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Review article

Indonesian Medicinal Plants with Anti-inflammatory Properties and Potency as Chronic Obstructive Pulmonary Disease (COPD) Herbal Medicine

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ABSTRACT

Indonesia is a tropical country with mega-biodiversity. Several medicinal plants locally have been recognized for their anti-inflammatory properties and are traditionally used to help treat respiratory diseases. Chronic obstructive pulmonary disease (COPD) is one of the diseases known as the high cause of death globally, and one of the treatment efforts is by using anti-inflammatory drugs. In developing alternative remedies for COPD, this review summarizes the potential of Indonesian medicinal plants and their ingredients known to have an anti-inflammatory activity to develop alternative remedies for COPD. Primarily, we focus on the medicinal plants that have been scientifically proven to pose some biological activities, such as *legetan warak* (*Adenostemma lavenia*), celery (*Apium graveolens*), *pegagan* (*Centella asiatica*), *kenikir* (*Cosmos caudatus*), and *kersen* (*Muntingia calabura*). This review is expected to provide more information about Indonesian medicinal plants and their potencies to be developed as COPD herbal medicine and, further, as a treatment to help patients suffering from coronavirus disease (COVID-19).

Key words: Anti-inflammatory, Bioactive compounds, Biological activity, Chronic obstructive pulmonary disease, Indonesian medicinal plants.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive inflammatory lung disease with irreversible obstructions in the respiratory tracts, initially causing shortness of breath and finally resulting in death from respiratory failure.[1] The pathological findings of COPD are characterized by the destruction of airway epithelial cells accompanied by impaired immune systems with harmful endogenous intracellular molecules and nonspecific inflammatory responses.[2] According to the World Health Organization (WHO), COPD is triggered by persistent inhalation of an irritant or toxin, such as cigarette smoke and microscopic particles (PM 2.5). In addition to shortness of breath, excessive phlegm production and chronic cough are common symptoms in the early stage of the disease progression.[1] In addition, during the progression, the symptoms shift to chronic bronchitis, bronchiolitis, and emphysema. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD increases morbidity and mortality globally.[3] In 2019, an estimated 3.23 million deaths were caused by this disease.[4]

Inflammation, a response to pathogens or damaged tissues, is the key symptom of COPD. Inflammation is often associated with fever, swelling, pain, and skin redness. Several biochemical indicators (enzyme activity, fluid extravasation, release of mediators, and cell migration) are used to evaluate the severity.[5] The inflammatory processes in various immune and endothelial cells are initiated by viral/bacterial infection and cell/tissue damage. In some cases, the immune system mistakenly activates inflammatory responses even when no injury appears.[6] The inflammatory process through enzyme activity begins with the formation of prostaglandins from arachidonic acid with the help of the enzyme cyclooxygenase (COX). There are two types of COX enzymes, namely COX-1 and COX-2. The former, COX-1, is the widely distributed enzyme that plays a role in platelet aggregation, stimulated by prostanoids and thromboxane. The COX-2 enzyme is induced by inflammation and plays a role in producing prostaglandins, mediators of fever, pain, and tissue damage.[7]

COPD is associated with an increased number of leukocytes, such as neutrophils, macrophages, CD8-T, and Th17 lymphocytes, as well as airway epithelial cells and fibroblasts in the lungs. These inflammatory cells release various mediators, such as leukotriene B4, interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), transforming growth factor-beta (TGF-β), chemokines-like cysteine (CC) and CXC (two N-terminal cysteines separated by one amino acid), neutrophil elastase (NE), and matrix metalloproteinase (MMP)-2, 9, 12, which damages the lungs.[8]

However, no or fewer treatments for COPD have been established. Some options for people with COPD are symptomatic therapies, changing to a better lifestyle, quitting smoking, and regular exercise. Therefore, patients with COPD need medication to reduce pain and inflammation. Some drugs, pain killers classified into non-steroidal anti-inflammatory drugs (NSAIDs), alleviate pain and inflammation by inhibiting COX-2, followed by

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the reduced formation of prostaglandins.[7] However, these drugs have side effects: gastric pain, kidney failure, gastrointestinal tract disease, and diabetes.[9] Therefore, currently, many alternative medicines using herbal plants are being developed.

Our research group at Tropical Biopharmaca Research Center (Trop BRC) of IPB University is conducting a study on several Indonesian medicinal plants to analyze their potential as anti-inflammatory through inhibiting the activity of COX-2 enzyme *in vitro*, including *legetan warak* (*Adenostemma lavenia*), *kenikir* (*Cosmos caudatus*), *kersen* (*Muntingia calabura*), and red ginger (*Zingiber officinale* Linn. Var Rubrum). These plants grow in some areas in Indonesia and have anti-inflammatory activity.[9-12] In addition, some other medicinal plants, such as celery (*Apium graveolens*)[13,14] and *pegagan* (*Centella asiatica*),[15] have also been studied and shown to have some biological activities and efficacies, including as antigout[13,14] and antihypertensive.[15] Therefore, it is thought that it may have potency as an anti-inflammatory.

