

ANTI-INFLAMMATORY ACTIVITY, ANTI-OXIDANT AND IMMUNOSTIMULATION EFFECT OF MUNTINGIA CALABURA L. FOR PREVENTION AND COMPLEMENTARY THERAPY AGAINST COVID-19: REVIEW AND PRESPECTIVE

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Abstract

Purpose: *Muntingia calabura L.* a Neotropic plant, is one of the many therapeutic plants found in Indonesia. This herbal medicine contains secondary metabolites such as flavonoids, terpenoids, alkaloids, tanins, saponins, polyphenols, and other compounds found in the plant's flower, fruit, leaves, stems, and bark. The purpose of this study is to review in order to know the extent of research on the pharmacological effects of the *Muntingia calabura L.* plant so that it can be used as an herbal medicine to prevent and complementary therapy against Covid-19.

Methodology: The authors process review and perspective, by searched and collected data related Covid-19, *Muntingia calabura L.*, Anti-Inflammatoty, Anti-oxidant and Immunnostimulation. The main search tools is Google Scholar, PubMed, Research Gate, Library Genesis and Science Direct.

Findings: Various studies mantion from molecular research, phytochemical tests, preclinical trials and scientific literature and other review literature stated that the chemical components of *Muntingia calabura L* have a potential as anti-inflammatory, anti-oxidant, and immunostimulant agents to prevent and treat pneumonia by the SARS-CoV-2 Coronavirus (Covid-19). *Muntingia calabura L.* could be prevent and compelementary therapy against Covid-19.

Limitation: The limitation of this study is that It is hoped that in the future *Muntingia calabura L.* research for preclinical trials and clinical trials will be carried out more so that this plant can be used as a category of traditional medicine

Contribution: This review research examines local plants that can be useful as traditional medicine with early stage studies through pharmacognostic, botanical and biochemical studies.

Keywords: Covid-19, *Muntingia calabura L.*, Anti-Inflammatory, Anti-Oxidant, Immunostimulation

1. Introduction

The current pandemic condition is due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that started when a cluster of cases of pneumonia has been reported for the first time in Wuhan Hubei China at 31 December 2019 and still spread throughtout the world at this time (Chen, 2005).

The common signs can be felt by patients who have exposed to coronavirus from mild to severe signs. The mild symptoms are fatigue, muscle pain, sneezing, sore throat, dry cough, high

fever, respiratory problems, etc. with some severe cases having pneumonia, serious respiratory syndrome, kidney failure even death (Huang et al., 2020).

Natural products and herbal medicines as prophylactic will be a vigorous approach to stop or at least slow down SARS-CoV-2 transmission. Tannic acid is one of compound of natural products that inhibited virus SARS-CoV with drug targets and the mechanism of action 3CLPro Inhibition of 3CLPro, IC₅₀: 3 μ M (Chen et al. 2005).

Based on recent in silico results, an array of natural products has been found highly potent in blocking enzyme function and membrane receptors of human coronavirus. Moderate dosing of such bioactive compounds may prevent or at least slow down SARS-CoV-2 infection process. In addition, the progression of COVID-19 is featured with uncontrolled inflammation, like cytokine release syndrome, so anti-inflammatory herbs will be a potential tool to suppress such fatal symptom. The stability of natural products and herbal medicines in human gastrointestinal tract is barely an issue. The low pH in gastric environment, digestive enzymes, and gut microbiome have less impact on the bioavailability of natural products and herbs compared to antibody and other prophylactics (Junqing Huang, 2020). One of the plants that has recently gained a medicinal plant status is *Muntingia calabura L.*

Cherry contains flavonoids, tannins, triterpenes, saponins, polyphenols showing presence of antioxidative activity. Beside that cherry leaves have indicated phytochemical compounds antioxidative and antimicrobial activity. Various types of flavonoids: flavones, flavonones, flavans, and biflavanes (Dyah Titin Laswati, 2018).

Part of *Muntingia calabura L.*, from the flower, fruit, leaves, stems and bark has compound chemical substances that can be useful for prevention and complementary therapy against Covid-19. The purpose of this study is to review in order to know the extent of research on the pharmacological effects of the *Muntingia calabura L* plant so that it can be used as an herbal medicine to prevent and complementary therapy against Covid-19

2. Literature review and hypotheses development

Reported about 2.2 million people have been infected in 210 countries and territories than with more than 0.15 million deaths globally. Despite great efforts, there is no treatment of this disease. However, prevention and management are the best options (Imran Ali, 2020).

