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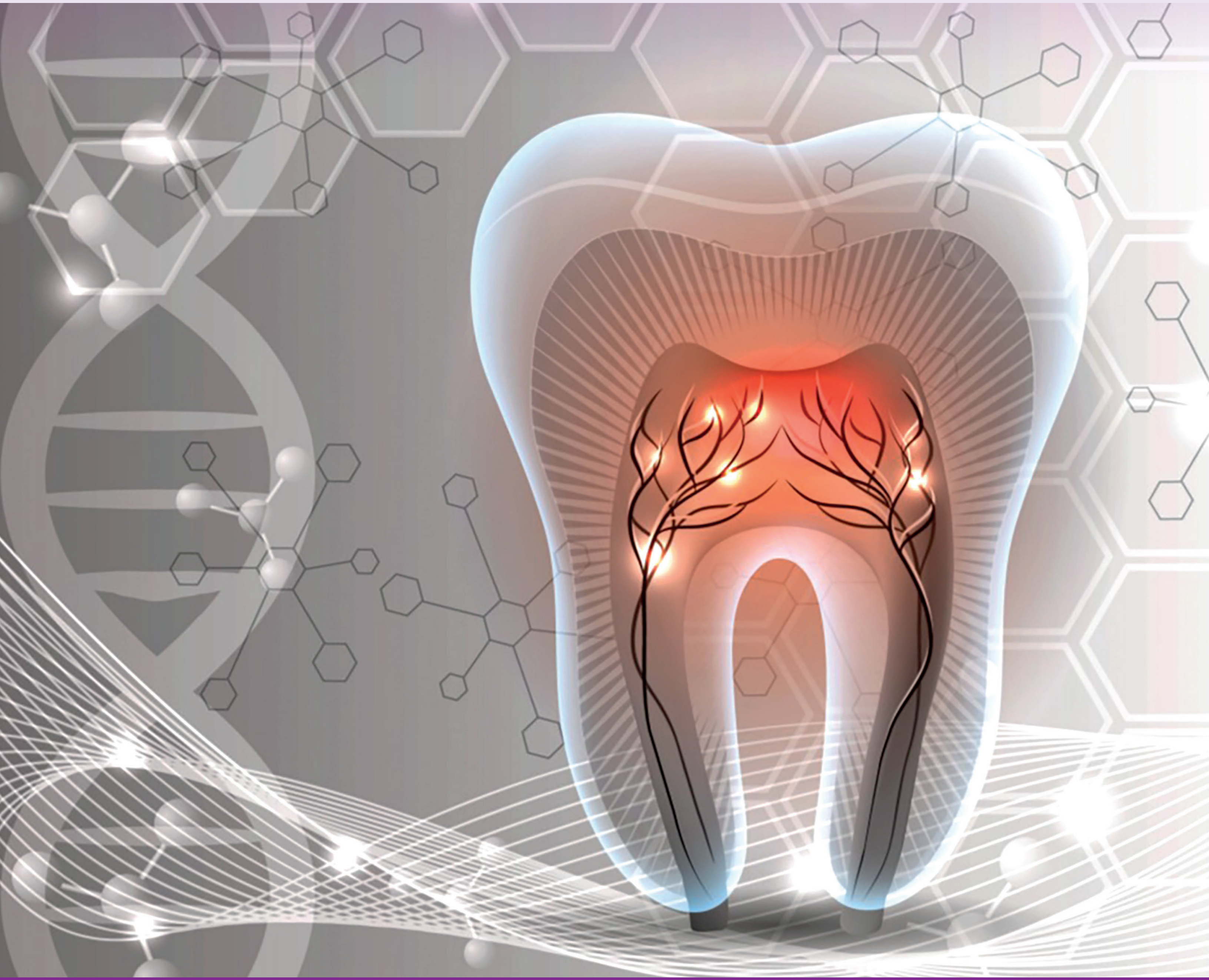

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Potential of *Moringa oleifera* as an Antibacterial in Root Canal and Tooth Surface Disease: A Comprehensive Review

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ABSTRACT

Moringa oleifera is a widespread plant in Southeast Asia, especially Indonesia. Moringa leaves are known to contain bioactive compounds Polyphenol, quercetin, tannin, and saponin compounds in moringa leaves exhibit anti-inflammatory, antidiabetic, and antibacterial activity. However, the potential of moringa leaf extracts as antibacterials needs to be tested in silico and in vitro to determine the suitability of specific bioactive compounds. The aim of the present comprehensive review was to assess the antibacterial and antibiofilmic potential of *Moringa oleifera* leaves in root canal disease and on tooth surfaces. The findings of this review indicate that the *M. oleifera* plant holds significant promise for drug development purposes, serving as a viable option for herbal remedies and as a foundational resource for pharmaceutical synthesis

KEYWORDS: *antibacterial, bioactive compound, Moringa oleifera*

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BACKGROUND

Dental disease remains a common problem suffered by humans of all ages.[1] The types of dental diseases caused by oral bacteria include tooth decay and periodontitis. Various types of pathogenic bacteria can cause oral infections, including fungi, viruses, and bacteria. Pathogenic bacteria, such as *Streptococcus mutans, Streptococcus sanguinis,* and *Enterococcus faecalis,* are common bacteria in the community and cause oral infections, including dental caries.[2,3] In addition, the growth of acid-producing microbial biofilms infects enamel and dentin.[4]

Certain bacteria, such as those named above, are associated with periodontitis and caries, and these bacteria collectively cause dental infections.[5] *S. mutans* and *S. sanguinis* play key roles in causing dental plaque. These cariogenic bacteria cause tooth demineralization and the onset of carious lesions on the teeth by fermenting sugars and producing lactic acid.[6] Among the oral bacteria that can cause root canal infections is *E. faecalis*. This pathogen can reside not only in saliva but also in root canals.[7] Conditions, such as low pH, high temperature, and high salinity enable *E. faecalis* to survive and form a biofilm,[8] consequently allowing an infection that can penetrate the dentinal tubules.[9]