This review covers the traditional use and scientific evidence of medicinal plants to treat inflammation and respiratory tract diseases and discusses the bioactive ingredients in these plants. By conducting a deeper literature study of these plants, we summarize their potencies to be developed as anti-inflammatory and COPD herbal medicine. Moreover, since inflammation in the respiratory tracts is associated with the severity of patients with coronavirus disease (COVID-19), hence, these plants can be further developed to treat the patients.

METHODS

We searched the articles from PubMed (https://pubmed.ncbi.nlm.nih.gov/). Using its advanced search feature, we filled the keywords and filtered the articles by the field of "Title/Abstract." If the results were less than 100 articles, we continued to select the articles with related topics, but if the results were more than 100 articles, we filtered again by the publication date from 2018/01/01 to 2020/11/30 selected the articles with related topics. Some articles with related topics might not include in this study. The keywords used were: "adenostemma lavenia;" "adenostemma lavenia" AND "inflammatory;" "adenostemma lavenia" AND "inflammation;" "adenostemma lavenia" AND "pulmonary disease;" "apium graveolens" OR "celery;" "apium graveolens" OR "celery" AND "inflammatory:" "apium graveolens" OR "celery" AND "inflammation;" "apium graveolens" OR "celery" AND "pulmonary disease;" "centella asiatica;" "centella asiatica" AND "inflammatory;" "centella asiatica" AND "inflammation"; "centella asiatica" AND "pulmonary disease;" "cosmos caudatus" AND "inflammatory"; "cosmos caudatus" AND "inflammation;" "cosmos caudatus" AND "pulmonary disease;" "muntingia calabura"; "muntingia calabura" AND "inflammatory;" "muntingia calabura" AND "inflammation;" "muntingia calabura" AND "pulmonary disease."

Adenostemma lavenia

Adenostemma lavenia (L.) Kuntze is distributed in Southeast Asia, Pakistan, India, and China. In Indonesia, this plant is known as *legetan warak, udu tai*, and *rumput babi,* categorized as a weed. Belong to the Asteraceae family, it is a valvate-herb with sticky and hairy plant, having white pink-dotted flowers. Plants in this group have some varieties, including *A. lavenia* (L.) Kuntze var. *latifolium* and *A. lavenia* (L.) Kuntze var. *lavenia*. Some literature also mentions this plant as having the synonym of *A. viscosum* Forst. & Forst.f.[16-19] while other sources state that *A. lavenia* (L.) Kuntze and *A. viscosum* Forst. & Forst.f. are distinct species and *legetan warak* known in the Java region as *A. viscosum* Forst. & Forst.f.[20]

A. lavenia is traditionally known to have several properties. The leaves effectively treat dysuria, aphthae, sore throat, sunburned skin, dysentery, and are used as an antispasmodic (as a reliever of muscle pain). Crushed leaves and stems are applied topically and believed to be effective for healing wounds, skin diseases, ulcers, headaches, toothaches, chest pain, diarrhea (rubbed on the stomach), and insect and caterpillar bites. A mixture of leaf paste and milk is used to treat dizziness. This fresh plant juice is also believed to effectively treat ear infections, reduce swelling and inflammation, and treat respiratory diseases such as lung congestion and pneumonia. The decoction of leaves and coconut water is gargled to treat toothaches. Moreover, this plant is also used in veterinary medicine to treat eye infections in chickens and skin disease.[20]

Several groups of secondary metabolites such as alkaloids, flavonoids, steroids, and terpenoids have been reported by workers.[21-24] The alkaloids include 4-O-[3-acetyl-1-(trimethylsilyl)-1h-indolyl]-D-glucose; 5h-1-pyridine; 3-methylindole; 1-cyano-3-methylisoquinoline; 6,7-dihydro-3-nitro-5h-cyclopenta[B] pyridin-2 (1h)-one; and 5,10-diethoxy-2,3,7,8-tetrahydro-1h, 6h-dipyrrolo[1,2-A; 1', 2'-D] pyrazine.[22] Meanwhile, the phenolics that have been reported are *p*-coumaric acid[10]; 4-allyl-2,6-dimethoxyphenol; and coniferyl alcohol.[22] The terpenes derived from 11-oxygenated kauran-19-oic acids that have been isolated include *ent*-11α,15α-dihydroxykaur-16-en-19-oic acid (Figure 1A); *ent*-11α-hydroxy-15α-acetoxykaur-16-en-19-oic acid (Figure 1B); *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid (Figure 1C); (16R)-ent-11α-hydroxy-15-oxokauran-19-oic acid (Figure 1D) and adenostemmoic acid A–G.[20,25-28] Linoleic acid has also been found.[22] These compounds have been shown to have several biological activities. Anti-tumor activity with low nonspecific cytotoxicity activity against L5178Y leukemia cells was shown by *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid and adenostemmoic acid B, and prolonged the survival of mice implanted with sarcoma-180.[16]