The Food and Drugs Administration (FDA) in 2020 issued an Emergency Use authorization (EUA) to help strengthen the nation's public health protection against Coronavirus disease, there is use of vaccines, drug, biological therapeutic products even the medical device for Covid-19. FDA approved natural product and their derivative more than one-third of all (Patridge, 2016).

Muntingia calabura L is kind of natural product as Neotropic plants that can live well in tropical climate such as Indonesia. This plant often used as a shade tree on the side of the road due to the arrangement of the leaves shady. The use of kersen as a medicinal and food ingredient is still minimal (Shady & suryady, 2018).

Muntingia calabura L. which is known as cherry plant or series. In some Kersen country is known by several names: datiles, aratiles, manzanitas (Philippines), khoom somz, takhob (Laos), krakhop barang (Cambodia), kerup siam (Malaysia), capulin blanco, cacaniqua, niqua, iguito (Spanish), jamaican cherry, panama berry, singapore cherry (English) and japanese kers (Netherlands) (Kosasih et al, 2013).

Several studies previously showed that the *Muntingia calabura L* contains several bioactive compounds such as saponins, flavonoids, and tannins (Surjowardojo, Sarwiyono, Thohari, & Ridhowi, 2014). specific for the fruit compounds are squalene, triglycerides, a mixture of linoleic acid, palmitic acid, and α linoleic acid and a mixture of β sitosterol and stigmasterol (Ragasa, Tan, Chiong, & Shen, 2015).

The substance of *Muntingia calabura L* which can be as an antimicrobial, antifungal, antibacterial and can reduce free radicals (antioxidant) (Surjowardojo, Sarwiyono, Thohari, & Ridhowi, 2014).

Preclinical test result from Sarimanah, J. et.al (2015) show that extract fruit and leave of that plant has anti-inflammatory effect. The β sitosterol from fruit and bark of *Muntingia calabura L* have activities for immune boosting and reduce free radicals (antioxidant), and this study has confirmed by research molecular docking of that substance (Khan & Siddiqui, 2020).

3. Research methodology

The authors process review and perspective, by searched and collected data related Covid-19-19, *Muntingia Calabura L*, Anti-Inflammatoty, Anti-oxidant and Immunnostimulation. The main search tools is Google Scholar, PubMed, Research Gate, Library Genesis and Science Direct.

The search terms used included: History begin coronavirus spread; signs; symptoms; approved FDA issued Emergenzy Use authorization (EUA) for infected coronavirus; synthetic drugs; FDA approved natural product; *Muntingia calabura L* as neutropic plant; pharmacology effect of this plant; activity and effect Anti-Inflammatoty, Anti-oxidant, Immunnostimulation of *Muntingia calabura L* herb against coronavirus labeled as SARS-CoV-2 (Covid-19-19).

The chosen articles were reviewed and interpreted by the authors. The perspective is an opinion of the authors regarding the pharmacology effect that is effect Anti- Inflammatoty, Anti-oxidant, Immunnostimulation of *Muntingia calabura L* to prevention and complementary therapy against COVID-19.

4. Results and discussions

Muntingia calabura L. (Elaeocarpaceae) has a long history of medicinal usage in many countries. Because it has shaded leaves and is easy to cultivate in Indonesia, this plant is frequently utilized as a shade plant (Zahara & Suryady, 2018). The plant components had cytotoxic, antiproliferative, insecticidal, hypotensive, antinociceptive, cardioprotective, antipyretic, antiplatelet aggregation, anti-oxidant, anti-inflammatory, anti-diabetic, antiulcer, and antibacterial properties (Salleh et al., 2014). This review is particularly focused on the three functions of this plant that prevent and supplement COVID-19 therapy.

The Taxonmy of *Muntingia calabura L*: (Sari et al, 2012)

Kingdom : Plantae
Division : Spermatophyta
Sub Division : Angiospermae
Class : Dicotyledoneae
Sub Class : Dialypetalae
Family : Malvales/Columniferae

Ordo : Elaeocarpaceae
Genus : Muntingia
Spesies : *Muntingia calabura L.*

a. Anti Inflammatory Activity

The lungs of COVID-19 patients show elevated levels of inflammatory cytokines (IL-1, TNF- α). This correlates with increased activity of HAS2 and the subsequent lung pathology induced by the SARS-CoV-2 infection. Therefore, the above clinical and research findings suggest that COVID-19 pathogenesis involves two phases: Phase 1, suppression of innate immune response, increases in oxidative stress and phase 2 acute inflammation-driven damaging phase (M. Mrityunjaya, 2020)

