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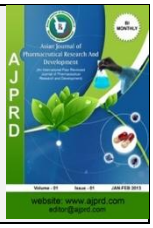

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Review Article

Potential anti-inflammatory effects of *Psidium guajava* L.: A review

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A B S T R A C T

Inflammation is a defence mechanism of a body against foreign substances. However, Inflammation also plays a key role in diseases such as diabetes, asthma, cardiovascular diseases, and cancer. Increasing scientific evidence has shown that fruits, vegetables, and legumes can have anti-inflammatory properties. This paper aims to provide recent studies on the anti-inflammatory properties of Psidium guajava L. A review was conducted on the studies of Psidium guajava L. anti-inflammatory properties performed during the past 10 years with the literature databases such as Pub Med, Science Direct, Google Scholar. Based on our eligibility criteria, a total of ten studies were included in this paper. The studies suggest that the anti-inflammatory activity of Psidium guajava occurs mainly through inhibition of PGE2, COX-2, NO, iNOS, ERK1/2, leukocyte cell migration, and suppression of edema, paw withdrawal latency as well as exhibited a membrane stabilization effect. This review has demonstrated the importance of Psidium guajava L. as a natural anti-inflammatory potential.

Keywords: Anti-inflammatory, Inflammation, Psidium guajava L.

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INTRODUCTION

Inflammation is an organism's defense mechanism against foreign substances. Systemic and local inflammatory responses aim to remove the triggering stimulus, facilitate tissue repair and healing, and develop immune memory in the case of infection so that in the future, the host mounts a more rapid and targeted response [1,2]. However, in some cases, Excessive and/or chronic inflammation may result in severe tissue damage, organ dysfunction, and death. The importance of inflammation in diseases as varied as cancer, atherosclerosis, reperfusion injury, diabetes and Alzheimer's disease has prompted a major research effort into the processes that activate and control the inflammatory response [3].

Nowadays, NSAIDs are some of the most widely prescribed medications in the world, and their analgesic, anti-inflammatory, and anti-pyretic properties are widely acknowledged. Like many other drugs, however, NSAIDs have a wide range of side effects, including cardiovascular (CV) and gastrointestinal (GI) events, high blood pressure, renal toxicity, and worsening of ongestive heart failure [4–7].

Natural medicines have become increasingly used in recent years as alternative treatments for inflammation because of their relatively mild side effects [8–11]. There is a strong interest in natural products that have few side effects. The previous research found that the various plants have distinct therapeutic activities, including anti-inflammatory behaviors [12–14]. Scientific increasing evidence indicates that fruits, legumes, and vegetables can have anti-inflammatory properties [15–17].

Psidium guajava L. is the most important fruit of the genus *Psidium*, which consists of around 150 species. Many parts of the plant, including the fruits, leaves, and bark, have long been used as herbal medicines for a range of ailments, including inflammation [18]. The vitamins C, which are relatively abundant in guava berries, which have high antioxidant ability, are even more essential. The presence of polyphenols such as flavonoids, phenolics, and tannins enhances this ability even more [18–21]. Carotenoids, such as

γ-carotene, β-carotene, β-cryptoxanthin, rubixanthin, cryptoflavin, lycopene, lutein, and neochrome, play an important role in the fruits' health benefits, including its superfood status. The fruits' high polyphenolic content, with about 40 mg gallic acid equivalent per gram, is a significant benefit that contributes to their antioxidant and pharmacological properties [22–24].

Currently, there is increasing interest in studying plants regarding their effects on several diseases, and for human health, it may be used as functional foods and/or nutraceuticals. [25]. Thus, this paper aims to provide the current studies on the anti-inflammatory of *Psidium guajava* L.

METHODS

The present review was performed using the databases, including Google Scholar, Science Direct, PubMed. In this update, the search terms were "Anti-inflammatory", "Inflammatory", "*Psidium guajava* L." using the publication from 2010 to 2020. Only accessible online articles in English or Indonesian were reviewed. All abstracts, and full-text articles were collected, examined, summarized, and conclusions made accordingly. The taxonomy of plants has been verified from the database "The Plant List" (www.theplantlist.org).

RESULTS AND DISCUSSION

Psidium guajava L. has anti-inflammatory activities, according to in vitro and in vivo studies. Based on our eligibility requirements, a total of 10 studies were included in this article. The anti-inflammatory properties of *Psidium guajva* L. are summarized in Table I.

