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 scientifically proven to pose some biological activities, such as anti-inflammatory activity to develop alternative remedies for COPD. Primarily, we focus on the medicinal plants that have been scientifically proven to have an anti-inflammatory activity to develop 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 herbal medicine and, further, as a treatment to help patients suffering from coronavirus disease (COVID-19).

Keywords: 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.3 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.4 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 prostanooids 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. However, these drugs have side effects: gastric pain, kidney failure, gastrointestinal tract disease, and diabetes. Therefore, currently, many alternative medicines using herbal plants are being developed.

Our research group at Tropical Biopharmacal 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. In addition, some other medicinal plants, such as celery (Apium graveolens) and pegagan (Centella asiatica), have also been studied and shown to have some biological activities and efficacies, including as antigout and antihypertensive. 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 and discusses the bioactive ingredients in these plants. By conducting this review, we summarize the traditional use and scientific evidence of medicinal plants to treat inflammation and respiratory tract diseases and discuss the bioactive ingredients in these plants.

### 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 inflammation;” “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 “inflammatory;” “apium graveolens” OR “celery” AND “inflammation;” “apium graveolens” OR “celery” AND “pulmonary disease;” “centella asiatica;” “centella asiatica” AND inflammation;” “centella asiatica” AND “inflammatory;” “centella asiatica” AND “inflammatory;” “centella asiatica” AND “inflammation;” “centella asiatica” AND “pulmonary disease;” “cosmos caudatus” AND inflammation;” “cosmos caudatus” AND inflammatory;” “cosmos caudatus” AND “inflammation;” “cosmos caudatus” AND “pulmonary disease;” “muntingia calabura;” “muntingia calabura” AND inflammation;” “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 rumpat 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.21

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-pyrindine; 3-methylindole; 1-cyano-3-methylsulfoximine; 6,7-dihydro-3-nitro-5h-cyclopenta[B] pyridin-2 (1h)-one; and 5,10-dioxy-2,3,7,8-tetrahydro-1h, 6h-dipyrolo[1,2-A; 1’, 2’-D] pyrazine.22 Meanwhile, the phenolics that have been reported are p-coumaric acid20; 4-allyl-2,6-dimethoxyphenol; and conifereral alcohol.22 The terpenes derived from 11-oxygenated kauren-19-oic acids that have been isolated include ent-11a,15a-dihydroxykauren-16-en-19-oic acid (Figure 1A); ent-11a-hydroxy-15a-acetoxykauren-16-en-19-oic acid (Figure 1B); ent-11a-hydroxy-15x-o xo-kauren-16-en-19-oic acid (Figure 1C); (16R)-ent-11a-hydroxy-15-oxo kauran-19-oic acid (Figure 1D) and adenostemmoic acid A–G.20,21-28 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 LS174T leukemia cells was shown by ent-11a-hydroxy-15-oxo kauran-16-en-19-oic acid and adenostemmoic acid B, and prolonged the survival of mice implanted with sarcoma-180.29

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

Figure 1: 11-oxygenated kauren-19-oic acids compounds from A. lavenia (A), ent-11a,15a-dihydroxykauren-16-en-19-oic acid (B), ent-11a-hydroxy-15a-acetoxykauren-16-en-19-oic acid (C), ent-11a-hydroxy-15x-oxo-kauren-16-en-19-oic acid (D), (16R)-ent-11a-hydroxy-15-oxo kaur an-19-oic acid.
activity in vitro.7,25,30 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-11a-hydroxy-15-oxo-kaur-16-en-19-oxic 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.29 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).30 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: Apioceae), 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: selendi). 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.32 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 apin (Figure 2B) are flavonoids found in celery leaves and seeds and are considered characteristic compounds found in these plants.32 Other compounds contained are caffeic acid (Figure 2C), chlorogenic acid (Figure 2D), quercetin, luteolin (Figure 2E), and some terpenoids.32,33 The distinctive aroma and taste come from 3-n-butylyphthalide (NBP) (Figure 2F) and sedanolide (Figure 2G) found in its essential oils.33,34 In addition, linanyl acetate and geranyl acetate are also found in the essential oils.30

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.30 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.31-40 The antioxidant activity, both in vitro and cellular level, has been widely reported.40,54 Antioxidant capacity is closely related to its potential for the treatment of some diseases caused by free radicals and oxidative stress, such as tumors,54,61,62,65 neurologic disease,51,55,57 autoimmune disease,53,54,56-61 and inflammation.40,52,53,62,63

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.48 Luteolin has also been shown to suppress the expression of COX-2 mRNA in carrageenan-induced mice.50 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.51 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.51

Water and methanol extracts decrease the release of TNFαs and IL-1β into the blood in Wistar rats treated with acetaminophen.52 Hydrolyzed ethanol 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.53 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.64 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.67 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, dasin 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.32

*Pegagan* is traditionally used as an anti-inflammatory, antidiote, 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.60 This herb is also used as a blood purifier to treat high blood pressure and antiaging.60 In Bangladesh, it is also believed to treat central nervous system diseases, such as mental disorders, memory loss, and insanity.61 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: Compounds 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. 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. The phenolics include kaempferol and quercetin. In addition, caffeoylquinic acid has also been studied and has the potential to improve cognitive function in mice modeled on Alzheimer's disease.

This plant's main triterpenoids include asiaticoside, asiatic acid, madecassoside, and madecassic acid (Figure 3). 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. In addition, it is also known as an anti-inflammatory, cardioprotector, and neuroprotector. The Eca233 standardized extract containing the four triterpenoid compounds has been tested for safety. Asiaticoside (Figure 3A) has been studied to have properties as an anti-inflammatory, lung protector, neuroprotector, and antiresorptive agent on the bone (bone protector). 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. 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. Asiatic acid also has anti-obesity properties. Madecassoside (Figure 3C), the major compound, is known to have some potencies as anti-rheumatoid arthritis and osteoarthritis, antischemia (cardioprotector), lung protector, and also neuroprotector. Madecassoside acid (Figure 3D) is reported to have an anti-inflammatory effect.

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. The asiaticoside can downregulate the NF-κb signaling pathway in LPS-induced RAW 264.7 macrophages. In addition, the compound also decreases the expression of COX-2 protein and the production of TNFα and IL-6 in mice with septic lung injury. Asiaticoside, asiatic acid, and madecassoside acid have been studied to have a similar effect on LPS-induced ALI mice and also, they could inhibit pulmonary inflammation and fibrosis response in mice. Pulmonary fibrosis and inflammation are the process of COPD development. In addition, the bioactive triterpenoids could also inhibit the migration and invasion of human lung cancer (A549) cells induced by radiation ionization in radiotherapy. 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 *kenisk* 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.