Quercetin is a well-known antioxidant with anti-inflammatory and antiviral bioactive. It inhibits TNF- α production in LPS induced macrophages (Geraets L, 2007). In the context of SARS virus infection, supercomputer SUMMIT drug-docking screen and gene set enrichment analyses (GSEA) finds that quercetin, VD, and estradiol interferes the functioning of 85, 70 and 61% of the SARS-CoV-2 viral proteins in human cells, respectively. Based on these observations the study also predicts tripartite combination (quercetin/VD/estradiol) compared to bipartite (VD/quercetin) of may affect 73% human genes encoding SARS-CoV-2 targets implicating a robust mitigating agents against the COVID-19 (Glinsky GV, et.al. 2020)

According to preclinical studies, the leaves, unripe, and ripe fruit of *Muntingia calabura L* were effective. They provided an anti-inflammatory effect at 50 mg/kg bw and 100 mg/kg bw doses when compared to Natrium diclophenac, respectively (Sarimanah et al., 2015).

b. Anti-Oxidant Activity

The lifespan of *Drosophila melanogaster* can last longer when consuming ethanol extract of *Muntingia calabura* leaves (EMCL) before starvation. Lifespan extension can be affected by several factors, including the increased expression of endogenous antioxidants. that the expression of *sod2* was increased in response to starvation. On the contrary, reduced expression of *sod1* was

observed in the starvation-treated group. Treatment of flies with EMCL at 1% and 5% increased the mRNA level of *sod1*, but did not affect the mRNA level of *sod2*. Taken together, our results demonstrated the potential effect of *Muntingia calabura* leaves in the modulation of *Drosophila* *sod1* and *sod2* gene expression in *Drosophila* (Shartian Liling, 2021).

Thin Layer Chromatography (TLC) analysis revealed that ethanol extracted from leaves and steamed *Muntingia calabura L.* had shown anti-oxidant activity in the *in vivo* tests. The presence of different secondary metabolites was established by this test, which was followed by the DPPH free radical scavenging assay, which was used to approximate the antioxidant activity of that section of the plant (Buhian et al., 2017). Using the DPPH method, ethanol extract of *Muntingia calabura L* leaves had an even stronger antioxidant than ethanol extracts of *Syzygium cumini*, *Ocimum basilicum*, and *Eleutherine bulbosa* (Haerani et al., 2019)

c. Immunostimulation Effect

Immunosuppressant, such as anti-rheumatoid drugs, could be considered as a potential approach for the treatment of cytokine storm in severe cases of COVID-19 (Figure 1). One possible limitation of immunosuppressants therapy is their inhibitory effects on host anti-viral immune response. So, the appropriate timing of immunosuppressants administration should be carefully considered (Zahra Bahari, 2021)

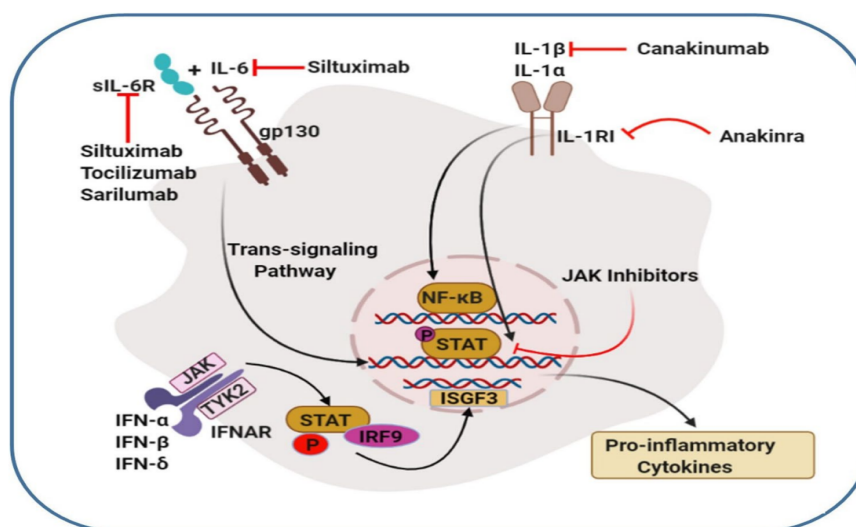


Figure 1. The targets of anti-rheumatoid agents in the host inflammatory pathway in COVID-19 infection.

The IL-1, IL-6, and IFNs bind to their own receptors (IL-1RI, sIL-6R, IFNAR, respectively) and trigger specific signaling cascades to activate the generation of multiple cytokines. IL-1 inhibitors, IL-6 inhibitors, and JAK inhibitors (ruxolitinib, tofacitinib, baricitinib, peficitinib, fedratinib, and upadacitinib) can limit cytokine storm and hyper inflammation by suppressing these signaling cascades. IL interleukin, IFN interferones, IFNAR type I IFNs receptor, ISGF IFN-stimulated gene factor, R receptor, sIL-6R soluble interleukin receptor, JAK Janus kinase, STAT signal transducer and activator of transcription, NF- κ B nuclear factor κ B. Figure created using BioRender software (Zahra Bahari, 2021).