In 2017, the number of dental caries in permanent teeth per 100,000 population in each country ranged from 20% to more than 50%. In this context, the dental caries rate in Indonesia in 2018 was 88.8%, with 56.6% of the total caries consisting of root caries, which were found in 92.6% of children between the ages of 5 and 9. According to the World Health Organization (WHO), the most common disease in the oral cavity is dental caries. Dental caries originate from microbial biofilm (plaque) that forms on the surface of the teeth. An estimated 2.4 billion people have permanent dental caries, and 486 million children have caries in primary teeth. Dental caries are a condition of cavities caused by bacteria.[10] Similarly, periodontal diseases are associated with either bacterial or fungal infections and are the cause of primary tooth decay in more than 560 million children. "Periodontal" is a general term used to describe chronic inflammatory conditions in the soft tissues or tissues surrounding the teeth. Periodontal infections are a major cause of tooth loss and can have a negative impact on health.[11]

Infections caused by bacteria can be treated with antibiotics. Antibiotics have long been used to cure various types of dental infections.[12] However, it has been reported that the use of antibiotics can cause side effects and resistance. Some of the antibiotics that have been used to treat dental infections are ampicillin, amoxicillin, penicillin, cefotaxime, cefazolin, methicillin, erythromycin,, lincomycin, clindamycin, and vancomycin, particularly against *S. mutans*. In adults, *S. mutans* exhibits the greatest resistance to amoxicillin (14.8%) and lincomycin (28.7%), while in children, it is resistant to penicillin (27.6%) and vancomycin (42.5%).[13,14] Indonesia is a country of significant biodiversity where many people use local plants for their daily needs and traditional medicine. One of the plants used as an antibacterial drug is *Moringa oleifera* L. Previous studies have shown that moringa or miracle tree plants are a source of nutrients that have medicinal properties.[15,16] Therefore, this review explores the activities of pathogenic bacteria that cause dental infections and the potential of *Moringa oleifera* L. as a natural antibacterial agent to cure dental infections.

Pathogenic Bacteria that Cause Oral Infections

Streptococcus mutans

S. mutans bacteria are responsible for a large number of dental caries. As a formulator of stable extracellular polysaccharides, *S. mutans* has the ability to colonize tooth surfaces at a relatively low level of acidity (pH). Therefore, it plays a very important role in the formation of dental caries. A number of other variables can also affect cariogenicity, such as diet, sucrose, antibiotic use, antiseptic mouthwash, oral hygiene, and oral cavity location.[17] *S. mutans* can form three-dimensional cariogenic biofilms by producing extracellular polysaccharides (EPS) in the extracellular matrix, creating a microenvironment rich in pathogens and carbohydrates.[18] Arginine can be a precursor for protein synthesis and is an important target for post-translational modifications involved in biofilm formation.[19]

Streptococcus sanguinis

S. sanguinis is a facultative anaerobic Gram-positive bacterium that does not produce spores. *S. sanguinis* is associated with oral disease because it is a bacterium that causes tooth decay. However, when fatty buildup or bacteria such as S. sanguinis enter the bloodstream during dental procedures, they can adhere to the heart valves or the endocardium, increasing the risk of infective endocarditis. The initial stage in biofilm formation is the attachment of *S. sanguinis* and other pioneer colonies to macromolecular complexes formed on saliva-coated tooth surfaces.[5] In addition to *S. mutans, S. sanguinis* is an important species in oral biofilm ecology and contributes significantly to biofilm formation.[20] Conversely, *S. sanguinis* bacteria can be beneficial in preventing the growth of *S. mutans* and other anaerobic bacteria that cause periodontal disease. This is achieved through the production of H_2O_2, which can serve as a means to generate additional O_2.[21]

The production of acquired enamel pellicle (AEP) by bacteria is facilitated by their attachment to the tooth surface, enabled by the presence of negatively charged residues and electrostatic interactions with hydrophilic areas present on salivary proteins. Although *S. sanguinis* can attach to the primary mineral in tooth enamel, hydroxyapatite, which is free of saliva, the initial attachment process is most likely to be triggered by the interaction of the streptococcal surface with saliva constituents. Interactions between protein-carbohydrate or protein-protein compounds and receptors on the bacterial surface mediate the salivary protein binding mechanism.[22] Dental plaque and AEP contain amylase, the most common salivary protein, which is bound by *S. sanguinis* exclusively through long filamentous pili.[23,24]

Enterococcus faecalis

E. faecalis is a facultative anaerobic Gram-positive bacterium. *E. faecalis* can form biofilms that allow bacteria to survive antibodies and antibacterials.[25] *E. faecalis* bacteria are the most common in recurrent root canal infections; their ability to invade the dentinal tubules is one of the causes.[26,27] *E. faecalis* is detected as a virulence factor that can survive in extreme environmental conditions and is resistant to several antibacterials in root canal treatment. The prevalence of *E. faecalis* bacteria as a cause of root canal treatment failure reaches 90%.[28,29] One of the reasons that the removal of pathogens such as *E. faecalis* is so difficult is their ability to produce biofilms that adhere to surfaces that exhibit a high level of resistance to planktonic competitors.[30]

Surface adhesin factors include biofilm formation and attachment to body tissue or dentin collagen.[31] The attachment of lipoteichoic acid factors to body tissues triggers the production of cytokines by monocytes, leading to inflammation and drug resistance after root canal therapy. Furthermore, during the inflammatory process, extracellular factors that produce superoxide damage cells and tissues.[32] Extracellular zinc metalloprotase, or gelatinase factor, has the ability to hydrolyze collagen and hyaluronidase enzymes found in dentin and periapical tissues that have been damaged. The final component is the ability to produce toxins and inhibit the growth of other bacteria, specifically cytolysin, AS-48, and bacteriocin.

E. faecalis is a deeply studied biological clue. In several laboratory studies, *E. faecalis* was tested against endodontic treatments; the results showed that *E. faecalis* is highly resistant to antimicrobial drugs. In addition, *E. faecalis* can survive in very harsh environments where there is a lack of nutrients and the alkaline pH reaches 11.5. *E. faecalis* can grow as a biofilm on the root canal wall and infect itself in root canal treatment without the help of other bacteria. This makes this pathogen highly resistant to antimicrobials.[33,34] Three studies have discussed treatment methods to reduce or eliminate *E. faecalis* from root canals and periradicular areas.[35] As other pathogenic bacteria, the treatment and prevention of *E. faecalis*,is usually involving antibiotics. One study [36] employed antimicrobial agents with strong antibacterial properties to fight *E. faecalis*.