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

Inflammatory studies conducted on the carrageenan-induced mouse model showed that *C. caudatus* reduced the volume of paw swelling by more than 50%. 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 *keren* or *keren*. It is a tree plant with small red fruits, called ceri (not *Prunus cerasus* or ser). Traditionally, this herb is used for sedation, cold and flu medicines, relieves muscle tension and spasms, controls blood pressure, and induces sweating. 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.

The secondary metabolites encompass flavones, flavonols, isoflavones, flavanones, chalcones, terpenes, phenolic acids, anthocyanins, kavalactone, and anthraquinone. 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-dihydroxycalcone; 2’, 4-dihydroxy-3-methoxycalcone; and isoliquiritigenin. The terpenes that have been reported are β-farnesene and dendrolacin. Other compounds include gallocatechin, epigallocatechin, naringenin, quercetin, gallic acid, gentisic acid, caffic acid, protocatechuic acid, cyanidin-3-O-glucoside, and 1, 2-benzene dicarboxylic acid diisooctyl ester.

Metabolomic analysis shows that of the 43 metabolites identified, 32 were compounds with biological activities. This plant material has been reported to be a candidate material for antitumor, antihypertensive, antiinfective, cardioprotector, antibacterial, antioxidant, hepatoprotector, anti-gastric ulcer and gastroprotector, antiglucosidase, antispasmodic, and antihyperuricemic.

The potency of *M. calabura* as an anti-inflammatory can be caused by inhibiting lipoygenase (LOX) activity, inhibiting paw swelling carrageenan-induced, paw of an animal model suppressing COX-2 expression, inhibit the formation of prostaglandins and pro-inflammatory cytokines (TNFα, IL-1β, and IL-6). 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

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

REFERENCES

1. Barner PJ. Inflammatory mechanisms in COPD. J Allergy Clin Immunol. 2016;138(1):1-40.
2. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet. 2016;388(10062):1351-40.
3. Pauwels R. Global Initiative for Chronic Obstructive Lung Diseases (GOLD): Time to act. Eur Respir J. 2001;18(6):901-2.
4. World Health Organization. Chronic obstructive pulmonary disease (COPD). 2021 June [cited 2022 April 16].
5. Ratnayake WMKM, Suresh TS, Abeysekera AM, Salim N, Chandrika UG. Acute anti-inflammatory and anti-nociceptive activities of crude extracts, alkaloid fraction and evo-litrine from Acronychia pedunculata leaves. J Ethnopharmacol. 2019;238:118272:1-11.
6. Affah HN. Outilpina, penyakit infarasi baru yang mematikan dan menyerang anak-anak. Farmasetika. 2016;1(3):1-2.
7. Simon LS. Role and regulation of cyclooxygenase-2 during inflammation. Am J Med. 2016;106(5B):375-425.
8. Ram A, Balachandar S, Vijayanthan P, Singh VP. Medicinal plants useful for treating chronic obstructive pulmonary disease (COPD): Current Status and Future Perspectives. Fitoterapia. 2010;82(2):1-12.
9. Jisha N, Vysakh A, Vijeesh V, Latha MS. Anti-inflammatory efficacy of methanolic extract of Muntingia calabura L. leaves in carrageenan induced paw edema model. Pathophysiology. 2019;26:3-4:323-30.
10. Chen JJ, Deng JS, Huang CC, Li PY, Liang YC, Chou CY, et al. p-Coumaric-acid-containing Adenostemma lavenia ameliorates acute lung injury by activating AMPK/Nrf2/HO-1 signaling and improving the anti-oxidant response. Am J Chin Med. 2018;47(7):1-24.
30. Hamamoto A, Isogai R, Maeda M, Hayazaki M, Horyama E, Takashima S, et al. The high content of enantiomers of 15-oxo-16-ene-15A,16-dihydro-17α-hydroxy-15-oxo-kaur-16-en-19-oxo-acid in Adenostemma lavenia (L.) O. Kuntze leaf extract: With preliminary in vivo assay. Foods. 2020;9(7):1-12.

31. Li J, Li X, Li Z, Zhang L, Liu Y, Ding H, et al. Isofraxidin, a coumarin component improves high-fat diet induced hepatic lipid homeostasis disorder and macrophage inflammation in mice. Food Funct. 2017;8(8):2686-96.

32. Al-Asmari AK, Athar MT, Kadasah SG. An updated phytopharmacological review on medical plant of Arab region: Apium graveolens Linn. Pharmacogn Rev. 2017;11(21):13-8.

33. Marco-Contelles J, Zhang Y. From seeds of Apium graveolens Linn. to a cellular ischemia medicine: The long journey of 3-n-Butylphthalide. J Med Chem. 2020;63(21):12485-910.

34. Wilson CW. Relative recovery and identification of carboxyl compounds from celery essential oil. J Food Sci. 1970;35:766-8.

35. Das S, Singh VK, Dwivedy AK, Chaudhari AK, Upadhyay N, Singh A, et al. Antimicrobial activity, antiflatoxigenic potential and in situ efficacy of novel formulation comprising of Apium graveolens essential oil and its major component. Pestic Biochem Physiol. 2019;160:102-11.

36. Gong Y, Liu W, Huang X, Hao L, Li Y, Sun S. Antifungal activity and potential mechanism of N-Butylphthalide alone and in combination with fluconazole against Candida albicans: Front Microb. 2019;10(1461):1-12.

37. Wandi FNB, Achidi AU, Ngemenya MN, Nyongbela KD, Tiencheu PO. Identification of a new angiotensin-converting enzyme (ACE) inhibitor from Thai edible plants. Food Chem. 2014;165:92-7.

38. Misic D, Tadic V, Korzeniowska M, Nisavic J, Aksentijevic K, Ali SS, et al. Anti-inflammatory and antioxidant effects of Apium graveolens L. extracts mitigate against fatal acetaminophen-induced acute liver toxicity. J Food Biochem. 2020;1(e13399):1-17.

39. Derouich M, Bouhila EDT, Bammou A, Hmidani A, Sellam K, Ali SS, et al. Beneficial effects of celery (Apium graveolens) on the oxidative stress in the liver of adjuvant-induced arthritic rats. J Sci Food Agr. 2021;101(6):2256-63.

40. Ghitu A, Schwiebs A, Radeke HH, Avram S, Zupko I, Bor A, et al. Neuroprotective potential of 3-N-Butylphthalide and its derivatives. BioMed Res Int. 2016;2016:5012341.

41. Crespo YA, Sanchez LR, Quintana YG, Cabrera AST, Soe ABD. Protective role of luteolin against bisphenol a-induced renal toxicity through suppressing oxidative stress, inflammation, and upregulating Nrf2/ARE/HO-1 pathway. IUBMB Life. 2019;71(7):1041-7.

42. Prakoso YA, Rini CS, Rahayu A, Sigit M, Widhowati D. Celery (Apium graveolens) seed extract: With preliminary in vivo assay. J Med Chem. 2020;9(14):2783-91.

