Potential of *Moringa oleifera* as a gingivitis inhibitor

Potensi Moringa oleifera sebagai penghambat gingivitis

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ABSTRACT
Anti-inflammatory drugs when used in the long term can reduce organ function, so non-pharmacological treatments are carried out, namely with herbal preparation therapy from various types of plants. Moringa leaves (Moringa oleifera) are one of the herbal medicinal plants that contain 1.4% tannins, 5% tritepenoids and 5% saponins and contain secondary metabolite compounds flavonoids, alkaloids, phenols. The flavonoid content in Moringa leaves provides anti-inflammatory activity. This literature review discusses the benefits of *M.oleifera* as an anti-inflammatory. *M.oleifera* extract has vitamin A, vitamin C, vitamin E, carotenoids, polyphenols, flavonoids, phenolic acids, alkaloids, tannins, and saponins that can be utilised as antioxidants, anti-inflammatory and antibacterial. It is concluded that *M.oleifera* with flavonoids content can be utilised as an anti-inflammatory that inhibits and treats gingivitis and other periodontal diseases.
Keywords: *Moringa oleifera*, anti-inflammatory, anti-bacterial, gingivitis, cytotoxicity, proliferation

ABSTRAK
Obat-obatan anti-inflamasi bila digunakan dalam jangka panjang dapat menurunkan fungsi organ tubuh maka dilakukan penanganan non-farmakologi, yaitu dengan terapi sediaan herbal dari berbagai jenis tumbuhan. Daun kelor (*Moringa oleifera*) merupakan salah satu tumbuhan obat herbal yang memiliki kandungan tanin 1,4%, tritepenoid 5% dan saponin 5% serta mengandung senyawa metabolit sekunder flavonoid, alkaloid, fenol. Kandungan flavonoid pada daun kelor memberikan aktivitas anti-inflamasi. Kajian pustaka ini membahas mengenai manfaat *M.oleifera* sebagai anti-inflamasi. Ekstrak *M.oleifera* memiliki kandungan vitamin A, vitamin C, vitamin E, karotenoid, polifenol, flavonoid, asam fenolat, alkaloid, tanin, dan saponin yang dapat dimanfaatkan sebagai antioksidan, anti-inflamasi dan antibakteri. Disimpulkan bahwa *M.oleifera* dengan kandungan flavonoid dapat dimanfaatkan menjadi anti-inflamasi yang menghambat dan mengobati gingivitis maupun penyakit periodontal lainnya.
Kata kunci: *Moringa oleifera*, anti-inflammatory, anti-bacterial, gingivitis
Received: 10 April 2023 Accepted: 1 January 2024 Published: 1 August 2024

INTRODUCTION

Inflammation is the body's response to harmful molecules, especially microbial infections or tissue injury. In the early response phase, innate immune cells such as neutrophils, natural killer (NK) cells, and macrophages signal the presence of invading pathogens using a group of cell surface and cytoplasmic receptors called pattern recognition receptors (PRRs). PRR can detect harmful molecules as pathogen-associated molecular patterns (PAMPs) or host-derived damage-associated molecular patterns (DAMPs), which lead to the triggering of intracellular signaling transduction. Various signaling pathways are activated during inflammatory activation, including nuclear factor-κB (NF-κB), resulting in increased production of pro-inflammatory mediators such as tumor necrosis factorα (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6). This transient inflammatory process induces clearance of harmful molecules and maintains tissue homeostasis in the resolution phase; however, uncontrolled inflammation can become a chronic risk factor contributing to many diseases such as cardiovascular disease, cancer, and osteoporosis. DAMPs derived from microorganisms are major inflammatory activators. Inflammation results from interactions.[1]

Gingivitis is an inflammation of the gingiva, which is clinically identified as causing bleeding with swelling, redness, exudate, change of normal contour, and occasional discomfort. Gingivitis is caused by the accumulation of plaque bacteria due to poor oral hygiene, calculus, mechanical irritation, and irregular tooth position can be contributing factors. Plaque bacteria in large numbers disrupt the host-parasite relationship and can cause dental caries and periodontal disease. As plaque generally accumulates in large quantities in narrow interdental spaces, gingival inflammation tends to start in the area of the interdental papillae and spread to the cervical area of the teeth. Each individual's response to plaque as a causative factor varies, some people have a minimal response to local factors. One of the treatments that appeals to the public's attention is using herbal plants at oral diseases.[2]