Antibacterials and Antibiofilms

Antibacterials

Antibacterials are compounds that have the ability to inhibit and eliminate harmful bacteria. Antibacterials fall into two categories: bacteriostatic (which inhibit bacterial growth) and bactericidal (which kill bacteria). The antibacterial used must have selective toxicity to microbes but not be toxic to the host.[37] Many synthetic pathways, such as those of protein biosynthesis, transcription, DNA replication, and bacterial cell wall biogenesis, are involved in bacterial inhibition.[38] During bacterial cell death, the peptidoglycan layer is destroyed.

Glycopeptides and β-lactam antibiotics both target pathways involved in peptidoglycan synthesis.[39] However, some bacteria have now developed various defense mechanisms against antibiotic attacks. These defense mechanisms involve either direct bacterial damage or structural modification of the antibiotic to prevent growth inhibition and allow the bacteria to survive. One way to combat antibiotic resistance is through enzymatic modification and degradation. This process, which has defeated resistance to several classes of antibiotics, such as β-lactam antibiotics and aminoglycosides, is an effective way to overcome antibiotic resistance. Some antibiotics have been shown to be inactivated by the hydrolysis process, which is carried out by a wide variety of hydraulics. The co-evolution of β-lactamases and β-lactam antibiotics serves as an illustration of how antibiotics and antibiotic resistance compete with each other. β-Lactamase is active during this process.[40]

In addition, bacterial activity can effectively be inhibited by targeting the cytoplasmic membrane. Repairing damaged membranes is usually very challenging. Through electrostatic interactions with cell membranes and hydrophobic bonding with lipid tails, which results in membrane lysis, cationic polymers inhibit various bacteria. Bacterial replication is based on DNA synthesis, and both processes are negatively affected by DNA damage. In addition, bacterial ribosomes are the site of protein synthesis, which makes them targets for inhibition by inhibitory compounds.[41]

Antibiofilms

Biofilms are multimicrobial colonies enclosed in a polymeric matrix attached to biotic or abiotic surfaces. Depending on the microbial species and environment, biofilms can be beneficial or detrimental to humans. According to the National Institutes of Health, more than 75% of microbial infections that occur in the body are triggered by biofilm formation and preservation.[42] Interference interactions have encouraged the design of alternative antibiotics to kill pathogenic bacteria.[43] Biofilms produced by bacteria can protect the latter from host defenses, as well as neutralize pH and temperature extremes. Biofilm cells can separate themselves and join other matrix systems, which makes it more difficult to suppress the population of biofilm-constituent cells compared to non-biofilm bacteria.[44]

Plaque biofilms are linked to a number of factors that lead to gum inflammation. These include the production and release of acids, which lower the pH of the surrounding environment and promote the growth of gram-negative microorganisms; acid tolerance, which is characteristic of obligate anaerobes; and the formation of intra- and extracellular polysaccharides.[45] These environmental changes cause an ecological shift, with Gram-negative microorganisms dominating and inflammatory components emerging. There is then a proliferation of microbes in the plaque community. Microbial flora mobilize when nutrients are available in the gingival crevice. This is the first stage of the inflammatory reaction, which, if left untreated, will lead to gingival inflammation.[46]

Antibacterial Mechanisms

In Indonesia, much research has been conducted on natural ingredients. This is motivated by the many active ingredients derived from secondary metabolism in plants, which have many health benefits. One of these benefits is found in nutrient-dense plants that have anti-bacterial, anti-cancer, and hypotensive properties and are inhibitors of fungal and bacterial activity.[47] Around the world, herbal-based alternative medicines are used to treat toxicity and similar disorders.[48,49] The antioxidant and non-derived radical scavenging properties of herbal medicines are beneficial to all organs, as they increase their strength and stability and stimulate organ regeneration and protection.[50] It is now more common to use herbal extracts in complementary and alternative medicine, and many plants that have traditional medical benefits have become common as alternative medicine in marketplace. Among these is *Moringa oleifera*, a plant which grows in many tropical and subtropical regions; it is very rich in nutrients and has pleiotropic medicinal properties.

Moringa oleifera and Its Application as Herbal Medicine

Moringa oleifera

Moringa oleifera Lam is an important medicinal plant that belongs to the Moringaceae family.[51] *M. oleifera* is a plant distributed in tropical and subtropic regions.[52] *M. oleifera* has 13 species that are widely used and well known in most parts of Asia and Africa.[53] *M oleifera* grows well at temperatures of 25–35 °C and can even survive the high temperatures that occur in tropical countries.[54] Moringa leaves are widely used in food and medicine, but few clinical trial studies have shown them to be effective in treatment. Moringa seed oil, which has a high oleic acid content (72%), is utilized as an alternative medicine.[55] There are many studies on the therapeutic benefits of moringa leaves,[56] which, in addition to their nutritional value, exhibit anti-inflammatory, anti-fibrotic, antimicrobial, anti-oxidant, anti-hyperglycemic, and anti-tumor properties.[57] Various parts of the moringa plant, including its leaves, seeds, stems, roots, and flowers, are used to produce various food products and medicines.[58,59] Research on the application of plants and extractions to oral health is still lacking, but in fact, derivatives of these plants have been included in several toothpaste and mouthwash formulations.[55]

Ethnomedicines

People have consumed *M. oleifera* in their diets for thousands of years due to its medicinal properties. For centuries, the plant has been used to make a wide variety of medicines that are considered to have ethnomedicinal properties in the treatment of disease. The leaves, pods, bark, sap, flowers, seeds, seed oil, and roots of this plant have been used to treat a wide range of diseases.[60] *M. oleifera* is used for its antihypertensive,[61] anti-anxiety, and anti-diarrheal[62] properties in pathological conditions. In addition, colitis[63] and dysentery can be treated with moringa. An effective treatment for inflammatory diseases, such as glandular inflammation, headaches, and bronchitis, is a poultice made from moringa leaves.[64] The pods are used to treat hepatitis and relieve joint pain.[65] The roots are commonly used to treat kidney stones,[66] liver disease,[67] inflammation,[68] ulcers,[69] and tooth and ear pain.[70] The bark can be used to treat wounds and skin infections.