43. Cho BO, Choi J, Kang HU, Chen DN, Shin JY, Kim JS, et al. Anti-obesity effects of a mixed extract containing Parlycydon grandiflorum, Apium graveolens and green tea in high-fat-diet-induced obese mice. Exp Ther Med. 2020;19(4):2783-91.

44. Momin RA, Nair MG. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from Apium graveolens Linn. seeds. Phytomedicine. 2002;9(4):312-8.

45. Kooti W, Daraei N. A review of the antioxidant activity of celery (Apium graveolens L). J Evid Based Complementary Alternate Med. 2017;22(4):1029-34.

46. Han L, Gao X, Xia T, Zhang X, Li X, Gao W. Effect of digestion on the phenolic content and antioxidant activity of celery leaf and the antioxidant mechanism via Nrf2/HO-1 signaling pathways against dexamethasone. J Food Biochem. 2019;43(12):1287(5):1-11.

47. Yao Y, Liu W, Zhou H, Zhang D, Li R, Li C, et al. The relations between minor components and antioxidant capacity of five fruits and vegetables seed oils in China. J Oleo Sci. 2019;68(7):625-35.

48. Sita GJA, Govthrami M, Srikant G, Krishna MM, Sireesha KR, Sajjarao M, et al. Protective role of luteolin against bisphenol a-induced renal toxicity through suppressing oxidative stress, inflammation, and upregulating Nrf2/ARE/HO-1 pathway. J Sci Food Agr. 2019;10(1461):1-12.

49. Emad AM, Ali SF, Abdel-Rahman EA, Meselhy MR, Farag MA, Ali SS, et al. Protective role and anti-inflammatory and antioxidant effects of Apium graveolens L. extracts mitigate against fatal acetaminophen-induced acute liver toxicity. J Food Biochem. 2020;1(e13399):1-17.

50. Han L, Gao X, Xia T, Zhang X, Li X, Gao W. Effect of digestion on the phenolic content and antioxidant activity of celery leaf and the antioxidant mechanism via Nrf2/HO-1 signaling pathways against dexamethasone. J Food Biochem. 2019;43(12):1287(5):1-11.

51. Crespo YA, Sanchez LR, Quintana YG, Cabrera AST, Soe ABD. Protective role of luteolin against bisphenol a-induced renal toxicity through suppressing oxidative stress, inflammation, and upregulating Nrf2/ARE/HO-1 pathway. IUBMB Life. 2019;71(7):1041-7.

52. Prakoso YA, Rini CS, Rahayu A, Sigit M, Widhowati D. Celery (Apium graveolens) seed extract: With preliminary in vivo assay. J Med Chem. 2020;9(14):2783-91.

53. Cho BO, Choi J, Kang HU, Chen DN, Shin JY, Kim JS, et al. Anti-obesity effects of a mixed extract containing Parlycydon grandiflorum, Apium graveolens and green tea in high-fat-diet-induced obese mice. Exp Ther Med. 2020;19(4):2783-91.

54. Momin RA, Nair MG. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from Apium graveolens Linn. seeds. Phytomedicine. 2002;9(4):312-8.
64. Danciu C, Zupko I, Bor A, Schwiebs A, Radeke H, Hancianu M. Botanical therapeutics: phytochemical screening and biological assessment of chamomile, parsley, and celery extracts against A375 human melanoma and dendritic cells. Int J Mol Sci. 2018;19(36):2-10.

65. Stefanson A, Bakovic M. Dietary polyacetylene falcarinol upregulated intestinal heme oxygenase-1 and modified plasma cytokine profile in late phase lipopolysaccharide (LPS)-induced acute inflammation in CB57BL/6 mice. Nutr Res. 2020;80:89-105.

66. Ziani L, Yongmei Z, Nang N, Ning T, Baolin L. Evaluation of the anti-inflammatory activity of luteolin in experimental animal models. Planta Med. 2007;73(2):221-6.

67. Shin JY, Che DN, Cho BO, Kang HJ, Kim JS, Jang SI. Anti-inflammatory effect of hydrolyzed celery leaves extract in murine primary splenocyte. J Food Biochem. 2019;1(ie12970):1-12.

68. Amini F, Jaladat AM, Atarzadeh F, Mosavat SH, Parvizzi MM, Zamani N. A review on the management of asthma in the Avicenna’s Canon of medicine. J Complement Integr Med. 2018;16(4):1-8.

69. Min J, Huo X, Xiang L, Qin Y, Chai K, Wu B, et al. Protective effect of Di-3n-butylphthalate on learning and memory impairment induced by chronic intermittent hypoxia-hypercapnia exposure. Sci Rep. 2014;4:1-9.

70. Farooqui AA, Farooqui T, Madan A, Ong JH, Ong W. Ayurvedic medicine for the treatment of dementia: mechanistic aspects. J Evid Based Complement Alternat Med. 2018;2018:2481076.

71. Uddin MJ, Zidorn C. Traditional herbal medicines against CNS disorders from Bangladesh. Nat Prod Bioprospect. 2020;10(6):377-410.

72. Sharma S, Gupta R, Thakur SC. Attenuation of collagen induced arthritis by Centella asiatica methanol fraction via modulation of cytokines and oxidative stress. Biomed Environ Sci. 2014;27(12):926-38.

73. Choi M, Zheng H, Kim JM, Lee KW, Park YH, Lee DH. Protective effects of Centella asiatica leaf extract on dimethyl nitrosamine-induced liver injury in rats. Mol Med Rep. 2016;14(5):4521-8.

74. Oyenihi AB, Chegou NG, Oguntibeju OQ, Masola B. Centella asiatica enhances hepatic antioxidant status and regulates hepatic inflammatory cytokines in type 2 diabetic rats. Pharm Biol. 2017;55(1):1671-8.

75. Hisami EEA, Rofiee MS, Khalid AM, Jalaluddin AF, Yusof MIM, Idris H, et al. Combined extract of Moringa oleifera and Centella asiatica modulates oxidative stress and senescence in hydrogen peroxide-induced human dermal fibroblasts. Turk J Biol. 2018;42(1):33-44.

76. Intararchukul T, Teerapattarak L, Rodsiri R, Tantisira M, Wohlgemuth G, Fiehn O, et al. Effects of Centella asiatica extract on antistressor and liver metabolism of rotenone-treated rats using GC–MS. Biomed Chromatogr. 2019;33(2):e4395.

77. Rochmah MA, Harini IM, Septyaningtias DE, Sari DCR, Susilowati M. Centella asiatica prevents increase of hippocampal tumor necrosis factor-α independently of its effect on brain-derived neurotrophic factor in rat model of chronic stress. Biomed Res Int. 2019;2019;33(2):e4395.

78. Chiroma SM, Babarudin MTH, Taib CNM, Amorn Z, Jagadeesan S, Adenan M, et al. Protective effects of Centella asiatica on cognitive deficits induced by D-gal/Al2O3 via inhibition of oxidative stress and attenuation of acetylcholinesterase level. Toxics. 2019;7:119:1-19.

