pomegranate rind extract	Pomegranate extract had the same effectiveness with 2% ketoconazole in inhibiting the *in vitro* growth of *Candida albicans* in vulvovaginal candidiasis	[42]
Hexane extract, chloroform extract, ethyl acetate extract of pomegranate rind	Having a significant effect in inhibiting the activity of protease katepsin D	[43]
Pomegranate rind infusion	Active against *Salmonella typhimurium* with inhibitory concentration of 1.1 mg/ml, reduced intestinal motility at dose of 800 mg/kg bw, and reduced diarrhea at doses of 400 and 800 mg/kg bw in rat	[44]
Standardized pomegranate rind extract	Anti-inflammatory and analgesic by inhibiting leukocyte infiltration and pro-inflammatory modulation cytokines IL-β and TNF-α	[45]
Standardized pomegranate rind extract	Effective as wound healing by increasing the excision wound contraction in wound and burn	[46]
Water extract of seed, fruit, and rind of pomegranate	Antioxidant for free radical such as NO, H_2O_2, OH, RNS, ROS	[47,48]
Pomegranate peel extract	Reduced 54% fat in mice induced peroxidase CCl_4	[49]
Flavonoid from pomegranate plant	Reduced the concentration of malondialdehyde, liver hydroperoxide on the heart and kidney in mice and increased the enzyme catalase, SOD, peroxidase and glutasion reductase	[50]
Methanol extract from pomegranate fruit	Broad-spectrum antimicrobial effect on 159 bacteria resistant to multiple drugs, from the isolated urine of patients with UTI	[51]
Water extract of pomegranate rind	Contained a lot of tannins which significantly inactivated HBV virus by inhibiting DNA polymerase	[52]
Punicalagin of pomegranate	Punicalagin was effective to suppress replication of viral DNA Human influenza (H3N2)	[53]
Water extract of pomegranate rind	Hepatoprotective effect in mice with an overdose of acetaminophen	[54]
Water extract of pomegranate rind	Reduced blood sugar level in mice	[55]
Pomegranate juice and pomegranate rind extract	Anti-atherosclerosis activity	[56]
Standardized pomegranate fruit extract	The toxicity test standardized fruit extract • LD_{50}>5 g/kg bw orally. • LD_{50} 217 mg/kg bw intraperitoneally • There were no significant value in clinical observation, body weight, ophthalmic test, observation of clinical pathology, food consumption, and organ weight • There were no abnormality in the histopathological test • Hematology and serum chemistry parameters showed significant differences compared to control, but it was not toxic effect in biological variation • NOAEL of standardized Pomegranate fruit extract was 600 mg/kg bw per day	[57]

IL-β: Interleukin beta, TNF-α: Tumor necrosis factor alpha, RNS: Reactive nitrogen species, ROS: Reactive oxygen species, SOD: Superoxide dismutase, UTI: Urinary tract infection, HBV: Hepatitis B virus, LD: Lethal dose, NOAEL: No observed adverse effect level

Table 5: Pharmacological effect and toxicity of kaempferia (*Kaempferia galanga* L.)

Tested sample	Effects	Source
Ethyl-p-methoxycinnamate of kaempferia	Anti-inflammatory by inhibiting cyclooxygenase 1 and 2, with IC_{50} 12 μM and 0.83 μM, respectively	[59]
Ethyl-p-methoxycinnamate of kaempferia	Inhibited proinflammatory cytokines and angiogenesis, and inhibited the growth of endothelial cells	[60]
Ethanol extract of kaempferia rhizome	Inhibited inflammation of 51.27±2.63% at dose of 45 mg/kg bw of Wistar rat	[58]
Methanol extract of kaempferia rhizome	Analgesic activity in the tail flick model ($p<0.001$) and a hot plate model ($p<0.001$)	[61]
Methanol extract of kaempferia rhizome	Prevented increasing level of hepatic enzymes in serum, and prevented decreasing antioxidant in serum	[62]
Hexane fraction of kaempferia rhizome	Larvicidal for *Culex quinquefasciatus* with LC_{50} 42.33 μg/ml, and had repellency against *Aedes aegypti* (ED_{50} 30.73 g cm^2)	[63]
Ether extract and chloroform extract of kaempferia rhizome	Larvicidal for *Aedes aegypti*. LC_{50} of ether extract and chloroform extract 64.08 μg/ml and 105.02 μg/ml, respectively	[64]
Alcohol extract of kaempferia rhizome	Significantly reduced the time required to epithelialization ($p<0.001$) and effectively delayed restore epithelialization by the effect of dexamethasone ($p<0.001$)	[65]
Methanol extract of kaempferia rhizome	Toxicity test of methanol extract of kaempferia rhizome showed: • There was no mortality at dose of 5 mg/kg bw • No significant difference in body weight and organ weight between control and test group in male and female. Hematological analysis showed no difference in any parameter tested (WBC, platelet, hematocrit and hemoglobin). However, differences were found leucocyte and lymphocyte at doses of 50 and 100 mg/kg bw group of male rat • Chemical analysis of blood found no abnormality in glucose, creatinine, BUN, AST, ALT, Alk-P, total protein and albumin in male and female group • No abnormal in pathology and histopathology • No irritation in the skin	[66]

WBC: Whole blood cell, BUN: Blood urea nitrogen, AST: Aspartate transaminase, ALT: Alanine transaminase, Alk-P: Alkaline phosphatase, LC: Lethal concentration

Table 6: Pharmacology effects and toxicity of black cumin (*Nigella sativa* L.)