Pharmacology

The people of Dakshin Kannada use *M. oleifera*, along with other herbs, to maintain their oral hygiene.[71] In addition, it is known that *M. oleifera* can remineralize enamel and dentin in patients with tooth wasting and erosion.[72] Furthermore, the efficacy of *M. oleifera* as an antimicrobial agent to prevent oral diseases has been demonstrated. In a similar vein, honey and *Quercus infectoria* have also exhibited antimicrobial properties against *S. mutans*.[73,74,75,76] The applications of *M. oleifera* in dentistry are shown in Table 1.

Moringa oleifera Pharmacology

Recent pharmacological studies have shown that extracts of different types of *M. oleifera* possess a wide range of pharmacological properties. These include antimicrobial,[59] antifungal,[74] anti-inflammatory,[54] antioxidant,[83] anticancer,[84] fertility,[85] wound healing,[86] and other pharmacological properties mentioned in Table 2.

Bioactive Compounds from *Moringa oleifera*

Phenolic Compounds

Many researchers have isolated phenolic compounds from moringa leaves and their bioactivity in in vitro and in vivo studies.[95] Phenolic compounds have mutually distinct chemical structures; these compounds can be found freely (aglycones) or are often attached to sugary groups (glycosides). *M. oleifera* leaves contain 22% more phenolic compounds than *M. peregrina* leaves, indicating that M. oleifera is a better source of bioactive compounds. Among other bioactive substances, phenolic compounds consist of at least 4 lignans, 4 flavonoids, and 3 phenolic acids; their derivatives are shown in Figure 1.[95]

Carbohydrates

Several scientific reports state that vegetative structures have been used to extract carbohydrates from moringa plants.[96] Plants containing carbohydrates can be consumed to prevent or treat various diseases. Moreover, dietary fiber, the indigestible part of the plant cell wall, has antihyperlipidemic and antihypertensive properties. The dietary fiber content in moringa seed flour is very high.

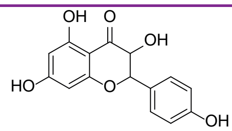
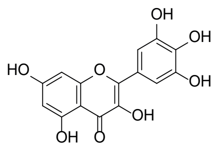
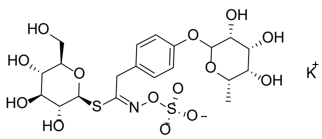
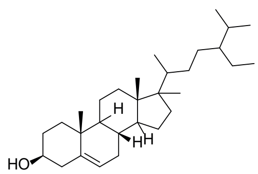
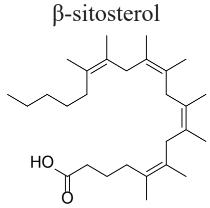
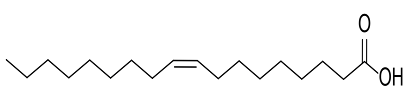
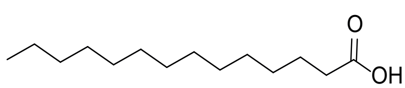
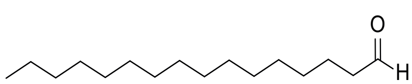
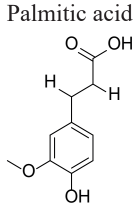
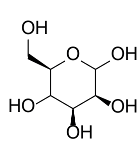
Fat and Protein

It has been reported that moringa seeds and leaves have protein content ranging from 22 to 36.7 grams per 100 grams of dry weight. Previous research has found that moringa seeds and leaves had the highest protein content of all plant parts, with the protein content of moringa stems and leaves being 29.4 and 7.8 grams per 100 grams of dry weight, respectively.[97,98] Studies have documented the presence of protein-based bioactive compounds obtained from moringa plants. These include alkaline peptides ranging in size from 6 to 16 kDa and lectins that exhibit water filtrating binding properties.[99]

Table 1. ***Moringa oleifera*** **Applications in Dentistry**

No.	Object of Study	Applications	References
1	To evaluate the antibacterial activity of *M. oleifera* compounds against oral bacteria	Compounds isolated from *M. oleifera* were active against *Streptococcus mutans* (MTCC 497), *Streptococcus salivarius, Lactobacillus fermentum, Streptococcus anginosus, Streptococcus gordonii,* and *Lactobacillus acidophilus.*	[71]
2	Assessing the antibacterial effect of *M. oleifera* extract as an irrigation solution against *E. faecalis*	*M. oleifera* extract at concentrations of 75% and 100% were as effective as 5.25% NaOCl against *E. faecalis.*	[77]
3	Making a safe mouthwash using *M. oleifera*	*M. oleifera* extract has demonstrated antibacterial and antiplaque properties.	[78]
4	To study the effectiveness of an *M. oleifera*-based paste to increase human dental calcium levels	The results of this study showed that an *M. oleifera* paste induced higher calcium levels post- versus pre-test and that an *M. oleifera* paste was thus effective for increasing calcium levels in human teeth.	[79]
5	To examine and compare the effects of *M. oleifera*, black tea, and green tea on artificially demineralized dentin and enamel	*M. oleifera* had the highest mean value on dentin. According to the research findings, moringa enhances the remineralization process and can therefore be a useful natural remineralizing agent.	[80]
6	To show that *Azadirachta indica* and *M. oleifera* are useful for treating gingivitis and oral health.	The authors stated that accumulative reduction percentages of *Staphylococcus* spp. and *Candida* spp. were found, demonstrating that the herbal mouthwash reduced gingival index and plaque, and indicating the possibility of using the herbal mouthwash as an oral health care product.	[81]
7	To evaluate the antimicrobial properties of *M. oleifera* leaf extracts	The extract showed antibacterial activity against *S. mutans* and prevented cariogenic biofilm formation.	[82]