Non-steroid anti-inflammation (NSAIDs) and anti-inflammation steroids (AIS) are a class of anti-inflammatory drugs that have the ability to suppress signs and symptoms of inflammation. On the other hand, herbal drugs have advantages over chemical and synthetic drugs on the market, namely constructive therapeutic effects and very small side effects, making them safer for consumption. Because the use of anti-inflammatory drugs if consumed in the long term can reduce the function of organs such as the kidneys, liver, organs in the digestive system, and even the heart function, inflammation is treated in addition to pharmacological therapy, namely herbal drugs from various types of plants.[3] The use of herbal plants in dentistry appears to be an affordable option for a large number of patients worldwide. A Brazilian ethno-

DOI 10.35856/mdj.v13i2.929

pharmacological study proved that a number of plant species commonly used in traditional medicine applied to the oral cavity can provide antiseptic and anti-inflammatory effects. One plant that has been proven to have anti-inflammatory activity is moringa (*Moringa oleifera*).[4]

M.oleifera contains several chemical compounds in the form of several bioactive compounds, one of which is flavonoids. Flavonoids are polyphenolic compounds produced from secondary metabolism in plants. The main flavonoids in moringa, which include quercetin, kaempferol glucoside, and flavonoid malonate, exhibit anti-inflammatory activity through inhibition of NO production in LPS-stimulated macrophages. Flavonoids are known to have a mechanism similar to non-steroidal anti-inflammatory drugs. Flavonoids can inhibit the activity of expression of proinflammatory mediators other than COX. *M.oleifera* can selectively inhibited iNOS and COX-2 production and significantly inhibited the secretion of NO and other inflammatory markers including PGE-2, TNF-, IL-6, and IL-1β in lipopolysaccharide cells in RAW264 cells. *M.oleifera* has demonstrated an excellent ability to protect against oxidative damage because its high content of polyphenols, flavonoids, and flavonols is an excellent source of antioxidants and is non-toxic.[5]

This literature review discusses the benefits of *M.oleifera* as an anti-inflammatory.

LITERATURE REVIEW

M.Oleifera is a tropical plant that is easy to grow in tropical areas such as Indonesia and other tropical regions worldwide. This plant is a shrub or tree with strong, long-lived roots, brittle woody stems (frangible), upright, dirty white in color, thin bark, rough surface, and rarely branches.[10] *M.oleifera* belongs to the *Moringaceae* family which has oval-shaped leaves with small sizes arranged in a compound arrangement on one stalk. Moringa plants have a slightly bitter taste, neutral, and not toxic. The moringa tree has several nicknames, including the *miracle tree, tree for life*, and *amazing tree*. The nickname arose because the parts of the moringa tree, starting from leaves, fruit, seeds, flowers, bark, and stems, to roots, have many benefits. Moringa plants are able to live in various types of soil, do not require intensive care, are resistant to drought, and are easy to breed.[11,12]

M.oleifera is known as a food source that is highly digestible and rich in protein. According to Sultana and Anwar, moringa leaves have many important compounds, such as protein, vitamins, calcium, zinc, ascorbic acid, and antioxidants (carotenoids, flavonoids, and phenols). Various developing and underdeveloped countries in the world feed their children with moringa. Busani et al. reported that the presence of many minerals and vitamins helps to increase immunity against various diseases. Moreover, moringa leaves contain various amino acids. Moringa leaves have a variety of uses, such as powdered coated capsule medicine, as a drink (Ziga drink), and tea. Because of their nutritional properties, *M.oleifera* is known as the miracle tree.[7-9]

M.oleifera has many effective medical uses. Every part of *M.oleifera* is considered an essential element that has medicinal value. Almost all parts of the moringa tree can be used as natural medicine. Abalaka et al. reported many pharmaceutical applications in the use of this plant as a traditional medicine. Moreover, the aqueous extract of moringa from the roots was found to be significant in anti-inflammatory, anti-ulcer, and antitumor activities.[11,12] *M.oleifera* as 1) antimicrobial and anthelmintic. Extracts from the leaves, flower root bark, and stem bark have antimicrobial and anthelmintic properties. *M.oleifera* was found to have antimicrobial activity against *E.coli, P.aeruginosa, Enterobacter species, K.pneumoniae, S.aureus, Proteus mirabilis, S.typhi A, Streptococcus,* and *C.albicans*;[11,12] 2) anti-cancer and antitumor. There is a direct relationship between reactive oxygen species (ROS) and cell death. Various environmental stresses lead to excessive production of ROS thereby causing progressive oxidative damage and eventually cell death. Compounds that are responsible as anticancer are glucosinolates, niazimicin, and benzyl isothiocyanate;[10,13] 3) antidiabetic and tissue healing. *M.oleifera* in research is an important element in diabetes control. In one study, it was found that moringa leaves were significant in reducing blood glucose levels immediately after drinking. The (aqueous) extract shows a significant prohealing effect in tissue wound healing;[14,15] 4) stimulant of blood circulation and antidiuretic. Alkaloid bioactive compounds from *M.oleifera* act as cardiac stimulants which are proven to stabilize blood pressure, have an effect on diuretic activity, reduce fat and cholesterol to prevent hyperlipidemia, and reduce serum triglycerides and serum cholesterol;[16] 5) an analgesic. A study found that leaves and roots can be used as an analgesic. Moringa leaf alcohol extract can be used as an identical analgesic. In another study, the methanol extract was tested on frogs and guinea pigs which showed that the plant was effective as an anesthetic in both animals;[16] 6) an antipyretic. *M.oleifera* was studied in mice using different extracts (ethanol, petroleum ether, ethyl acetate, etc.) in which the seed extracts (ethanol and ethyl) showed significant antipyretic activity.[17]