79. Matthews DG, Caruso M, Munchison CF, Zhu JY, Wright KM, Harris CJ, et al. Centella asiatica improves memory and promotes antioxidative signaling in 5xFAD mice. Antioxidants. 2019;8(12):630.

80. Park DW, Jeon H, So R, Kang SC. Centella asiatica extract prevents visual impairment by promoting the production of rhodopsin in the retina. Nutr Res Pract. 2020;14(3):203-17.

81. Sulistiyowati E, Jan R, Liou S, Chen Y, Wu B, Hsu J, et al. Vasculoprotective effects of Centella asiatica, Justicia gendarussa and Imperata cylindrica decoction via the NOx-Ros-ROS-NF-kB pathway in spontaneously hypertensive rats. J Trad Complement Med. 2019;10(4):378-88.

82. Sieberi BM, Omwenga GI, Wambua RK, Samoei JC, Ngungi MF. Screening of the dichloromethane: methanolic extract of Centella asiatica for antibacterial activities against Salmonella typhi, Escherichia coli, Shigella sonnei, Bacillus subtilis, and Staphylococcus aureus. Scientific World J. 2020;2020:6378712.

83. Micheli L, Mannelli LDC, Mattoli L, Tamini S, Flaminì E, Garetto S, et al. Intra-articular route for the system of molecules 14G1862 from Centella asiatica: pain relieving and protective effects in a rat model of osteoarthritis. Nutrients. 2020;12:1618:1-21.

84. Firdaus Z, Singh N, Prajapati SK, Krishnamurthy S, Singh TD. Centella asiatica prevents D-galactose-induced cognitive deficits, oxidative stress and neurodegeneration in the adult rat brain. Drug Chem Toxicol. 2022;45(3):1417-26.

85. Gray NE, Magana AA, Lak P, Wright KM, Quinn J, Stevens JF, et al. Centella asiatica – Phytochemistry and mechanisms of neuroprotection and cognitive enhancement. Phytochem Rev. 2018;17(1):161-94.

86. Gunathilake KDPP, Ranaweera KKDS, Rupasinghe HPV. Response surface optimization for recovery of polyphenols and carotenoids from leaves of Centella asiatica using an ethanol-based solvent system. Food Sci Nutr. 2019;7:2:528-36.

87. Wang C, Zhao Y, Yang R, Liu H. Simultaneous analysis of five triterpenes in Centella asiatica by high performance liquid chromatography with cyclodextrins as the mobile phase additives. Sci Rep. 2020;10:18577:1-8.

88. Sun B, Wu L, Wu Y, Zhang C, Qin L, Hayashi M, et al. Therapeutic potential of Centella asiatica and its Triterpenes: a review. Front Pharmacol. 2020;11(568032):1-24.

89. Wu Z, Li W, Zhou J, Liu X, Lun W, Chen B, et al. Oleane- and ursane-type triterpene saponins from Centella asiatica exhibit neuroprotective effects. J Agr Food Chem. 2020;68(26):6977-96.

90. Chong NJ, Aziz Z. A systematic review on the chemical constituents of Centella asiatica. Res J Pharm Biol Chem Sci. 2011;2:445-59.

91. Matthews DG, Caruso M, Magana AA, Wright KM, Maier CS, Stevens JF, et al. Caffeoylquinic acids in Centella asiatica reverse cognitive deficits in male 5xFAD alzheimer’s disease model mice. Nutrients. 2020;12(14881):1-9.

92. Nghiem NX, Tai BH, Quang TH, Kiem PV, Minh CV, Nam NH, et al. A new ursane-type triterpenoid glycoside from Centella asiatica leaves modulates the production of nitric oxide and secretion of TNF-α in activated RAW 264.7 cells. Bioorg Med Chem Let. 2011;21(6):1777-81.

93. Bylka W, Paulina Z, Elżbieta S, Brzezinska M. Centella asiatica in cosmetology. Postepy Dermatologii i Alergologii. 2013;30(3):46-9.

94. Hou Q, Li M, Lu Y, Liu DH, Li CC. Burn wound healing properties of asiaticoside and madecassoside. Exp Ther Med. 2016;12(3):627-84.

95. Shen X, Guo M, Yu H, Liu D, Lu Z, Yu L. Propionibacterium acne related anti-inflammation and skin hydration activities of madecassoside, a pentacyclic triterpene saponin from Centella asiatica. Biosci Biotechnol Biochem. 2018;83(3):561-8.

96. Ahmed AS, Taher M, Mandal UK, Jaffri JM, Susanti J, Mahmood S, et al. Pharmacological properties of Centella asiatica hydrogel in accelerating wound healing in rabbits. BMC Complement Altern Med. 2019;19(13):1-7.

97. Wannasart S, Puttarak P, Kaewkrong K, Wivattanapatee R. Strategies for improving healing of the gastric epithelium using oral solid dispersions loaded with pentacyclic triterpene-rich Centella Extract. AAPS PharmSciTech. 2019;20(77):1-13.
98. Shedoeva A, Leavesley D, Upton Z, Fan C. Wound healing and the use of medicinal plants. J Evid Based Complement Altern Med. 2019;2019(2684108):1-30.

99. Razali NNM, Ng CT, Fong LY. Cardiovascular protective effects of *Centella asiatica* and its triterpenes: a review. Planta Medica. 2019;85(16):1203-15.

100. Arora R, Kumar R, Agarwa A, Reeta KH, Gupta YK. Comparison of three different extracts of *Centella asiatica* for anti-aminease, antioxidant and anticholinergic activities: in vitro and in vivo study. Biomed Pharmacother. 2018;105:1344-52.

101. Teerapattarakarn N, Benya-aphikul H, Tansawat R, Wanakachornkrai O, Tantsira MH, Rodsiri R. Neuroprotective effect of a standardized extract of *Centella asiatica* ECA233 in rotenone-induced Parkinsonism rats. Phytomedicine. 2018;44:65-73.

102. Yadav MK, Singh SK, Singh M, Mishra SS, Singh AK, Tripathi JS, et al. Neuroprotective activity of *Evolvulus alsinoides* & *Centella asiatica* Ethanol Extracts in scopolamine-induced amnesia in swiss albino mice. Open Access Maced J Med Sci. 2019;7(7):1099-68.

103. Boonljun Y, Songyut P, Tantsira MH, Tapechum S, Tilaksukulchai K, Pakapot N. Inverted U-shaped response of a standardized extract of *Centella asiatica* (ECA 233) on memory enhancement. Sci Rep. 2019;9(8404):1-11.

104. Hanapi NA, Anshad ASM, Abdullah JM, Muhammed TST, Yusof SR. Blood-brain barrier permeability of asiaticoside, madecassoside and asiatic acid in porcine brain endothelial cell model. J Pharm Sci. 2021;110(2):698-706.