Table 2. ***Moringa oleifera*** **pharmacology**

Compound structures	Bioactivity	References
 Isorhamnetin	Antioxidants	[87]
 Myricetin	Antioxidants	[88]
 Glucomoringin	Anti-inflammatory, antioxidant, antihypertensive	[89]
 β-sitosterol	Anti-inflammatory	[90]
 Arachidic acid	Increases milk production	[91]
 Oleic acid	Lowers blood pressure and reduces free radical damage to cells	[91]
 Myristic acid	Anxiolytic effect, used in membrane localization of enzymes	[14]
 Palmitic acid	Anti-leukemic	[92]
 Ferulic acid	Cardioprotective, anticancer, anti-inflammatory, antioxidant	[93]
 D-mannose	Treatment for acute urinary tract infection	[94]

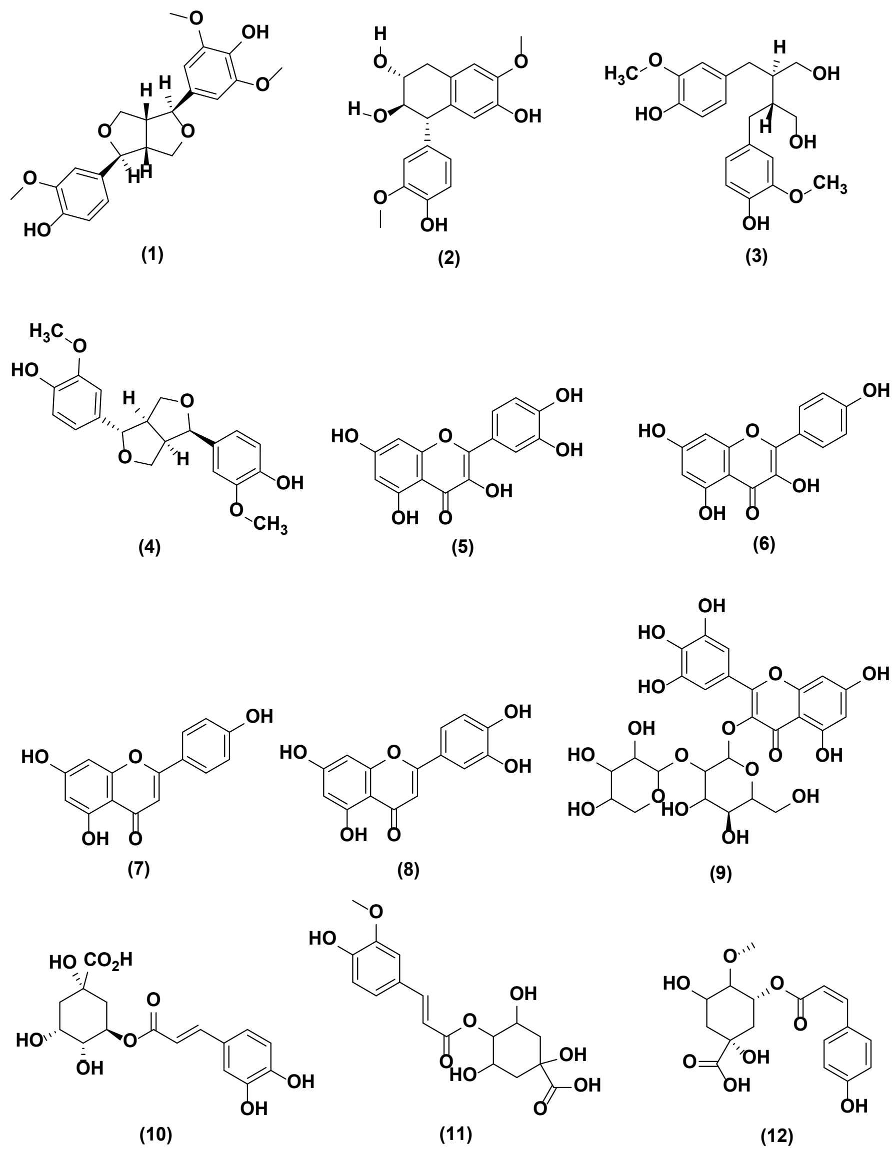


Figure 1. Phenolic compounds: (1) medioresinol; (2) isolariciresinol 9′-β-D-glucopyranoside; (3) secoisolariciresinol; (4) pinoresinol; (5) quercetin; (6) dihydrokempferol; (7) naringenin; (8) 3-O- galactopyranoside ; (9) linariifolioside; (10) chlorogenic acid; (11) 3-feruloylquinic acid; (12) pyridine-3-carboxamide

With moringa plants, it is important to consider protein content and diversity, as this group can include peptides and proteins with a wide range of bioactivities and applications in human nutrition and industrial processes, acting as antioxidants, antidiabetics, antihypertensives, antimicrobials, and caseinolytic agents.[100

Physicochemicals

Moringa seed oil, known for its applications in food manufacturing and its nutritional benefits for human health, has physicochemical characteristics comparable to other vegetable oils. Fatty acids are the main components of moringa oil, especially oleic, palmitic, heptadecanoic, stearic, arachidic, linoleic, linolenic, eicosenoic, and behenate acids.[97,101–103] Unsaturated fatty acids, such as palmitoleic, oleic, and eicosenoic acids, are present in the largest amounts in at least six moringa plant species.[104] Oleic acid is the most abundant unsaturated acid in *M. oleifera* (73.5%) and *M. peregrina* (74.3%) seed oils, which can be a healthy alternative to partially hydrogenated vegetable oils.[102,103]

Antibacterial Activity of *Moringa oleifera L.*

Numerous studies have been conducted to assess the antimicrobial activity of moringa species, yielding the finding that extracts from different parts of the *M. oleif-*

era plant, such as seeds, stem bark, leaves, and root bark, have antimicrobial potential.[71] For example, the growth, survival, and cell permeability of several species of pathogenic bacteria were inhibited by water-soluble lectins derived from *M. oleifera* seed extracts.[105] In addition, it has been reported that *M. oleifera* root extract contains pterygospermin, an active antibiotic with strong antibacterial and fungicidal properties.[71] The antibacterial and antifungal properties of ethanol extract of *M. oleifera* root bark were attributed to deoxy-niazimicin aglycone derived from the chloroform fraction.[106] The active compound components of *M. oleifera* plants have been confirmed to have antimicrobial properties, as they were able to stop the activity of several microorganisms. In a recent study, researchers found that bacteria and pathogens such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* could be inhibited using an aqueous extract of *M. oleifera* plants.[107] The antibacterial activities are shown in Table 3.