Research from cheng, et al (2020) concluded that dietary β -sitosterol supplementation could regulate serum cholesterol level, promote immune function, and improve intestinal oxidative status and morphology in broilers. Bouic and Lamprecht reported in a review of their immunomodulating that this phytosterol complex seems to target specific T-helper lymphocytes, the Th1 and Th2 cells, helping normalize their functioning and resulting in improved T-lymphocyte and natural killer cell activity. The re-establishment of these immune parameters may be of help in numerous disease processes relating to chronic immune-mediated abnormalities, including chronic viral infections, tuberculosis, rheumatoid arthritis, allergies, cancer, and autoimmune diseases.

Bouic et al. concluded that phytosterols could be used to prevent the subtle immunosuppression associated with excessive physical stress. There are many studies which have reported the immunostimulant activity of the phytosterols. Immunomodulatory therapies have the potential to inhibit cytokines, but the role of elevated cytokines with lung pathology is unclear. The overall lack of evidence and recommendations has forced practitioners to use their own judgment regarding use of immunomodulatory therapy (Daniel B. Chastain, 2020).

d. *Muntingia calabura L* effective in Covid Management

Following WHO and regional health authorities' safety standards is one approach to stay safe from new coronavirus illnesses because prevention is better than cure. Pharmacological treatments for coronavirus disease have been indicated for antiviral action with single or combination usage, anti-malaria, anti-inflammatory and immunomodulatory activity, adjunct treatment, inhibit sintesis RNA virus, and plasma therapy (Riyaz Beg et al., 2020)

Approximately 75% of plant-based therapeutic medications are utilized globally, and it is remarkable to realize that 70% of current therapeutic pharmaceuticals are derived from natural resources. They are either utilized directly after separation and purification in their original form, or a variety of synthetic equivalents have been produced from archetype phytoconstituents acquired from plant sources. (S. Sen et al, 2016).

This emphasized the importance of natural products as a COVID-19 therapy option since they are both safe and effective, and they have several therapeutic features such as powerful antiviral, immunomodulatory, anti-inflammatory, and antioxidant activity (JS, Mani et al. 2020).

Table 1. Preliminary qualitative phytochemical screening on extract of *Muntingia calabura* bark (Chaundari et al., 2020)

No	Phytochemical	Result n-Hexane Extract	Test Name
1	Terpenoids	+++	Salkowski test
2	steroids	+++	Salkowski test , Liebermann–Burchard
3	Flavanoids	+++	Lead acetate test, Sodium hydroxide test, Shinoda test
		++	Ferric chloride test
4	Carbohydrates	++	Molisch’s test, Fehlings test, Benedict test
5	Glycosides	+	Keller–Kiliani test, Legal’s test
6	Alkaloids	-	Mayers test, Wagner test, Hager’s test, Dragendorff ’s test
7	Saponins	-	Foam test, Hemolytic test
8	Tannins	-	Ferric chloride test, Lead acetate test, Potassium dichromate test, Dilute KMno4

Where; +++: Very positive, ++: Strong positive, +: Fair positive, -: Absent

In the current study, preliminary phytochemical screening revealed the presence of terpenoid, steroid, flavonoid, carbohydrate, and glycosides. An isocratic elution technique was used to collect 115 fractions from column chromatography utilizing benzene as a solvent. At 366 nm, HPTLC fingerprinting revealed the presence of β -sitosterol. β -Sitosterol is well known for its numerous biological effects and is separated for phytochemical analysis from an n-hexane extract of the bark of *M. calabura*. The same fraction was FTIR characterized, yielding absorption peaks

that resemble the β -sitosterol structure. The presence of β -sitosterol was detected by β -sitosterol fingerprinting at 366 nm. The same fraction was FTIR characterized, yielding absorption peaks that resemble the β -sitosterol structure (Chaundari et al., 2020).