The anti-melanogenic, antiaging, and antioxidant activities were also exhibited. The aqueous extracts and chloroform fraction, rich in *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid, show antiglycation

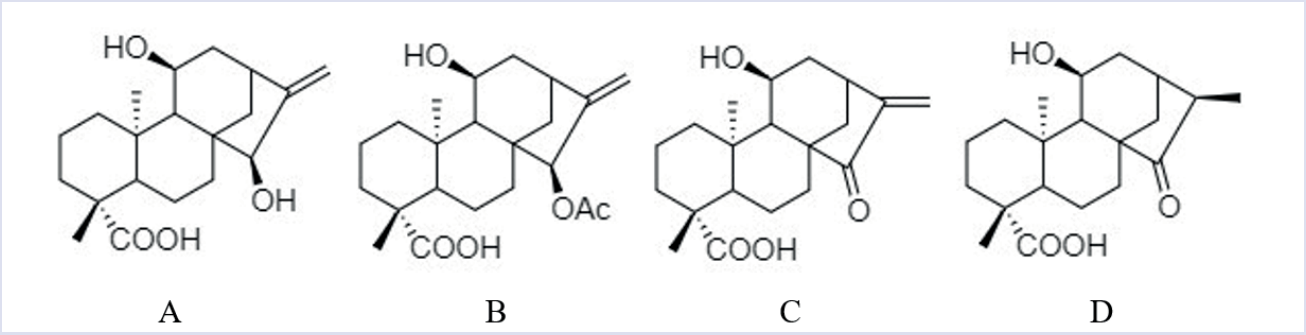

Figure 1: 11-oxygenated kauran-19-oic acids compounds from *A. lavenia* (A). *ent*-11α,15α-dihydroxykaur-16-en-19-oic acid; (B). *ent*-11α-hydroxy-15α-acetoxykaur-16-en-19-oic acid; (C). *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid; (D). (16R)-*ent*-11α-hydroxy-15-oxokauran-19-oic acid.

activity *in vitro*.[29,30] In addition, this water extract and chloroform fraction also show anti-melanogenic activity against murine melanoma B16F10 cell line. Antioxidant activity was demonstrated *in vitro* and at the cellular level against *Schizosaccharomyces pombe* yeast by improving its growth and longevity. Moreover, *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid activates nuclear factor E2-related factor 2 (Nrf2), which leads to the expression of the heme oxygenase (HO-1) gene in B16F10 cells.[29] *p*-Coumaric acid obtained from the ethyl acetate fraction of the ethanol extract of *A. lavenia* (EAAL) has also been reported to have antioxidant effects by activating the antioxidant enzymes, catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx), as well as the protein expressions of HO-1 and Nrf2 in LPS-stimulated cells and lung in mice.[10] These show the potential of this herb to be developed as an antiaging agent;[31] and a drug for treating patients with aging-related skin disorders, such as melisma.[30]

The anti-inflammatory effect was studied *in vitro* using the murine macrophage RAW 246.7 cell line and an animal model of mice. Macrophages were stimulated with lipopolysaccharides (LPS) and mice to create acute lung injury (ALI). All plant parts were extracted using 75% ethanol, followed by fractionation using *n*-hexane, ethyl acetate, and butanol (BuOH). The EAAL showed the best anti-inflammatory activity compared to the other two fractions, which has been shown to reduce the response of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). The EAAL also reduced histological changes in lung tissue in ALI mice, inhibited inflammatory cell infiltration and protein concentration in bronchoalveolar lavage fluid (BALF). The EAAL prevented the protein expression of inducible NO synthase (iNOS) and COX-2, phosphorylation of IκB-α, MAPKs, and AMP-activated protein kinase (AMPK).[10] The study we conducted on 70% ethanolic extract of *A. lavenia* to the *in vitro* inhibition assay of COX-2 also showed the potential as an anti-inflammatory (unpublished data).

Apium graveolens

Apium graveolens (L.) (family: Apiaceae), also known as celery, was first cultivated as a food plant in Europe, especially in France and Italy, and spread throughout the world, including Indonesia (local name: *seledri*). The roots of this plant are short and thick, the stems are branched and stiff, the leaves are thin and ovate, and the flowers are small and greenish-white in color.[32]

Celery is used in Ayurvedic medicine. The seeds, roots, and herbs are antispasmodic laxatives, nerve sedatives, anticonvulsants, diuretics, menstrual smoothers, and breastfeeding agents. In powder form, this plant treats diarrhea, rheumatism, kidney problems, dysentery, hoarseness, indigestion, and loss of appetite. This plant is also used as an insect repellent. The green leaves are eaten to stop bleeding in the mouth and problems in the lungs.[24] African people use this plant to treat stomach aches, lower blood pressure, and increase breast milk production. In addition, this plant can be used as an antioxidant, antifungal, and anti-inflammation.[32] In Indonesia, celery is used as a vegetable and is believed to effectively treat patients with hypertension and inflammation and reduce uric acid levels in the blood.