Table: 1. Summary of anti-inflammatory properties of Psidium guajava L. (In vivo and In vitro studies)

Type of extract or Formulation	Plant part and source used for studies	Dose/ concentration	Experimental Model	Animal or disease models or Cell/specimen	Reported activity	Region	Ref.
Ethyl acetate and methanol extract	Leaves	200 mg/kg bw	Carrageenan-induced paw edema (In vivo)	The wistar albino rat	The extracts exhibited significant anti-inflammatory activity	India	26
Aqueous extract	Leaves	125, 250, and 500 mg/kg BW	Carrageenan-induced paw edema (In vivo)	Male Sprague-Dawley rats	The aqueous extract exhibited anti-inflammatory properties through decreasing edema	Indonesia	27
Methanolic extract	Leaves	300 and 500 mg/ml	Carrageenan-induced paw edema (In vivo)	Swiss albino mice	The crude extract of *Psidium guajava* leaves significantly decreased paw edema	Ethiopia	28
Mixture of solvents (Chloroform, Methanol, Pet. ether) extract	Leaves	200 and 400 mg/kg	Carrageenan-induced paw edema (In vivo)	Wistar albino rats	The mixture extract showed a significant anti-inflammatory activity	India	29
Decoction and infusion	Leaves	- 10% : 8% - 5% : 5% - 8% : 10%	Carrageenan-induced paw edema (In vivo)	Wistar Rat	The extract showed an anti-inflammatory effect	Indonesia	30
Essential oil	Leaves	100 mg/kg	Lipoposaccharide-induced pleurisy (In vivo)	Male Swiss mice	The essential oils showed anti-inflammatory activity	Brazil	31
Ethanolic extract	Leaves	100, 200, and 400 mg/kg 5, 10, 30, or 50 µg /mL	Freund's complete adjuvant induced arthritis (In vivo) LPS-stimulated RAW264.7 macrophage model (In vitro)	1. Male Sprague-Dawley rats 2. RAW264.7 macrophage cells	The ethanolic extract exhibited significant anti-inflammatory activity	Korea	32
Methanol and ethanol extract	Leaves	10,000 µg/ml	Hypotonicity induced human red blood cell (HRBC) membrane stabilization (In Vitro)	Human Red Blood Cell (HRBC)	The methanol and ethanol extracts showed membrane stabilization effect by inhibiting hypotonicity-induced lysis of erythrocyte membrane.	India	33
Ethanol extract	Leaves	10, 25, 50, and 100 µg/mL	LPS-stimulated RAW264.7 macrophage model (In vitro)	RAW 264.7 macrophage cells	The ethanolic extract showed an anti-inflammatory effect through inhibiting NO production.	Korea	34
Acetone–water extract and aqueous extract	Leaves	50, 100 and 200 mg/kg	Carrageenan-induced peritonitis (In vivo)	Female Swiss mice	The extract exhibited anti-inflammatory effect	Brazil	35

Effect of Psidium guajava L. on inhibition of carrageenan-induced edema

The carrageenan-induced oedema assay was used to search for possible activity against pro-inflammatory mediators. This model also has two phases: an early phase that starts 6 hours after carrageenan injection and lasts 72 hours, and a later phase that starts 6 hours after carrageenan injection and lasts 72 hours. Inflammation reaches its highest between 48 and 72 hours [36]. In the early stages of this experiment, histamine, serotonin, and increased prostaglandin synthesis were identified (between 1 h and 2 h after injection). Direct prostaglandins released by damaged tissue, as well as bradykinin, leukotrienes, polymorphonuclear cells, and macrophage-produced prostaglandins, trigger the later stage of oedema [37,38] . There are several previous studies that have shown anti-inflammatory activity of *Psidium guajava* L. through reducing edema, as the following research :