105. Songyut P, Charivayavilaskul P, Tantsira MH, Khemawoot P. Safety and pharmacokinetics of standardized extract of *Centella asiatica* (ECA 233) capsules in healthy thai volunteers: a phase 1 clinical study. Planta Medica. 2019.85(6):483-90.

106. Zhang LN, Zheng J, Zhang L, Gong X, Huang H, Wang C, et al. Protective effects of asiaticoside on septic lung injury in mice. Exp Toxicol Pathol. 2011;63(6):519-25.

107. Wan YG, Gong X, Jiang R, Zhang Z, Zhang L. Antipyretic and anti-inflammatory effects of asiaticoside in lipopolysaccharide-treated rat through up-regulation of heme oxygenase-1. Phytotherapy Research. 2012;27(8):1136-42.

108. Qiu J, Yu L, Zhang X, Wu Q, Wang D, Wang X. Asiaticoside attenuates lipopolysaccharide-induced acute lung injury via down-regulation of NF-κB signaling pathway. Int Immunopharmacol. 2015;26(1):181-7.

109. He L, Hong G, Zhou L, Zhang J, Fang J, He W, et al. Asiaticoside, a component of *Centella asiatica* attenuates RANKL-induced osteoclastogenesis via NFATc1 and NF-κB signaling pathways. J Cell Physiol. 2019;234(4):4267-76.

110. Zhou Y, Wang S, Zhao J, Fang P. Asiaticoside attenuates neonatal hypoxic–ischemic brain damage through inhibiting TLR4/NF-κB/STAT3 pathway. Ann Transl Med. 2020;8(10):641-51.

111. Zhang T, Dai J, Ye W, Cai L, Wei J, Chen M, et al. Asiaticoside attenuates bleomycin-induced pulmonary fibrosis in A2aR−/− mice by promoting the BMP7/Smad1/5 signaling pathway. Biochem Biophys Res Commun. 2020;527(3):662-7.

112. Subaraja M, Vanisree AJ. The novel phytoconponent asiaticoside-D isolated from *Centella asiatica* exhibits monoamine oxidase-B inhibiting potential in the rotenone degenerated cerebral ganglia of *Lumbricus terrestris*. Phytomedicine. 2019;58(12983):1-13.

113. Zhang L, Li H, Gong X, Luo F, Wang B, Hu N, et al. Protective effects of Asiaticoside on acute liver injury induced by lipopolysaccharide/D-galactosamine in mice. Phytomedicine. 2010;17(1):811-9.

114. Huang SS, Chiu CS, Chen HJ, Hou WJ, Sheu MJ, Lin YC, et al. Antinociceptive activities and the mechanisms of anti-inflammation of asiatic acid in mice. J Evid Based Complement Altern Med. 2011;2011(1895657):1-10.

115. Chen S, Yin ZJ, Jiang C, Ma QZ, Fu Q, Qu R, et al. Asiaticoside attenuates memory impairment induced by transient cerebral ischemia–reperfusion in mice through anti-inflammatory mechanism. Pharmacol Biochem Behav. 2014;122:7-15.

116. Pakdeecheote P, Bunbupha S, Kungkongsirirat U, Prachaney R, Khraisapant W, Kungkongsirirat V. Asiatic acid alleviates hemodynamic and metabolic alterations via restoring eNOS/NOS expression, oxidative stress, and inflammation in diet-induced metabolic syndrome rats. Nutrients. 2014;6(1):395-70.

117. Lee JW, Park HA, Kwon OK, Jang YG, Kim JY, Choi BK, et al. Asiatic acid inhibits pulmonary inflammation induced by cigarette smoke. Int Immunopharmacol. 2016;39:208-17.

118. Li Z, Xiao Y, Yang M. Asiatic acid inhibits lipopolysaccharide-induced acute lung injury in mice. Inflammation. 2016;39(5):1624-8.

119. Dong SH, Liu YW, Wei F, Tan WZ, Han ZH. Asiatic acid ameliorates pulmonary fibrosis induced by bleomycin (BLM) via suppressing pro-fibrotic and inflammatory signaling pathways. Biomed Pharmacother. 2017;89:1297-309.

120. Meeran MFN, Goyal SN, Suchal K, Sharma C, Patil CR, Ojha SK. Pharmacological properties, molecular mechanisms, and pharmaceutical development of asiatic acid: a pentacyclic terpenoid of therapeutic promise. Front Pharmacol. 2018;9(982):1-35.

121. Weibat JU, Chaisawpong P, Pannangrong W, Wigmore P. Neuroprotective properties of asiatic acid against 5-fluorouracil chemotherapy in the hippocampus in an adult rat model. Nutrients. 2018;10(8):1-11.

122. Kong D, Fu P, Zhang Q, Ma X, Jiang P. Protective effects of Asiatic acid against pelvic inflammatory disease in rats. Exp Ther Med. 2019;17(6):4867-92.

123. Rather MA, Thenmozhi AJ, Manivasagam T, Saravanababu C, Guillemin GJ, Essa MM. Asiatic acid attenuated aluminum chloride-induced tau pathology, oxidative stress and apoptosis via AKT/GSK-3β signaling pathway in wistar rats. Neurotoxicity Res. 2019;35(4):955-68.

124. Zhu Q, Zeng J, Li J, Chen X, Miao J, Jin Q, et al. Effects of compound centella on oxidative stress and Keap1-Nrf2 ARE pathway expression in diabetic kidney disease rats. J Evid Based Complement Altern Med. 2020;2020:9817392.

125. Ma Y, Wen J, Wang J, Wang C, Zhang Y, Zhao L, et al. Asiaticoside antagonizes proliferation and chemotherapeutic drug resistance in hepatocellular carcinoma (hcc) cells. Med Sci Monit. 2020;26:e924435.

126. Wang L, Guo T, Guo Y, Xu Y. Asiaticoside produces an antidepressant-like effect in a chronic unpredictable mild stress model of depression in mice, involving reversion of inflammation and the PAKαpCREB/BDNF signaling pathway. Mol Med Rep. 2020;22(3):2364-72.

127. Uddandaro VVS, Rameshreddy P, Brahmanaidu P, Ponnusamy P, Balakrishnan S, Ramavat RN, et al. Antiobesity efficacy of asiatic acid: down-regulation of adipogenic and inflammatory processes in high fat diet induced obese rats. Arch Physiol Biochem. 2020;126(5):453-62.

128. Liu M, Dai Y, Yao X, Li Y, Luo Y, Xia Y, et al. Anti-rheumatoid arthritic effect of madecassoside on type II collagen-induced arthritis in mice. Int Immunopharmacol. 2008;8(11):1561-6.

129. Li H, Gong X, Zhang L, Zhang Z, Luo F, Zhou Q, et al. Madecassoside attenuates inflammatory response on collagen-induced arthritis in DBA/1 mice. Phytother. 2017;115:1-11.