Several active compounds in celery have been isolated and widely studied. The phenolic compounds apigenin (Figure 2A) and apiin (Figure 2B) are flavonoids found in celery leaves and seeds and are considered characteristic compounds found in these plants.[26] Other compounds contained are caffeine acid (Figure 2C), chlorogenic acid (Figure 2D), quercetin, luteolin (Figure 2E), and some terpenoids.[27,31] The distinctive aroma and taste come from 3-*n*-butylphthalide (NBP) (Figure 2F) and sedanolide (Figure 2G) found in its essential oils.[33,34] In addition, linayl acetate and geranyl acetate are also found in the essential oils.[35]

The biological activity has also been widely reported. Celery can be used in the form of a single extract or combination and an active compound preparation isolated from it. This plant can be used as antibacterial and antifungal reagents.[35-40] Some active compounds with antibacterial and antifungal activities are derived from essential oils such as NBP, sedanolide, linalyl acetate, and geranyl acetate.[35-37,40] Several studies also have reported the active compounds that can treat patients with metabolic syndrome diseases such as hypertension, hyperglycemia, hyperlipidemia, and obesity.[41-45] The antioxidant activity, both *in vitro* and cellular level, has been widely reported.[46-54] Antioxidant capacity is closely related to its potential for the treatment of some diseases caused by free radicals and oxidative stress, such as tumors,[38,43,55,56] neurologic disease,[33,53,55,57] autoimmune disease,[13,14,58-61] and inflammation.[46,50,52,62-65]

The mechanism of the anti-inflammatory activity of celery has been studied *in vitro*, in cell culture, and *in vivo* models. The isolated active compounds from seeds inhibit the COX-2 enzyme *in vitro*.[46] Luteolin has also been shown to suppress the expression of COX-2 mRNA in carrageenan-induced mice.[66] Moreover, luteolin can also reduce the release of TNFα, IL-6, and IL-1β in rat blood treated with bisphenol-A. The activity as a hepatoprotector has also been demonstrated in luteolin.[50] Celery seeds extracted by supercritical fluid CO2 and added to RAW 246.7 macrophages treated with oxidized low-density lipoprotein have been demonstrated to reduce the release of pro-inflammatory cytokines, TNFα, and IL-6. The same response has also been shown in the isolated isofraxidin when added to human hepatocyte carcinoma HepG2 cells treated with oleic acid.[62,31]

Water and methanol extracts decrease the release of TNFα and IL-1β into the blood in Wistar rats treated with acetaminophen.[52] Hydrolyzed ethanolic extract and apigenin have also been shown to reduce the mRNA expression for pro-inflammatory molecules in Th1, Th2, and Th17 in the splenocyte in BALB/c mice treated with concanavalin A.[67] The expression of IL-1β and IL-6 mRNA in LPS-induced rats can also be suppressed by NBP treatment.[63] Celery has traditionally been used to treat allergic and respiratory diseases, such as asthma.[68] In addition, NBP has also been studied to protect against memory impairment caused by exposure to chronic intermittent hypoxia-hypercapnia (CIHH), which is also responsible for COPD pathogenesis.[69] Celery should be developed as a COPD drug in future studies, especially its anti-inflammatory properties.

Centella asiatica

Centella asiatica (L.) (family: Apiaceae), also known as *gotu kola*, is a plant that grows in tropical Asia. The local name in Indonesia is *pegagan*, *daun tapak kuda*, and *antanan*. It is a small, herbaceous plant that grows throughout the year and grows vines. The stem is creeping, has many branches, and each of these branches will form new plants. The leaves are in the form of kidney stones; at the tip of the leaf, the edges are serrated and located around the stem. The flowers will appear in the axillary area and continue to form like an umbrella, and usually, there are three white or pink flowers. It has small oval-shaped fruit and tastes bitter but has a fragrant smell.[20]

Pegagan is traditionally used as an anti-inflammatory, antidote, diuretic, fever reliever, and antiaging. Besides, it can also treat skin diseases, including ulcers and acne, jaundice, digestive tract disorders, diarrhea, venereal disease, malaria, cough, and tuberculosis, and improve brain function.[20] This herb is also used as a blood purifier to treat high blood pressure and antiaging.[70] In Bangladesh, it is also believed to treat central nervous system diseases, such as mental disorders, memory loss, and insanity.[71] In Indonesia, however, it is consumed as a vegetable or processed into herbal medicine (*jamu)*, which is believed to be a longevity remedy and is used to improve blood circulation, smooth skin; treat joint pain and coughs.