A study conducted by Bera et al. reported that the ethyl acetate and methanol extracts of *Psidium guajava L.* leaf exhibited significantly reduced carrageenan-induced rat paw oedema after a period of 4 h. The two *Psidium guajava* extracts tested were effective in both the early and late phases. It was discovered that the methanol extract was significantly more active than the ethyl acetate extract [26]. Aqueous leaves extract of *Psidium guajava* L. at doses of 125, 250, and 500 mg/kg was observed to show potent anti-inflammatory activity. The extract at a dose of 250 mg/kg gives the best effect among the three doses tested. The impact is better than Indomethacin beginning at the 4th hour in reducing edema [27]. In another study revealed that the 80 percent methanolic extract inhibited oedema for 5 hours period, which is possibly due to inhibition of various chemical mediators of inflammation. The 80 percent methanol extract of *Psidium guajava* leaves at doses of 300 and 500 mg/ml significantly reduced carrageenan-induced paw oedema at all time points assessed after administration ($p<0.001$). At both test doses of 300 and 500 mg/kg, the extract had the greatest anti-inflammatory activity at the third hour after administration. Carrageenan-induced edema was decreased by 51% and 57%, respectively, while the standard medication at a dosage of 20 mg/kg prevented edema by 58.5 percent as compared to the control group. It was discovered that the plant extract's anti-inflammatory activity was largely due to the inhibition of second-phase chemical mediators such as prostaglandins [28]. Similarly, at doses of 200 mg/kg and 400 mg/kg, a mixture of solvent extract of *Psidium guajava* leaf demonstrated important anti-inflammatory activity using the Carrageenan mediated rat paw edema method using the Plethysmometer. The 400 mg/kg dose demonstrated strong activity as compared to the normal dose and the 200 mg/kg dose. When compared with control, the anti-inflammatory activity had a significant effect [29]. Marsh fleabane roots (*Pluchea indica* L.) and guava leaves (*Psidium guajava* L.) were combined at a concentration of 5% : 5% and showed anti-inflammatory effects through edema suppression. It's a better mix than the others, and it's equivalent to the positive control [30].

Effect of Psidium guajava L. on alterations in MAPK signalling pathways and regulation of inflammatory mediators

Macrophages, which release pro-inflammatory mediators and proteins such as cyclooxygenase-2 (COX-2), interleukin-6 (IL-6),inducible nitric oxide synthase (iNOS), and tumour necrosis factor- α (TNF- α) are important players in inflammatory diseases and the immune response [39]. When activated by lipopolysaccharide (LPS), the RAW 264.7 mouse macrophage cell line produces proinflammatory cytokines and other inflammatory mediators, such as a prostaglandin E2 (PGE2) and nitric oxide (NO), which are produced by COX-2 and iNOS, respectively [40]. COX-2 is a prostaglandin-producing enzyme that is stimulated by proinflammatory cytokines and other activators including LPS, resulting in a significant amount of PGE2 being released at inflammation sites. As a result, discovering COX-2 inhibitors is thought to be a promising strategy for preventing inflammation and tumorigenesis [41,42]. NO, a well-known pro-inflammatory mediator developed by iNOS, is involved in a number of physiological and pathological processes. Suppression of NO output has recently been promoted as a novel pharmacological technique for treating inflammation-related diseases. The inhibition of iNOS activity is a promising therapeutic target for a number of pathological conditions [41]. Recent studies have discovered that MAPK signalling pathways are important in the regulation of the inflammatory response and in the coordination of the induction of many genes that code for inflammatory mediators. The three main MAPK pathways are composed of a family of highly conserved protein kinases called ERK, JNK, and p38. Immune responses also including pro-inflammatory cytokine production, mitosis, differentiation, and cell survival/apoptosis are all regulated by these kinases. For LPS-treated RAW264.7 cells and peritoneal macrophages, ERK is important for COX-2 expression. LPS-induced NO synthesis was suppressed by the ERK1/2 inhibitor, PD98059 and the p38 inhibitor, SB203580, according to the study [43,44]. There are several previous studies that have shown anti-inflammatory activity of *Psidium guajava* L. through inhibition of PGE2, COX-2, NO, iNOS, ERK1/2, as the following reported:

The anti-inflammatory activities of *Psidium guajava* ethanolic leaf extract were observed in vitro and in vivo. The results show that guava leaf extract (GLE) significantly decreased the production of inflammatory mediators including nitric oxide and prostaglandin E2 induced by lipopolysaccharide (LPS). GLE also inhibited the expression and activity of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in RAW264.7 macrophages by inhibiting ERK1/2 activation [32].