METHODS

The method used in this journal article is the literature review. The literature review study method collects information originating from research articles related to literature review studies. Literature reviews taken in this journal were obtained from platforms such as PubMed, Google Scholar, Science Direct, and Scopus.

DISCUSSION

M.oleifera is an alternative herbal species belonging to the monogeneric family *Moringaceae* and native to the sub-Himalayan region of Northwest India. It has a wide spectrum of pharmacological activity. *M.oleifera* Lam contains flavonoids, saponins, tannins, alkaloids, vitamins A, B1, B2, and C, and has anti-inflammatory, antipyretic, and antiscorbutic pharmacological effects. *M. oleifera* has anti-inflammatory properties, and contains flavonoids and tannins which work by stimulating cells such as macrophages to produce growth factors and cytokines such as EGF, TGF-β, IL-1, IL-4, IL-8, TGF-β, and

DOI 10.35856/mdj.v13i2.929

EGF induce the proliferation and migration of fibroblasts as well as induce fibroblasts in the production of extracellular matrix. IL-1, IL-4, and IL-8 function to induce chemotaxis of fibroblasts and keratinocytes, activating fibroblast proliferation.[18,19]

Almost every part of the *M.oleifera* tree (leaves, roots, bark, fruit flowers, pods, and immature seeds) has a high nutritional value making it a highly valued plant. Previous studies have proven its anti-inflammatory and analgesic activity. The ethanol extract of *M.oleifera* has been tested for its antimicrobial activity against species such as *E. Coli*, *P.aeruginosa*, *S.aureus*, and Salmonella typhi with positive results. The antibacterial property of *M.oleifera* has been attributed to the presence of flavonoids, tannins, glycosides, and terpenoids. A recent study where the cytotoxicity of *M.oleifera* leaf extract on periodontal ligament fibroblast cells has been evaluated.[18]

In an in vivo study conducted by Buakaew et al, who evaluated a mouthwash containing citrus hystrix DC., *M. oleifera Lam* and *Azadirachta indica* A. Juss. In his study, mouthwash containing KL, KL+MO, and KL+NE showed a significant reduction in GI and PI scores. Increasing the percentage of accumulative reduction of both *Staphylococcus spp*. and *Candida spp*. after 15 days of use were observed in the KL+MO and KL+NE groups compared to baseline. Although the GI scores in the KL+NE group were not statistically different, the trend of decline was similar for the KL and KL+MO groups. The results of the GC-MS analysis indicated that the volatile substances in the terpenoid group might be responsible for the anti-inflammatory activity of these medicinal plants. The findings show that a mouthwash containing KL, MO, and NE leaf extracts has the potential to reduce dental plaque formation and reduce gingival inflammation as an alternative oral care product for adjunctive treatment of microbial-induced gingivitis.[5]

Based on research conducted by Asmawati, et al showed that the application of *M.oleifera Lam* oil had an effect on increasing the number of fibroblasts in the gingival mucosa of male Wistar rats (*R.norvegicus*) on days 3 and 7.[1] This is also supported by Gothai, et al, regarding the efficacy of the ethyl acetate fraction of MO leaves on cell viability, proliferation, and migration (rate of wound closure) in normal human dermal fibroblast (HDF-N) cells. The results showed that lower concentrations (12.5 µg/mL, 25 µg/mL, and 50 µg/mL) of the ethyl acetate fraction of MO leaves showed remarkable proliferative and migratory effects on normal human skin fibroblasts. This study shows that the ethyl acetate fraction of MO leaves allows it to be a potential therapeutic agent in skin wound healing by promoting the proliferation and migration of fibroblasts by increasing the rate of wound closure which corroborates its traditional use. However, administration in higher concentration (>125 µg/mL) showed decreased results. This indicates a strong anti-proliferative activity, possibly due to the strong accumulation of phenolic compounds which is associated with caspase activation and induces apoptosis.[19]