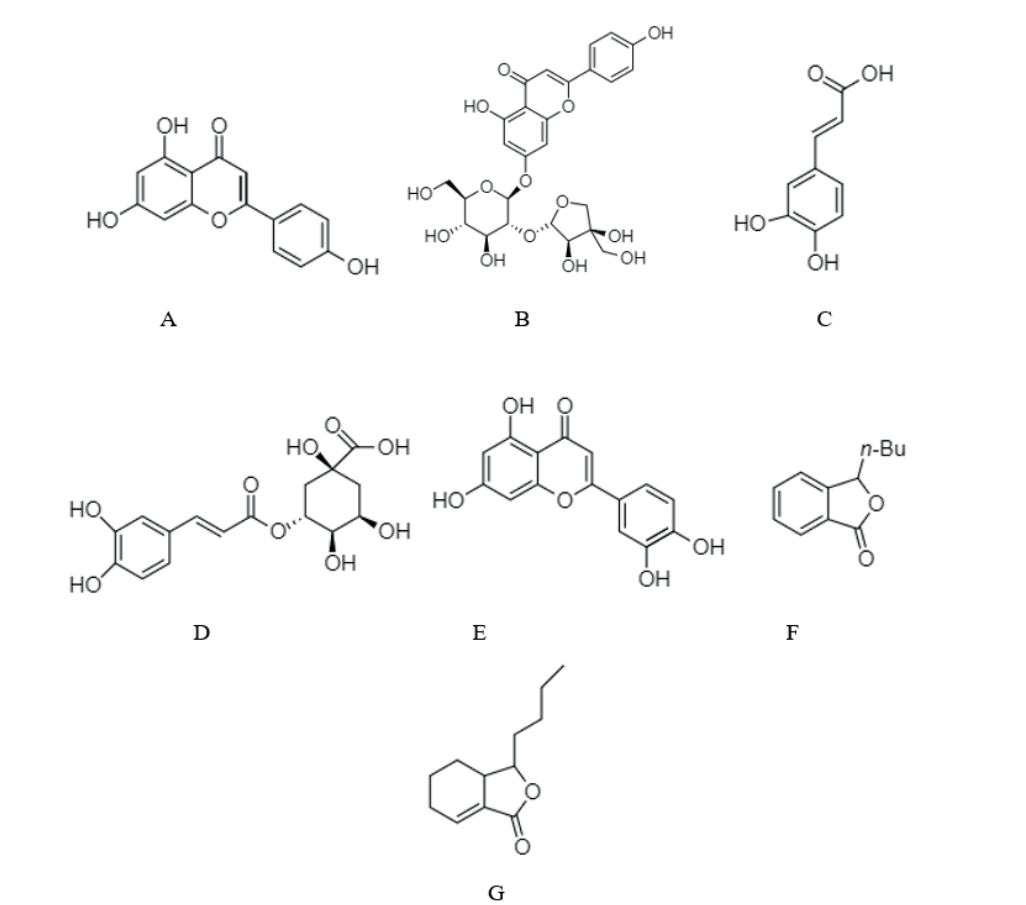

Figure 2: Compounds isolated from celery (*A. graveolens* (L.)): (A). apigenin; (B). apiin; (C). caffeic acid; (D). chlorogenic acid; (E). luteolin; (F). 3-*n*-butylphthalide (NBP); and (G). sedanolide .