Table 3. Antibacterial Activity of Several Active Compounds from *Moringa oleifera*

No	Active Compounds	Bioactivity	References
1	Pterygospermin	Antibacterial and fungicide	[108]
2	4-(4′-O-acetyl-α-Lrhamnopyranosyloxy) benzyl isothiocyanate, 4-(α-Lrhamnopyranosyloxy) benzyl isocyanate, niazimicin, benzyl isocyanate and 4-(α-Lrhamnopyranosyloxy) benzyl glucosinolate, and Sspirochin	Antibacterial	[109]
3	Moringin alkaloids	Antifertility	[110]
4	Nitril, glycoside mustard oil and thiocarbamate glycosides	Anti-hypertension	[111]
5	β-sitosterol	Anti-cholesterol	[112]
6	Polifenol	Hypoglycemic effect	[112]
7	Quercetin and kaempferol	Antioxidant and hepatoprotective	[113]

Conclusion

This review revealed that the *M. oleifera* plant has great potential for drug development applications, both as a candidate for herbal medicines and as a raw material for the production of pharmaceuticals. *M. oleifera* is known to have a large number of secondary metabolites that influence antibacterial activity. It has been researched for use in dental treatment as an irrigation solution against *E. faecalis* and as a mouthwash, and it has been evaluated for its antibacterial effects in vitro. This bioactivity is related to the function of the group of compounds in *M. oleifera* that prevent the growth of bacteria in the oral cavity that cause infection.

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Potential of Moringa oleifera as an Antibacterial in Root Canal and Tooth Surface Disease: A Comprehensive Review

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Review Article

Potential of *Moringa oleifera* as an Antibacterial in Root Canal and Tooth Surface Disease: A Comprehensive Review

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ABSTRACT

Moringa oleifera is a widespread plant in Southeast Asia, especially Indonesia. Moringa leaves are known to contain bioactive compounds Polyphenol, quercetin, tannin, and saponin compounds in moringa leaves exhibit anti-inflammatory, antidiabetic, and antibacterial activity. However, the potential of moringa leaf extracts as antibacterials needs to be tested in silico and in vitro to determine the suitability of specific bioactive compounds. The aim of the present comprehensive review was to assess the antibacterial and antibiofilmic potential of *Moringa oleifera* leaves in root canal disease and on tooth surfaces. The findings of this review indicate that the *M. oleifera* plant holds significant promise for drug development purposes, serving as a viable option for herbal remedies and as a foundational resource for pharmaceutical synthesis

Keywords: *antibacterial, bioactive compound, Moringa oleifera*

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Background

Dental disease remains a common problem suffered by humans of all ages.[1] The types of dental diseases caused by oral bacteria include tooth decay and periodontitis. Various types of pathogenic bacteria can cause oral infections, including fungi, viruses, and bacteria. Pathogenic bacteria, such as *Streptococcus mutans, Streptococcus sanguinis,* and *Enterococcus faecalis,* are common bacteria in the community and cause oral infections, including dental caries.[2,3] In addition, the growth of acid-producing microbial biofilms infects enamel and dentin.[4]

Certain bacteria, such as those named above, are associated with periodontitis and caries, and these bacteria collectively cause dental infections.[5] *S. mutans* and *S. sanguinis* play key roles in causing dental plaque. These cariogenic bacteria cause tooth demineralization and the onset of carious lesions on the teeth by fermenting sugars and producing lactic acid.[6] Among the oral bacteria that can cause root canal infections is *E. faecalis*. This pathogen can reside not only in saliva but also in root canals.[7] Conditions, such as low pH, high temperature, and high salinity enable *E. faecalis* to survive and form a biofilm,[8] consequently allowing an infection that can penetrate the dentinal tubules.[9]

In 2017, the number of dental caries in permanent teeth per 100,000 population in each country ranged from 20% to more than 50%. In this context, the dental caries rate in Indonesia in 2018 was 88.8%, with 56.6% of the total caries consisting of root caries, which were found in 92.6% of children between the ages of 5 and 9. According to the World Health Organization (WHO), the most common disease in the oral cavity is dental caries. Dental caries originate from microbial biofilm (plaque) that forms on the surface of the teeth. An estimated 2.4 billion people have permanent dental caries, and 486 million children have caries in primary teeth. Dental caries are a condition of cavities caused by bacteria.[10] Similarly, periodontal diseases are associated with either bacterial or fungal infections and are the cause of primary tooth decay in more than 560 million children. "Periodontal" is a general term used to describe chronic inflammatory conditions in the soft tissues or tissues surrounding the teeth. Periodontal infections are a major cause of tooth loss and can have a negative impact on health.[11]

Infections caused by bacteria can be treated with antibiotics. Antibiotics have long been used to cure various types of dental infections.[12] However, it has been reported that the use of antibiotics can cause side effects and resistance. Some of the antibiotics that have been used to treat dental infections are ampicillin, amoxicillin, penicillin, cefotaxime, cefazolin, methicillin, erythromycin,, lincomycin, clindamycin, and vancomycin, particularly against *S. mutans*. In adults, *S. mutans* exhibits the greatest resistance to amoxicillin (14.8%) and lincomycin (28.7%), while in children, it is resistant to penicillin (27.6%) and vancomycin (42.5%).[13,14] Indonesia is a country of significant biodiversity where many people use local plants for their daily needs and traditional medicine. One of the plants used as an antibacterial drug is *Moringa oleifera* L. Previous studies have shown that moringa or miracle tree plants are a source of nutrients that have medicinal properties.[15,16] Therefore, this review explores the activities of pathogenic bacteria that cause dental infections and the potential of *Moringa oleifera* L. as a natural antibacterial agent to cure dental infections.