Freund's complete adjuvant is widely used to cause arthritis in animal models by causing inflammation in the hind paw of rats. The FCA-induced inflammatory hyperalgesia rat model is a well-known model for testing drug analgesic efficacy. During the first week following the intervention, FCA-injected rats have elevated serum IL-6, extreme hyperalgesia, and oedema [45,46]. Jang et al. reported that

administration of *Psidium guajava* leaf extract exhibited inhibitory activity in FCA-induced paw withdrawal latency [32]

In addition, the ethanolic extract demonstrated an anti-inflammatory effect through inhibiting NO production and exhibited a concentration-dependent inhibitory effect on NO production when treated with guava leaf extract. This study showed a significant NO inhibitory effect of 50.4% at 100 µg/mL [34].

Effect of Psidium guajava L. on lysosomal membrane stabilization

Acute and chronic inflammatory disorders are regulated by lysosomal enzymes. Inflammatory mediators such as oxygen radicals and prostaglandins are activated when lysosomal enzymes are released into the cytoplasm. By preventing the release of lysosome constituents, lysosomal membrane stabilization is essential in reducing the inflammatory response [47]. Membrane stabilizers inhibit the release of lytic enzymes and active mediators of inflammation, which prevent serum protein and fluid leakage through the cell membrane [48].

A study with a different method on membrane stabilization effect conducted by Hotta et al., the study reported that methanol and ethanol leaf extracts of *Psidium guajava* L. were found to have a membrane-stabilizing effect by inhibiting hypotonicity-induced erythrocyte membrane lysis, according to the report. The methanol leaf extract of *Psidium guajava* had the strongest anti-inflammatory function, while the ethanol leaf extract had the weakest [33].

Effect of Psidium guajava L. on inhibition of leukocyte migration

Exogenous and endogenous agents lead to pulmonary damage, with the involvement of several inflammatory mediators and enzymes. Inflammation, in particular, plays an important role in lung damage. During the early phase of lung injury, an increase in the percentage of leukocytes, eosinophils, neutrophils, lymphocytes, and macrophages in bronchoalveolar lavage fluid (BALF), and there was an increase in the production of inflammatory cytokines. [49]. Exogenous stimulus derived from gram-negative bacteria, lipopolysaccharide (LPS), when administered to experimental animals, induces pathological lung damage [50]. Tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL1β) are several of the pro-inflammatory mediators that can be activated by LPS. Furthermore, LPS stimulation triggers cell death and activates the TLR4-mediated NF-κβ signalling pathway, resulting in endotoxin shock and death [51].

The anti-inflammatory activity of the essential oils from *Psidium guajava* L. was evaluated. To evaluate the inflammatory response, researchers used a lipopolysaccharide-induced pleurisy model and measured the inhibition of total leukocyte, neutrophil, and eosinophil migration in the pleural lavage of mice. The essential oils from *Psidium guajava* L. were found to be successful in preventing inflammatory diseases through mechanisms that include eosinophil inhibition and, to a lesser degree, neutrophil and mononuclear cell migration inhibition [31]. In addition, in another study by De Araújo et al., the aqueous and acetone-aqueous extracts of *Psidium guajava* showed anti-inflammatory activity, these extracts significantly reduced the migration of leukocytes [35].

CONCLUSIONS AND FUTURE PROSPECTS

Herbal remedies provide significant guidance for the development of drugs, such as anti-inflammatory medications. The importance of *Psidium guajva* L. as an anti-inflammatory agent has been demonstrated in this study. Several molecular pathways have been used to evaluate the anti-inflammatory properties of *Psidium guajava* L. in vitro and in vivo. *Psidium guajava* L. has been reported to significantly reduce TNF- α and IL-6 levels, as well as inhibit COX-2, PGE2, NO, iNOS, ERK1/2, leukocyte cell migration, and suppression of edema. In addition, the *Psidium guajava* L. also showed a significantly reduce paw withdrawal latency as well as exhibited a membrane stabilization effect by inhibiting hypotonicity-induced lysis of erythrocyte membrane. However, more research is needed to better understand metabolism in the body and the role of metabolites in anti-inflammatory action, which may contribute to the production of new anti-inflammatory drugs in the future. Furthermore, Future research on the anti-inflammatory activity of *Psidium guajava* L. should include clear sources and specifications for the ingredients used, particularly when plant extracts are used. To ensure the anti-inflammatory activity of *Psidium guajava* L., the methods and conditions used in vitro and in vivo must be validated.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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