Research conducted by Sugiharto, et al showed that *M.oleifera* leaf extract had an anti-inflammatory effect on inflammation caused by the bacterium *P.gingivalis*. In a study conducted by Sugiharto, et al using samples of male Wistar rats were randomly allocated to different groups. Sampling of the study was carried out using a simple random sampling technique after fulfilling the inclusion and exclusion criteria. Then, the induction of *P.gingivalis* bacteria was carried out by injecting the bacterial suspension into the periodontal tissues of the experimental animals. *M.oleifera* extract can reduce the production of proinflammatory cytokine IL-6 induced by *P.gingivalis* bacteria in periodontitis. Other studies that support the mechanism of *M.oleifera* have shown its excellent ability to protect against oxidative damage because its high content of polyphenols, flavonoids, and flavonols is an excellent and non-toxic source of antioxidants.[20]

Nourhan et al, in his research on the mechanism of wound healing and the antioxidant potential of *M.oleifera* seed extract. Topical administration of *M.oleifera* extract to excised wounds resulted in a substantial increase in wound healing rate ($p<0.001$), increased TGF-β1, VEGF, collagen type I relative expression, and reduced inflammatory markers such as IL-1β and TNF-α. *M.oleifera* seed extract or MEBO® treatment for 14 days showed a significant decrease in TNF-α and IL-1β mRNA expression when compared to the untreated group at ($p< 0.001$). The expression of TNF-α and IL-1β in wounds treated with *M.oleifera* seed extract was significantly lower than in the group treated with MEBO®. Pro-inflammatory cytokines (IL-1β and TNF-α) must be expressed appropriately to recruit neutrophils to the wound site. They have also been identified as dynamic inducers of metalloproteinase (MMP) production in inflammatory cells and fibroblasts. MMP destroys and removes damaged extracellular matrix (ECM) during wound healing to aid wound repair. However, a prolonged inflammatory phase interferes with the healing process, and these cytokines and proteinases damage tissue and contribute to chronic wound formation.[21]

Based on the results of a study conducted by Asmawati et al, that the extract of *M.oleifera lamk* was effective in healing the gingival wounds of white rats which were characterized by an increase in the thickness of collagen in the wounds of white rats. *M.oleifera lam* also contains tannin and saponin compounds which function as antibacterial so that the wound area is protected from bacterial invasion and supports wound healing. Likewise, the results of research by Asmawati et al. showed the increasing the number of fibroblasts in the gingival mucosa of white rats with a significant value after the application of *M.oleifera* extract on the gingival wounds of white rats.

Fibroblasts play a role in the wound healing process. At the proliferative stage, an epithelial process occurs, after the wound occurs morphological changes in the keratinocytes at the edges of the wound.[19]

In a study conducted by Sugiharto, et al it was found that *M.oleifera* extract could reduce NF-κB levels in the treatment group lower than in the control group. This

DOI 10.35856/mdj.v13i2.929

means that the degree of inflammation in the periodontal tissues can be reduced, especially the gingival junctional epithelium, by reducing the levels of NF κB.[22]

Ilyas, et al in their research administered moringa extract at a safe dose of 2.2 g/kg orally. Moringa leaf extract was not known to be toxic in rats with a body weight of 2000 mg/kg. In his research on the comparative evaluation of the cytotoxicity of *M.oleifera* leaf extract and calcium hydroxide on periodontal ligament fibroblast cells. This research was conducted by acute administration of moringa extract at a safe dose of 2.2 g/kg orally. Moringa leaf extract is known to be non-toxic to animals at 2000 mg/kg body weight in an acute toxicity study reported by Adedapo et al. Many other studies have also reported that moringa leaf extract is safe to use at very high doses (5000-6400 mg/kg) (Diallo et al, Awodele et al). The local moringa used in this study has also been shown to be safe for oral supplementation. In hematological parameters, there was a slight but not significant decrease in the levels of red blood cells, Hb, hematocrit, MCV, MCH, and MCHC content in rats given moringa leaf and seed extracts which could occur due to hemolysis by these extracts. The Hb content can decrease due to the decrease in Hb synthesis which causes interruption of the supply of oxygen to different tissues, which in turn causes a reduction in the number of red blood cells through hemolysis.[23]

It is concluded that *M.oleifera Lam* contains various substances such as flavonoids, saponins, tannins, alkaloids, glycosides and has anti-inflammatory, antipyretic, and antiscorbutic pharmacological effects which will suppress inflammatory mediators so that they can become inhibitors of gingivitis. *M.oleifera* can be an anti-inflammamatory and antimicrobial agent to prevent gingivitis and other periodontal diseases. *M.oleifera L* showed a dose-dependent antimicrobial effect with a decrease in the number of colonies with an increase in concentration.

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DOI 10.35856/mdj.v13i2.929