Pathogenic Bacteria that Cause Oral Infections

Streptococcus mutans

S. mutans bacteria are responsible for a large number of dental caries. As a formulator of stable extracellular polysaccharides, *S. mutans* has the ability to colonize tooth surfaces at a relatively low level of acidity (pH). Therefore, it plays a very important role in the formation of dental caries. A number of other variables can also affect cariogenicity, such as diet, sucrose, antibiotic use, antiseptic mouthwash, oral hygiene, and oral cavity location.[17] *S. mutans* can form three-dimensional cariogenic biofilms by producing extracellular polysaccharides (EPS) in the extracellular matrix, creating a microenvironment rich in pathogens and carbohydrates.[18] Arginine can be a precursor for protein synthesis and is an important target for post-translational modifications involved in biofilm formation.[19]

Streptococcus sanguinis

S. sanguinis is a facultative anaerobic Gram-positive bacterium that does not produce spores. *S. sanguinis* is associated with oral disease because it is a bacterium that causes tooth decay. However, when fatty buildup or bacteria such as S. sanguinis enter the bloodstream during dental procedures, they can adhere to the heart valves or the endocardium, increasing the risk of infective endocarditis. The initial stage in biofilm formation is the attachment of *S. sanguinis* and other pioneer colonies to macromolecular complexes formed on saliva-coated tooth surfaces.[5] In addition to *S. mutans, S. sanguinis* is an important species in oral biofilm ecology and contributes significantly to biofilm formation.[20] Conversely, *S. sanguinis* bacteria can be beneficial in preventing the growth of *S. mutans* and other anaerobic bacteria that cause periodontal disease. This is achieved through the production of H_2O_2, which can serve as a means to generate additional O_2.[21]

The production of acquired enamel pellicle (AEP) by bacteria is facilitated by their attachment to the tooth surface, enabled by the presence of negatively charged residues and electrostatic interactions with hydrophilic areas present on salivary proteins. Although *S. sanguinis* can attach to the primary mineral in tooth enamel, hydroxyapatite, which is free of saliva, the initial attachment process is most likely to be triggered by the interaction of the streptococcal surface with saliva constituents. Interactions between protein-carbohydrate or protein-protein compounds and receptors on the bacterial surface mediate the salivary protein binding mechanism.[22] Dental plaque and AEP contain amylase, the most common salivary protein, which is bound by *S. sanguinis* exclusively through long filamentous pili.[23,24]

Enterococcus faecalis

E. faecalis is a facultative anaerobic Gram-positive bacterium. *E. faecalis* can form biofilms that allow bacteria to survive antibodies and antibacterials.[25] *E. faecalis* bacteria are the most common in recurrent root canal infections; their ability to invade the dentinal tubules is one of the causes.[26,27] *E. faecalis* is detected as a virulence factor that can survive in extreme environmental conditions and is resistant to several antibacterials in root canal treatment. The prevalence of *E. faecalis* bacteria as a cause of root canal treatment failure reaches 90%.[28,29] One of the reasons that the removal of pathogens such as *E. faecalis* is so difficult is their ability to produce biofilms that adhere to surfaces that exhibit a high level of resistance to planktonic competitors.[30]

Surface adhesin factors include biofilm formation and attachment to body tissue or dentin collagen.[31] The attachment of lipoteichoic acid factors to body tissues triggers the production of cytokines by monocytes, leading to inflammation and drug resistance after root canal therapy. Furthermore, during the inflammatory process, extracellular factors that produce superoxide damage cells and tissues.[32] Extracellular zinc metalloprotase, or gelatinase factor, has the ability to hydrolyze collagen and hyaluronidase enzymes found in dentin and periapical tissues that have been damaged. The final component is the ability to produce toxins and inhibit the growth of other bacteria, specifically cytolysin, AS-48, and bacteriocin.

E. faecalis is a deeply studied biological clue. In several laboratory studies, *E. faecalis* was tested against endodontic treatments; the results showed that *E. faecalis* is highly resistant to antimicrobial drugs. In addition, *E. faecalis* can survive in very harsh environments where there is a lack of nutrients and the alkaline pH reaches 11.5. *E. faecalis* can grow as a biofilm on the root canal wall and infect itself in root canal treatment without the help of other bacteria. This makes this pathogen highly resistant to antimicrobials.[33,34] Three studies have discussed treatment methods to reduce or eliminate *E. faecalis* from root canals and periradicular areas.[35] As other pathogenic bacteria, the treatment and prevention of *E. faecalis*,is usually involving antibiotics. One study [36] employed antimicrobial agents with strong antibacterial properties to fight *E. faecalis*.

Antibacterials and Antibiofilms

Antibacterials

Antibacterials are compounds that have the ability to inhibit and eliminate harmful bacteria. Antibacterials fall into two categories: bacteriostatic (which inhibit bacterial growth) and bactericidal (which kill bacteria). The antibacterial used must have selective toxicity to microbes but not be toxic to the host.[37] Many synthetic pathways, such as those of protein biosynthesis, transcription, DNA replication, and bacterial cell wall biogenesis, are involved in bacterial inhibition.[38] During bacterial cell death, the peptidoglycan layer is destroyed.