130. Yang CLH, Or TCT, Ho MHK, Lau ASY. Scientific basis of botanical medicine as alternative remedies for rheumatoid arthritis. Clin Rev Allergy Immunol. 2013;44(3):284-300.
131. Moqbel SSA, He Y, Xu L, Ma C, Ran J, Xu K, et al. Rat chondrocyte inflammation and osteoarthritis are ameliorated by madecassoside. Oxid Med Cell Longev. 2020;2020:7540197.

132. Luo Y, Yang YP, Liu J, Li WH, Yang J, Sui X, et al. Neuroprotective effects of madecassoside against focal cerebral ischemia reperfusion injury in rats. Brain Res. 2014;1565:37-47.

133. Sasmita AO, Ling APK, Voon KGL, Koh RY, Wong YP. Madecassoside activates anti-neuroinflammatory mechanisms by inhibiting lipopolysaccharide-induced microglial inflammation. Int J Mol Med. 2018;41(5):3033-40.

134. Peng LY, Shi HT, Yuan M, Li JH, Song K, Huang JN, et al. Madecassoside protects against LPS-induced acute lung injury via inhibiting TRIF/NF-κB activation and blood-air barrier permeability. Front Pharmacol. 2020;11(807):1-8.

135. Won JH, Shin JS, Park HJ, Jung HJ, Koh DJ, Jo BG, et al. Anti-inflammatory effects of madecassoside acid via the suppression of NF-κB pathway in LPS-Induced RAW 264.7 macrophage cells. Planta Medica. 2010;76:251-7.

136. Saha ST, Singha T, Maity TK. Evaluation of analgesic and anti-inflammatory activity of Cosmus caudatus leaves using liquid chromatography coupled with mass spectrometry. J Chromatogr B Analyt Technol Biomed Sci. 2010;878:199-204.

137. Hafiz ZZ, Amin M, James RMJ, Teh LK, Salleh MZ, Adenan MI. The Effects of Centella asiatica (Ulam Raja): a scoping review. Complement Altern Med. 2019;19(245):1-15.

138. Sukketsiri W, Tanasawet S, Moolsap F, Tantisira MH, Hutamekalin R. Evaluation of antithrombotic activity of Centella asiatica. Am J Chin Med. 2010;38(5):1045-64.

139. Kusumastuti SA, Nugrahaningsih DAA, Wahyuningsih MSH. Madecassic acid activates anti-neuroinflammatory mechanisms by inhibiting lipopolysaccharide-induced microglial activation. Int J Mol Med. 2017;18(3):1-6.

140. Han AR, Lee S, Han S, Lee YJ, Kim JB, Seo EK, et al. Inhibition of inflammatory responses by Centella asiatica in cytokine-induced 3T3-L1 adipocytes and RAW 264.7 macrophages. Drug Discov Ther. 2019;13(5):267-1.

141. Hafiz ZZ, Amin M, James RMJ, Teh LK, Salleh MZ, Adenan MI. Inhibitory effects of raw-extract Centella asiatica (RECA) on acetylcholinesterase, inflammations, and oxidative stress activities via in vitro and in vivo. Molecules. 2020;25(892):1-20.

142. Giribabu N, Karim K, Ilahi EK, Nelli SR, Salleh N. Oral administration of Centella asiatica (L.) Urb leave aqueous extract ameliorates cerebral oxidative stress, inflammation, and apoptosis in male rats with type-2 diabetes. Inflammopharmacol. 2020;28(6):1599-622.

143. Cho YC, Vuong HL, Ha J, Lee S, Park J, Wibow AE, et al. Inhibition of inflammatory responses by Centella asiatica via suppression of IRAK1-TAK1 in mouse macrophages. Am J Chin Med. 2020;48(5):1103-20.

144. Han AR, Lee S, Han S, Lee YJ, Kim JB, Seo EK, et al. Triterpenoids from the leaves of Centella asiatica inhibit ionizing radiation-induced migration and invasion of human lung cancer cells. J Evid Based Complement Altern Med. 2020;2020:3685460.

145. Shui G, Leong LP, Wong SP. Rapid screening and characterisation of antioxidants of Cosmus caudatus using liquid chromatography coupled with mass spectrometry. J Chromatogr B Analyt Technol Biomed Sci. 2005;827(1):127-38.

146. Cheng SH, Barakatun-Nisak MY, Anthony J, Ismail A. Potential medicinal benefits of Cosmus caudatus (Ulam Raja): a scoping review. J Res Med Sci. 2015;20(10):1-10.

147. Javadi N, Abas F, Mediani A, Hamid AA, Khatib A, Simoh S, et al. Effect of storage time on metabolite profile and alpha-glucosidase inhibitory activity of Cosmus caudatus leaves e GCMS based metabolomics approach. J Food Drug Anal. 2015;23(3):433-41.

148. Wan-Nadjiah WA, Akhtar MT, Shaari K, Khatib A, Hamid AA, Hamid M. Variation in the metabolites and alpha-glucosidase inhibitory activity of Cosmus caudatus at different growth stages. BMC Complement Altern Med. 2019;19(1):1-15.

149. Cheng S, Ismail A, Anthony J, Ng OC, Hamid AA, Barakatun-Nisak MY. Eight weeks of Cosmus caudatus (Ulam Raja) supplementation improves glycemic status in patients with type 2 diabetes: a randomized controlled trial. J Evid Based Complement Alter Med. 2015;20(10):406615:1-7.

150. Cheng SH, Ismail A, Anthony J, Ng OC, Hamid AA, Yusof BM. Effect of Cosmus caudatus (Ulam raja) supplementation in patients with type 2 diabetes: study protocol for a randomized controlled trial. BMC Complement Alter Med. 2016;16(84):1-8.

151. Mohammed N, Khee SGS, Shuid AN, Muhammad N, Suhaimi F, Othman F, et al. The effects of Cosmus caudatus on structural bone histomorphometry in ovariectomized rats. J Evid Based Complement Altern Med. 2012;2012(817814):1-6.

152. Mohammed N, Sah hugi Z, Ramli ESM, Muhammad N. The effects of Cosmus caudatus (ulam raja) on dynamic and cellular bone histomorphometry in ovariectomized rats. BMC Res Notes. 2013;6(329):1-6.

153. Rahman HA, Sahib NG, Saari N, Abas F, Ismail A, Mumtaz MW, et al. Anti-obesity effect of ethanolic extract from Cosmus caudatus kuhn leaf in lean rats fed a high fat diet. BMC Complement Alter Med. 2017;17(122):1-17.

154. Moshawiw S, Cheema MS, Ibraheem ZQ, Talain ND, Hakim MN. Cosmus caudatus extractfractations reduce smooth muscle cells migration and invasion in vitro: A potential benefit of suppressing atherosclerosis. Porto Biomed J. 2017;2(6):293-300.