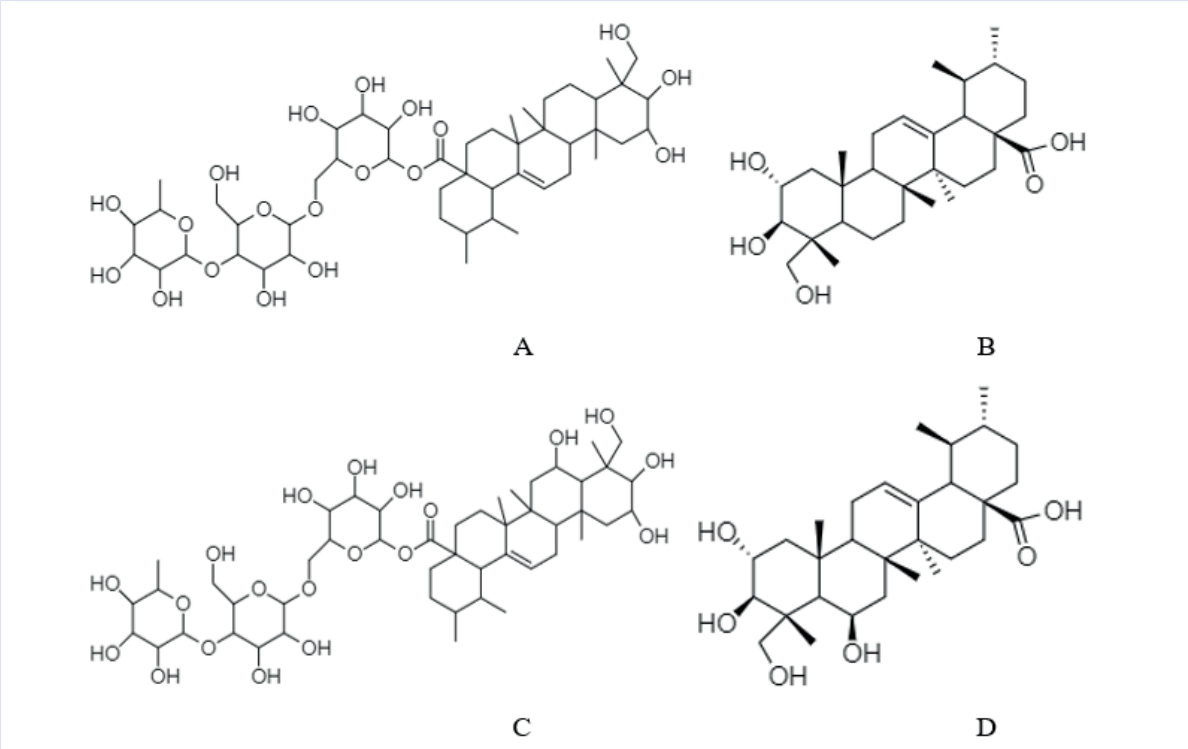

Figure 3: Compouds isolated from *C. asiatica* (L.)): (A). asiaticoside; (B). asiatic acid; (C). madecassosid; (D). madecassic acid.

The properties of *C. asiatica* have been studied extensively. These plant extracts, either singly or in combination, have some potencies including antioxidant, antiarthritic, hepatoprotector, neuroprotector, antihypertensive, antibacterial, and an agent for preventing eye damage.[13,72-84] Several compounds, including from the phenolic groups such as flavonoids and isoprenoids (terpenoids and saponins), have been isolated and have also been studied to have extensive biological activity.[85-89] The phenolics include kaempferol and quercetin.[90] In addition, caffeoylquinic acid has also been studied and has the potential to improve cognitive function in mice modeled on Alzheimer's disease.[91]

This plant's main triterpenoids include asiaticoside, asiatic acid, madecassoside, and madecassic acid (Figure 3).[89,92] These compounds have been reported to have healing properties and can be used for skincare, such as acne medication, and helps disguise stretch marks and keloids.[93-98] In addition, it is also known as an anti-inflammatory, cardioprotector, and neuroprotector.[99-104] The ECa233 standardized extract containing the four triterpenoid compounds has been tested for safety.[105] Asiaticoside (Figure3A) has been studied to have properties as an anti-inflammatory, lung protector, neuroprotector, and antiresorptive agent on the bone (bone protector). [106-111] Asiaticoside D is known to inhibit the activity of monoamine oxidase-B, whose dysfunction is implicated in neurodegeneration and behavioral disorders, being recognized asiaticoside D as a potential neuroprotector.[112] Asiatic acid (Figure 3B) has pharmacological properties such as antioxidant, anti-inflammatory, anti-depressant, anti-hyperglycemia, antihypertensive, antihyperlipidemic, anti-tumor, and anti-cancer such as breast, prostate, colon, liver, lung, and nerve cancers.[99,113-126] In addition, asiatic acid also has anti-obesity properties.[127] Madecassoside (Figure 3C), the major compound, is known to have some potencies as anti-rheumatoid arthritis and osteoarthritis,[128-131] antiischemia (cardioprotector),[128] lung protector,[132] and also neuroprotector.[132-134] Madecassic acid (Figure 3D) is reported to have an anti-inflammatory effect.[135]

The efficacy of *C. asiatica* as a lung protector is thought to be due to its anti-inflammatory effects. In general, the anti-inflammatory mechanism is through suppressing the activity of inflammatory mediator (such as prostaglandin [PGE2]) formation and release by decreasing the expression of COX-2 mRNA and the expression of pro-inflammatory cytokines (TNFα, IL-6, and IL1β) mRNA.[136-142] The asiaticoside can downregulate the NF-κb signaling pathway in LPS-induced RAW 246.7 macrophages.[108] In addition, this compound also decreases the expression of COX-2 protein and the production of TNFα and IL-6 in mice with septic lung injury.[106] Asiaticoside, asiatic acid, and madecassoside have been studied to have a similar effect on LPS-induced ALI mice,[118,134] and also, they could inhibit pulmonary inflammation and fibrosis response in mice. Pulmonary fibrosis and inflammation are the process of COPD development.[111,117,119] In addition, the bioactive triterpenoids could also inhibit the migration and invasion of human lung cancer (A549) cells induced by radiation ionization in radiotherapy.[143] These findings show that *C. asiatica* is a latent material to be developed as an alternative treatment for patients with COPD.