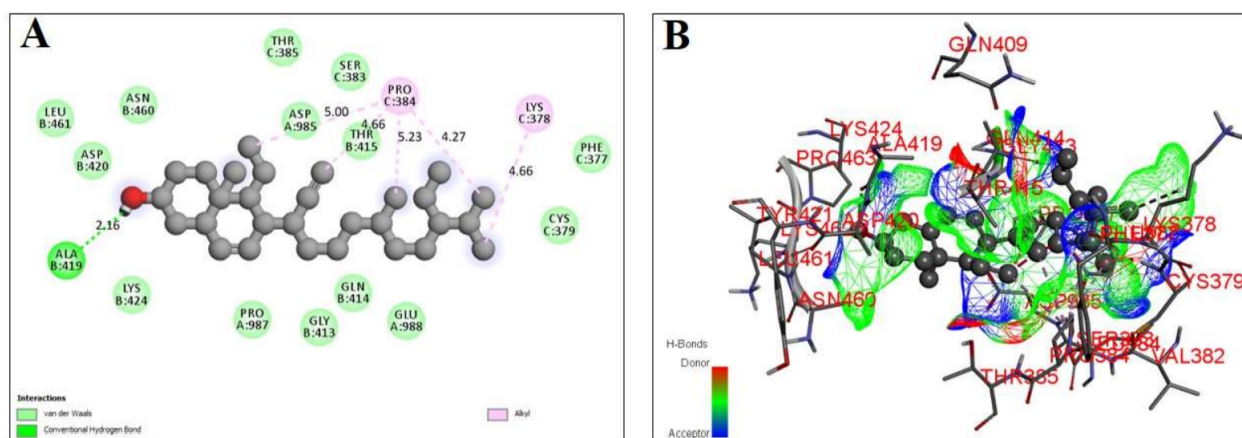


Figure 2. Docking poses of the β -sitosterol (A) 2D-Docking Pose (B) 3D-Docking Pose with Receptor Binding Domain (RBD) of SARS-CoV-2 Spike Glycoprotein (Khan & Siddiqui, 2020)

Table 2. The Interacting Residues, Bond Length, and Binding Affinity of β -sitosterol

Binding Affinity (kcal/mol)	Types of Bond	Active Amino Residues with Bond Length (\AA)
-7.8	Hydrogen Bond	Ala-B:419 (2.16 \AA)
	Alkyl Bond	Pro-C:384 (5.0 \AA ⁰ , 4.66 \AA ⁰ , 5.23 \AA ⁰ , 4.27 \AA ⁰), Lys-C:378 (4.66 \AA ⁰)
	Van Der Waals	Thr-C:385, Ser-C:383, Asp-A:985, Thr-B:415, Phe-C:377, Cys-C:379, Glu-A:988, Gln-B:414, Gly-B:413, Pro-A:987, Lys-B:424, Asp-B:420, Leu-B:461, Asn-B:460

source: (Khan & Siddiqui, 2020)

Receptor Binding Domain (RBD) comprises of amino acid residues from chain A, chain B, and chain C as well, therefore, the most potent inhibitor will be the one which interacts with amino acid residues from all the chains. β -sitosterol has showed a binding affinity of 7.8 kcal/mol with 0 RMSD lower and upper bound. The 2D- and 3D-Docking poses of the β -sitosterol represented in figure 2A & 1B respectively. As β -sitosterol is interacting with amino acids from

every chain (A, B, C), it indicates that it is a potent inhibitor of RBD of SARS-CoV-2 spike glycoprotein. The interacting residues, bond length, and binding affinity are represented in table 2 (Khan & Siddiqui, 2020).

According to the findings of the study, this method can be considered a standard method for isolating β -sitosterol from *M. calabura* bark. Favipiravir has a lower binding affinity, 5.7 kcal/mol, than β -sitosterol, which has a binding affinity of 6.9 kcal/mol. Favipiravir forms four hydrogen bonds, as opposed to β -sitosterol, which forms just one with SARS-CoV-2 Mpro (Chaundari et al., 2020).

Mpro (molecular weight: 34 kDa), also known as the 3C-like protease (3CLpro), is the major CoV protease that regulates virus proliferation and host cell response. The COVID-19 virus genome is 30,000 nucleotides in length, and its replicase gene encodes the overlapping polyproteins pp1a and pp1ab required for viral replication and transcription. As a result, Mpro is an appealing target for developing antiviral therapeutics against coronavirus (N, Rasool et al. 2020).

5. Conclusion

Various studies mention from molecular research, phytochemical tests, preclinical trials and scientific literature and other review literature stated that the chemical components of *Muntingia calabura* L have a potential as anti-inflammatory, anti-oxidant, and immunostimulant agents to prevent and treat pneumonia by the SARS-CoV-2 Coronavirus (Covid-19). *Muntingia calabura* L. could be prevent and complementary therapy against Covid-19.

Limitation and study forward

As for the limitations of the review, It is hoped that in the future *Muntingia calabura* L. research for preclinical trials and clinical trials will be carried out more so that this plant can be used as a category of traditional medicine

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