155. Andarwulan V, Batari R, Sandrasari DA, Bolling B, Wijaya H. Flavonoid content and antioxidant activity of vegetables from Indonesia. Food Chem. 2010;121(4):1231-5.

156. Mediani A, Abas F, Ping TC, Khatib A, Lajis NH. Influence of growth stage and season on the antioxidant constituents of Cosmus caudatus. Plant Foods Hum Nutr. 2012;67(4):344-50.

157. Mediani A, Abas F, Khatib A, Tan CP. Cosmus caudatus as a potential source of polyphenolic compounds: optimisation of oven drying conditions and characterisation of its functional properties. Molecules. 2013;18(9):10452-64.

158. Mediani A, Abas F, Tan CP, Khatib A. Effects of different drying methods and storage time on free radical scavenging activity and total phenolic content of Cosmus caudatus. Antioxidants. 2014;3(2):358-70.

159. Abdullah A, Dhaliwal KK, Roslan NFN, Lee CH, Kalaiselvam M, Radmad HM, et al. The Effects of Cosmus caudatus (Ulam Raja) on detoxifying enzymes in extrahepatic organs in mice. J Appl Pharma Sci. 2015;5(1):82-8.

160. Mahmood ND, Mamat SS, Kamarizan FA, Yahya F, Kamarolzaman MFF, Nasir N, et al. Amelioration of paracetamol-induced hepatotoxicity in rat by the administration of methanol extract of Muntingia calabura. Molecules. 2014;19(4):10452-64.

161. Mahmood ND, Nasir NLM, Rofiee MS, Teh LK, Chen IS. The Effects of Muntingia calabura on the levels of immunohistochemical markers in the liver of rats fed with methanol extract of Muntingia calabura. Food Sci. 2015;5(1):82-8.

162. Mahmood ND, Nasir NLM, Rofiee MS, Teh LK, Chen IS. The Effects of Muntingia calabura on the levels of immunohistochemical markers in the liver of rats fed with methanol extract of Muntingia calabura. Molecules. 2014;19(4):10452-64.

163. Cheng S, Ismail A, Anthony J, Ng OC, Hamid AA, Barakatun-Nisak MY. Eight weeks of Cosmus caudatus (Ulam Raja) supplementation improves glycemic status in patients with type 2 diabetes: a randomized controlled trial. J Evid Based Complement Alter Med. 2015;20(10):406615:1-7.

164. Cheng SH, Ismail A, Anthony J, Ng OC, Hamid AA, Yusof BM. Effect of Cosmus caudatus (Ulam raja) supplementation in patients with type 2 diabetes: study protocol for a randomized controlled trial. BMC Complement Alter Med. 2016;16(84):1-8.

165. Mohammed N, Khee SGS, Shuid AN, Muhammad N, Suhaimi F, Othman F, et al. The effects of Cosmus caudatus on structural bone histomorphometry in ovariectomized rats. J Evid Based Complement Altern Med. 2012;2012(817814):1-6.

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Liao HR, Chen JJ, Chen YH, Lin SZ, Lin S, Tseng CP. 5-hydroxy-7-methoxyflavone inhibits N-formyl-L-methionyl-L-leucyl-L-phenylalanine-induced superoxide anion production by specific modulate membrane localization of TGF-β1 with a PISK independent mechanism in human neutrophils. Biochem Pharmacol. 2012;84(2):182-91.

Kuo WL, Liao HR, Chen JJ. Biflavans, flavonoids, and a dihydrochalcone from the stem wood of Muntingia calabura and their inhibitory activities on neutrophil pro-inflammatory responses. Molecules. 2014;19(12):20521-35.

Zolkeflee NKZ, Ismail NA, Maulidiani M, Hamid NAA, Ramli NS, Azlan A. Metabolite variations and antioxidant activity of Muntingia calabura leaves in response to different drying methods and ethanol ratios elucidated by NMR-based metabolomics. Phytochem Anal. 2021;32(1):69-83.

Sulfian AS, Ramasamy K, Ahmad N, Zakaria ZA, Yusof MIM. Isolation and identification of antibacterial and cytotoxic compounds from the leaves of Muntingia calabura L. J Ethnopharmacol 2013;146(1):198-204.

Yusof MIM, Salleh MZ, Kek TL, Ahmad N, Azmin NFN, Zakaria ZA. Activities of isolated bioactive compounds with antinociceptive Activity from Muntingia calabura L. leaves using the formalin test. J Evid Based Complement Altern Med. 2013;17(5):704-71. 9.

Lin JT, Chang YY, Chen YC, Shen BY, Yang DJ. Molecular mechanisms of ethanolic extract from Muntingia calabura Linn. fruit against lipopolysaccharide-induced pro-inflammatory mediators in macrophages. Food Funct. 2017;8(3):1245-53.

Lin JT, Chen YC, Chang YZ, Chen TY, Yang DJ. Effective compounds in the fruit of Muntingia Calabura Linn. cultivated in Taiwan evaluated with scavenging free radicals and suppressing LDL 3 oxidation. Food Funct. 2017;8(4):1504-11.

Pereira GA, Arruda HS, Morais DR, Eberlin MN, Pastore GM. Carbohydrates, volatile and phenolic compounds composition, and antioxidant activity of calabura (Muntingia calabura L.) fruit. Food Res Int. 2018;108:264-73.

Kaneda N, Pezzuto JM, Soejarto DD, Kinghorn AD, Farnsworth NR, Santsuk T, et al. Plant anticancer agents, XLVIII. New cytotoxic flavonoids from Muntingia calabura roots. J Nat Prod. 1991;54(1):196-206.

Zakaria ZA, Mohamed AM, Jamil NSM, Rofiee MS,Hussain MK, Sulaiman MR, et al In vitro antiproliferative and antioxidant activities of the extracts of Muntingia calabura leaves. Am J Chin Med. 2011;39(1):183-200.

Nasir NLM, Kamsani NE, Mohtarrudin N, Othman F, Tohid SFM, Zakaria ZA. Anticarcinogenic activity of Muntingia calabura leaves methanol extract against the azoxymethane-induced colon cancer in rats involved modulation of the colonic antioxidant system partly by flavonoids. Pharma Biol. 2017;55(1):2102-9.

Jisha N, Vysakh A, Vijeesh V, Latha MS. Ethyl acetate fraction of Muntingia calabura L. exerts anti-colorectal cancer potential via regulating apoptotic and inflammatory pathways. J Ethnopharmacol. 2020;261(113064):1-12.

Jisha N, Vysakh A, Vijeesh V, Anand PS, Latha MS. Methanolic Extract of Muntingia calabura L. mitigates 1,2-dimethyldihydrazine induced colon carcinogenesis in wistar rats. Nutr Cancer. 2021;73(11-12):2263-75.