Cosmos caudatus

Cosmos caudatus (L.) (family: Asteraceae) comes from tropical countries of Central and South America, especially Cuba and Mexico. Known as *kenikir* in Indonesia, it is commonly consumed as a vegetable. This plant grows annually with tubular stems and longitudinal lines; the height can reach one meter. The leaves are long-stemmed and sit opposite, pinnately divided into 2-3 stalks. This plant has a distinctive aroma like resin, when it is crushed. The flowers are red with yellow spots in the middle, arranged on a head that is abundant at the end of the stem and on the axilla of the top leaves. The seeds are beak-shaped. Traditionally, this plant improves blood circulation, strengthens bones, treats burns, muscle tension, spasms, antiaging, and treats infectious diseases.[20,144,145]

Because studies on the compounds are limited, we should further explore the potencies *C. caudatus*. Some metabolites were detected in this plant, catechin, α-tocopherol, cyclohexen-1-carboxylic acid, benzoic acid, myoinositol, stigmasterol, lycopene, quercetin, quercetin 3-O-arabinofuranoside, quercetin 3-O-rhamnoside, quercetin 3-O-glucoside, quercetin 3-O-xyloside, routine, and chlorogenic acid, which inhibit α-glucosidase activity so that they have the potency as antidiabetic.[146,147] Clinical trials for evaluating antidiabetic activities have also been conducted.[148,149] Other bioactivities are the prevention of osteoporosis,[150,151] antiobesity,[152] prevention of atherosclerosis, and antioxidants.[153] The compounds with antioxidant activity are proanthocyanidins.[144,154-157] The mechanism of antioxidants is thought to be through their ability to increase the detoxifying enzyme activity in the lungs and kidneys.[158]

Inflammatory studies conducted on the carrageenan-induced mouse model showed that *C. caudatus* reduced the volume of paw swelling by more than 50%.[11] An *in vitro* anti-inflammatory study reveals that the ethanolic extract can inhibit COX-2 activity moderately. Combining this herb with other plants is thought to be able to increase its anti-inflammatory properties (unpublished data) and develop it as an alternative treatment for COPD.

Muntingia calabura

Muntingia calabura L. (family: Muntingiaceae, only one species) is a plant spread in tropical areas, including Indonesia, with the local name *kersen* or *kersem*. It is a tree plant with small red fruits, called *ceri* (not *Prunus cerasus*) or *seri*. Traditionally, this herb is used for sedation, cold and flu medicines, relieves muscle tension and spasms, controls blood pressure, and induces sweating.[20] In addition, the flowers and stems are used to reduce swelling and as an antiseptic. The decoction of leaves is believed to be able to treat gastric ulcer disease and treat headaches.[159,160]

The secondary metabolites encompass flavones, flavonols, isoflavones, flavanones, chalcones, terpenes, phenolic acids, anthocyanidins, kavalactone, and anthraquinone.[161-166] The flavones include 5,7-dihydroxy-3,8-dimethoxyflavone; 5-hydroxy-3,7-dimethoxyflavone; 3,5,7-trihydroxy-8-methoxyflavone; 5-hydroxy-3,7,8-trimethoxyflavone; and calaburone. The chalcone compounds are 2',4'-dihydroxychalcone; 2', 4'-dihydroxy-3'-methoxychalcone; and isoliquiritigenin. The terpenes that have been reported are *β*-farnesene and dendrolacin. Other compounds include gallocatechin, epigallocatechin, naringenin, quercetin, gallic acid, gentisic acid, caffeic acid, protocatechuic acid, cyanidin-3-O-glucoside, and 1, 2-benzene dicarboxylic acid diisooctyl ester.[159-171] Metabolomic analysis shows that of the 43 metabolites identified, 32 were compounds with biological activities.[166] This plant material has been reported to be a candidate material for anticancer,[172-176] antihypertensive,[177,178] antinociceptive,[167,179-182] cardioprotector,[183] antibacterial,[166] antioxidants,[167,169-171,184-187] anti-gastric ulcer and gastroprotector,[188-192] hepatoprotector,[185,159,160,193,194] antispasmodic[195], and antihyperuricemic.[196]

The potency of *M. calabura* as an anti-inflammatory can be caused by inhibiting lipoxygenase (LOX) activity,[184] inhibiting paw swelling carrageenan-induced paw of an animal model,[186] suppressing COX-2 expression, inhibit the formation of prostaglandins and pro-inflammatory cytokines (TNFα, IL-1β, and IL-6).[187,169,170] Our study showed that ethanolic extract could inhibit COX-2 activity *in vitro*. Although it has not been widely reported regarding the anti-inflammatory activity of *M. calabura*, especially in the lung, further

studies of its potency as an anti-inflammatory in the respiratory tracts can be carried out. More investigations on this plant can be continued using inflammatory cells or animal models for pneumonia.