Tested sample	Effects	Source
Oil of black cumin seed	Cumin's oil showed cardioprotective effect by decreasing fat peroxidation, histopathology normal heart, improving status of antioxidant enzyme and oxidation of cellular protein	[67]
Alcohol extract of black cumin seed	Hepatoprotective effect in rat induced by D-GalN	[68]
Methanol extract of black cumin seed	Anti-inflammatory and analgesic effect	[69]
Oil of black cumin seed	Reduced serum total cholesterol, LDL, and triglycerides. Significantly increased HDL	[70]
Water extract of black cumin	Cytotoxic against breast cancer cells MCF-7	[71]
Black cumin powder	Inhibited oxidative stress caused by oxidation of corn oil in mice	[72]
Water extract of black cumin	Reduced blood sugar level in rat induced by STZ	[73]
Oil of black cumin seed	Black cumin in large doses had toxic effect on the kidney and liver histology structure	[74]
TQRFNE from black cumin	Toxicity test of *Thymoquinone*: • No significant changes in body weight, organ weight, consumption of food and drink, the amount of urine or feces • Test histology found no damage to the tissue • Showed increasing in plasma urea, creatinine, enzymes (ALT, LDH, CPK)	[75]
Ethanol extract of black cumin seed	Antifertility activity in male rat	[76]

D-GalN: D-Galactosamine, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, MCF: Michigan Cancer Foundation, STZ: Streptozocin, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, CPK: Creatine phosphokinase, TQRFNE: *Thymoquinone*-rich fraction nanoemulsion

Researches of pharmacological effect about black cumin could be seen in Table 6.

DISCUSSION

Some plants had been studied regarding their pharmacological effect. One plant could have more than one pharmacological activity, and different part of the plant could give different content and different effect [8-10,24,33,42,61,74,75].

Coriander (*C. sativum*) is a plant known as spices could be seen in Table 1, has many usage such as treatment of hyperlipidemia and atherosclerosis [8], hepatoprotector [11], anticancer [15], anti-atherosclerosis [12], antioxidant [14]. Although the acute toxicity test LD_{50} stated that *Coriandrum* was safe at dose of more than 5000 mg/kg bw, but subchronic toxicity test found that there were a significant reduction in body weight and fat plasma [18]. *Coriandrum* also had antifertility activity [19].

Liman (*E. scaber*) is a plant that grows wild, traditionally has many benefits for both women and for other diseases, the effects of which have been studied were anticancer [24,25], hepatoprotector [22,23], antidiabetic [29], and antimicrobe [27]. LD_{50} in acute toxicity test was claimed more than 5000 mg/kg bw [30,31]. It was indicated that liman safely consumed and used as ingredients.

Fennel (*F. vulgare*), growing plants spread and long-lived in Indonesian is widely cultivated as a medicinal plant and spices, traditionally this plant has a lot of uses. Some studies showed that fennel had effects as galactogogue [32], antideppressant [33], anti-inflammatory dan analgesic [35], hepatoprotector [37], gastric mucosal protector [38], and antimicrobe [39]. Acute toxicity test on fennel essential oil was LD_{50} 1326 mg/kg bw [40], anetol of fennel seeds LD_{50} 2090 mg/kg bw, while the ethanol extract of fennel seeds at dose of 3 g/kg bw caused piloerection and suppressed locomotor activity but did not cause death [39].

Pomegranate (*P. granatum*) had pharmacological effect, such as antifungal [42], antioxidant [47,48,49], anti-inflammatory dan analgesic [45], antimicrobe [51], antiviral [52,53], antidiabetic [54,55], and anti-atherosclerosis [56]. Toxicity test of pomegranate showed LD_{50}>5 g/kg bw orally in rat, LD_{50} of 217 mg/kg bw intraperitoneally [57].

kaempferia (*K. galanga*) is a tropical plant that grows in various regions, in Indonesia, this plant was used as traditional medicine and as a spice in cooking, some pharmacological effect of kaempferia were an anti-inflammatory [58,59,60], analgesic [61], and hepatoprotector [62]. Based on the results of toxicity test revealed that no mortality at dose of 5 g/kg bw kaempferia, and no abnormality in hematology and histology, did not affect weight gain and organ weight, and did not irritate the skin.

Black cumin (*N. sativa*) is a plant that has traditionally been used for centuries in Asia, middle East, and Africa to treat various diseases. Several studies have found that the pharmacological effect of black cumin were cardioprotector [67], hepatoprotector [68,70], anti-inflammatory and analgesic [69], anticancer [71], and antidiabetic [73]. Toxicity test in mice showed that black cumin had no effect on body weight, relative organ weight, water and food consumption, hematology, histopathology, and clinical biochemistry [75], but at dose of 2 g/kg bw showed an antifertility effect in rats [76].

CONCLUSION

Plants are traditionally often used for women's health medications are coriander, liman, fennel, pomegranate, and kaempferia dan black cumin. These plants have lots of pharmacological effects that are beneficial for humans, although the toxicity test has been carried out on these plants there were fewer development toxicity test included teratogenic test ever reported, whereas it is very important because some of these plants are used for women's health medications.

Now-a-day, we are conducting research using the brine shrimp test to see the teratogenic effect on these plants.

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