Shih CD, Chen JJ, Lee HH. Activation of nitric oxide signaling pathway mediates hypotensive effect of Muntingia calabura L. (Tiliaceae) leaf extract. Am J Chin Med. 2006;34(5):857-72.

Shih CD. Activation of nitric oxide/cGMP/PKG signaling cascade mediates antihypertensive effects of Muntingia calabura in anesthetized spontaneously hypertensive rats. Am J Chin Med. 2009;37(6):1045-58.

Zakaria ZA, Sulaiman MR, Jais AMM, Somchit MN, Jayaraman KV, Balakrishnan G, et al. The antinociceptive activity of Muntingia calabura aqueous extract and the involvement of -arginine/nitric oxide/cyclic guanosine monophosphate pathway in its observed activity in mice. Fundam Clin Pharmacol. 2006;20(4):365-72.

Zakaria ZA, Mustapha S, Sulaiman MR, Jais AMM, somchit MM, Abdullah FC. The Antinociceptive action of aqueous extract from Muntingia calabura leaves: The role of opioid receptors. Med Prin Pract. 2007;16(2):130-6.

Sani MIM, Zakaria ZA, Balan T, Teh LK, Salleh MZ. Antinociceptive activity of methanol extract of Muntingia calabura leaves and the mechanisms of action involved. J Evid Based Complement Altern Med. 2012;2012(890361):1-10.

Zakaria ZA, Sani MIM, Cheema MS, Kader AA, Kek TL, Salleh MZ. Antinociceptive activity of methanolic extract of Muntingia calabura leaves: further elucidation of the possible mechanisms. BMC Complement Altern Med Ther. 2014;14(63):1-12.

Nivethetha M, Jayasri J, Brindha P. Effects of Muntingia calabura L. on isoproterenol-induced myocardial infarction. Singapore Med J. 2009;50(3):300-2.

Balan T, Sani MIM, Ahmad SHM, Suppaiyah V, Mohtarrudin N, Jamaludin F, et al. Antioxidant and anti-inflammatory activities contribute to the prophylactic effect of semi-purified fractions obtained from the crude methanol extract of Muntingia calabura leaves against gastric ulceration in rats. J Ethnopharmacol. 2015;164:1-15.

Zakaria ZA, Mahmood ND, Mamat SS, Nasir N, Omar NH. Endogenous antioxidant and LOX-mediated systems contribute to the heptaprotective activity of aqueous partition of methanol extract of Muntingia calabura L. leaves against paracetamol intoxication. Front Pharmacol. 2018;9(802):1-14.

Jisha N, Vysakh A, Vijeesh V, Latha MS. Anti-inflammatory efficacy of methanolic extract of Muntingia calabura L. leaves in Carrageenan induced paw edema model. Pathophysiol. 2019;26(3):323-30.

Zakaria ZA, Mahmood ND, Omar NH, Taher M, Basir R. Methanol extract of Muntingia calabura leaves attenuates CCl4-induced liver injury: possible synergistic action of flavonoids and volatile bioactive compounds on endogenous defense system. Pharma Biol. 2019;57(1):335-44.

Balan T, Sani MIM, Suppaiyah V, Mohtarrudin N, Suhaili Z, Ahmad Z, et al. Antilulcer activity of Muntingia calabura leaves involves the modulation of endogenous nitric oxide and nonprotein sulphhydryl compounds. Pharma Biol. 2014;52(4):410-8.

Zakaria ZA, Balan T, Suppaiyah V, Ahmad S, Jamaludin F. Mechanism(s) of action involved in the gastroprotective activity of Muntingia calabura. J Ethnopharmacol. 2014;151(2014):1184-93.

Zakaria ZA, Zainol ASN, Salmah A, Salleh NI, Hizami A, Mahmood ND, et al. Gastroprotective activity of chloroforom extract of Muntingia calabura and Melastoma malabathricum leaves. Pharma Biol. 2015;54(5):812-26.

Zakaria ZA, Balan T, Azemi AK, Omar MH, Mohtarrudin N, Ahmad Z, et al. Mechanism(s) of action underlying the gastroprotective effect of ethyl acetate fraction obtained from the crude methanolic leaves extract of Muntingia calabura. BMC Complement Altern Med Ther. 2016;16(78):1-17.

Halim SZ, Zakaria ZA, Omar NH, Mohtarrudin N, Wahab IRA, Abdullah MNH. Synergistic gastroprotective activity of methanolic extract of a mixture of Melastoma malabathricum and Muntingia calabura leaves in rats. BMC Complement Altern Med Ther. 2017;17(488):1-16.

Zakaria ZA, Mahmood ND, Omar NH, Taher M, Basir R. Methanol extract of Muntingia calabura leaves attenuates CCl4-induced liver injury: possible synergistic action of flavonoids and volatile bioactive compounds on endogenous defense system. Pharma Biol. 2019;57(1):335-44.

Rofiee MS, Yusof MIM, Hisam EEA, Bannur Z, Zakaria ZA, Somchit MN, et al. Isolating the metabolic pathways involved in the heptaprotective effect of Muntingia calabura against CCl4-induced liver injury using LCMS Q-TOF. J Ethnopharmacol. 2015;166:109-18.

Vadiel K, Rani NM, Pradeepkhrishna CH, Manoharbabu S. Ex- vivo antispasmodic activity of aqueous leaf extract of muntingia calabura linn on isolated frog rectum. Int J Pharma Res Nov Sci. 2017;3(1):354-7.

Safira S, Sabri M. Effect of Muntingia calabura L. stem bark extracts on uric acid concentration and renal histopathology in diabetic rats. Medicina. 2019;55(699):1-8.
1. *Adenostemma lavenia* (Legetan warak)

A. 11-oxygenated kauren-19-oic acid
B. ent-11α-hydroxy-15a-acetoxykauren-16-en-19-oic acid
C. ent-11α-hydroxy-15-oxokauren-16-en-19-oic acid
D. (16R)-ent-11α-hydroxy-15-oxokauren-19-oic acid

2. *Apium graveolens* (Celery)

E. apigenin
F. apin
G. caffeic acid
H. chlorogenic acid
I. luteolin
J. 3-n-butylphthalide (NBP)
K. secoisolide

3. *Centella asiatica* (Pegagan)

L. asiaticoside
M. asiatic acid
N. madecassosid
O. madecassic acid

4. *Cosmos caudatus* (Kenikir)

- Flavonoids, α-tocopherol, cyclohexen-1-carboxylic acid, benzoic acid, myo-inositol, stigmasterol, lycopene, chlorogenic acid

5. *Muntingia calabura* (Kersen)

- Flavones, flavonols, isoflavones, flavanones, chalcones, terpenes, phenolic acids, anthocyanidins, kavalactone, anthraquinone

Graphical Abstract: Five Indonesian medicinal plants potential as Chronic Obstructive Pulmonary Disease (COPD) herbal medicine.
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