CONCLUSION

This literature study concluded that all the five plants have the potencies to be developed as anti-inflammatory and COPD herbal medicine, even though further studies still need to be performed to explore their efficacies, especially for *C. caudatus* and *M. calabura*. In addition to their potencies as anti-inflammatory and COPD herbal medicine, these plants can be further developed as an alternative option to give a contribution to treating patients with COVID-19.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-2
IL	Interleukins
NBP	3-*n*-butylphthalide
NSAIDs	Non-steroidal anti-inflammatory drugs
TNFα	Tumor Necrosis Factor alpha

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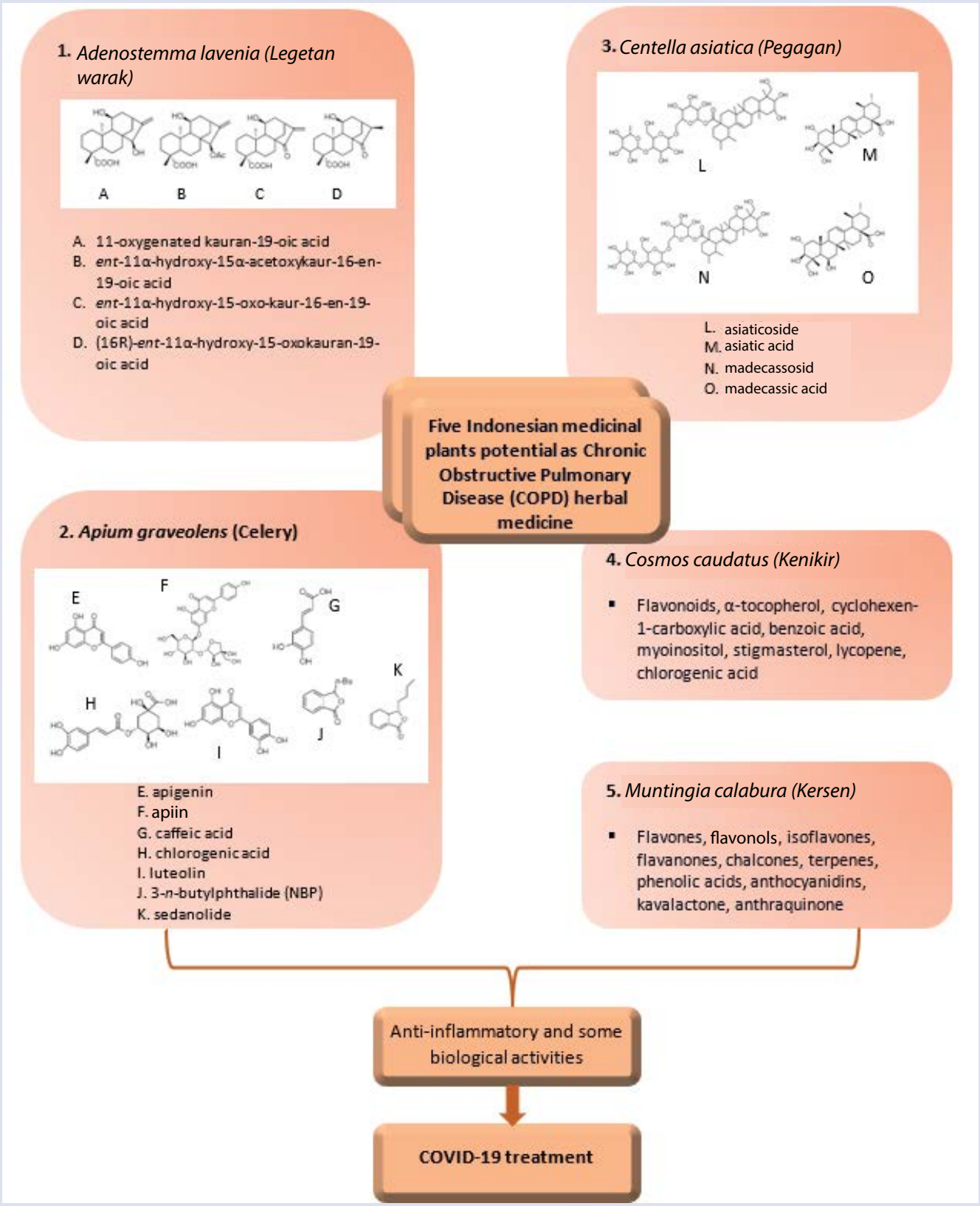
GRAPHICAL ABSTRACT



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