Glycopeptides and β-lactam antibiotics both target pathways involved in peptidoglycan synthesis.[39] However, some bacteria have now developed various defense mechanisms against antibiotic attacks. These defense mechanisms involve either direct bacterial damage or structural modification of the antibiotic to prevent growth inhibition and allow the bacteria to survive. One way to combat antibiotic resistance is through enzymatic modification and degradation. This process, which has defeated resistance to several classes of antibiotics, such as β-lactam antibiotics and aminoglycosides, is an effective way to overcome antibiotic resistance. Some antibiotics have been shown to be inactivated by the hydrolysis process, which is carried out by a wide variety of hydraulics. The co-evolution of β-lactamases and β-lactam antibiotics serves as an illustration of how antibiotics and antibiotic resistance compete with each other. β-Lactamase is active during this process.[40]

In addition, bacterial activity can effectively be inhibited by targeting the cytoplasmic membrane. Repairing damaged membranes is usually very challenging. Through electrostatic interactions with cell membranes and hydrophobic bonding with lipid tails, which results in membrane lysis, cationic polymers inhibit various bacteria. Bacterial replication is based on DNA synthesis, and both processes are negatively affected by DNA damage. In addition, bacterial ribosomes are the site of protein synthesis, which makes them targets for inhibition by inhibitory compounds.[41]

Antibiofilms

Biofilms are multimicrobial colonies enclosed in a polymeric matrix attached to biotic or abiotic surfaces. Depending on the microbial species and environment, biofilms can be beneficial or detrimental to humans. According to the National Institutes of Health, more than 75% of microbial infections that occur in the body are triggered by biofilm formation and preservation.[42] Interference interactions have encouraged the design of alternative antibiotics to kill pathogenic bacteria.[43] Biofilms produced by bacteria can protect the latter from host defenses, as well as neutralize pH and temperature extremes. Biofilm cells can separate themselves and join other matrix systems, which makes it more difficult to suppress the population of biofilm-constituent cells compared to non-biofilm bacteria.[44]

Plaque biofilms are linked to a number of factors that lead to gum inflammation. These include the production and release of acids, which lower the pH of the surrounding environment and promote the growth of gram-negative microorganisms; acid tolerance, which is characteristic of obligate anaerobes; and the formation of intra- and extracellular polysaccharides.[45] These environmental changes cause an ecological shift, with Gram-negative microorganisms dominating and inflammatory components emerging. There is then a proliferation of microbes in the plaque community. Microbial flora mobilize when nutrients are available in the gingival crevice. This is the first stage of the inflammatory reaction, which, if left untreated, will lead to gingival inflammation.[46]

Antibacterial Mechanisms

In Indonesia, much research has been conducted on natural ingredients. This is motivated by the many active ingredients derived from secondary metabolism in plants, which have many health benefits. One of these benefits is found in nutrient-dense plants that have anti-bacterial, anti-cancer, and hypotensive properties and are inhibitors of fungal and bacterial activity.[47] Around the world, herbal-based alternative medicines are used to treat toxicity and similar disorders.[48,49] The antioxidant and non-derived radical scavenging properties of herbal medicines are beneficial to all organs, as they increase their strength and stability and stimulate organ regeneration and protection.[50] It is now more common to use herbal extracts in complementary and alternative medicine, and many plants that have traditional medical benefits have become common as alternative medicine in marketplace. Among these is *Moringa oleifera*, a plant which grows in many tropical and subtropical regions; it is very rich in nutrients and has pleiotropic medicinal properties.

Moringa oleifera and Its Application as Herbal Medicine

Moringa oleifera

Moringa oleifera Lam is an important medicinal plant that belongs to the Moringaceae family.[51] *M. oleifera* is a plant distributed in tropical and subtropic regions.[52] *M. oleifera* has 13 species that are widely used and well known in most parts of Asia and Africa.[53] *M oleifera* grows well at temperatures of 25–35 °C and can even survive the high temperatures that occur in tropical countries.[54] Moringa leaves are widely used in food and medicine, but few clinical trial studies have shown them to be effective in treatment. Moringa seed oil, which has a high oleic acid content (72%), is utilized as an alternative medicine.[55] There are many studies on the therapeutic benefits of moringa leaves,[56] which, in addition to their nutritional value, exhibit anti-inflammatory, anti-fibrotic, antimicrobial, anti-oxidant, anti-hyperglycemic, and anti-tumor properties.[57] Various parts of the moringa plant, including its leaves, seeds, stems, roots, and flowers, are used to produce various food products and medicines.[58,59] Research on the application of plants and extractions to oral health is still lacking, but in fact, derivatives of these plants have been included in several toothpaste and mouthwash formulations.[55]

Ethnomedicines

People have consumed *M. oleifera* in their diets for thousands of years due to its medicinal properties. For centuries, the plant has been used to make a wide variety of medicines that are considered to have ethnomedicinal properties in the treatment of disease. The leaves, pods, bark, sap, flowers, seeds, seed oil, and roots of this plant have been used to treat a wide range of diseases.[60] *M. oleifera* is used for its antihypertensive,[61] anti-anxiety, and anti-diarrheal[62] properties in pathological conditions. In addition, colitis[63] and dysentery can be treated with moringa. An effective treatment for inflammatory diseases, such as glandular inflammation, headaches, and bronchitis, is a poultice made from moringa leaves.[64] The pods are used to treat hepatitis and relieve joint pain.[65] The roots are commonly used to treat kidney stones,[66] liver disease,[67] inflammation,[68] ulcers,[69] and tooth and ear pain.[70] The bark can be used to treat wounds and skin infections.

Pharmacology

The people of Dakshin Kannada use *M. oleifera*, along with other herbs, to maintain their oral hygiene.[71] In addition, it is known that *M. oleifera* can remineralize enamel and dentin in patients with tooth wasting and erosion.[72] Furthermore, the efficacy of *M. oleifera* as an antimicrobial agent to prevent oral diseases has been demonstrated. In a similar vein, honey and *Quercus infectoria* have also exhibited antimicrobial properties against *S. mutans*.[73,74,75,76] The applications of *M. oleifera* in dentistry are shown in Table 1.

Moringa oleifera Pharmacology

Recent pharmacological studies have shown that extracts of different types of *M. oleifera* possess a wide range of pharmacological properties. These include antimicrobial,[59] antifungal,[74] anti-inflammatory,[54] antioxidant,[83] anticancer,[84] fertility,[85] wound healing,[86] and other pharmacological properties mentioned in Table 2.

Bioactive Compounds from *Moringa oleifera*

Phenolic Compounds

Many researchers have isolated phenolic compounds from moringa leaves and their bioactivity in in vitro and in vivo studies.[95] Phenolic compounds have mutually distinct chemical structures; these compounds can be found freely (aglycones) or are often attached to sugary groups (glycosides). *M. oleifera* leaves contain 22% more phenolic compounds than *M. peregrina* leaves, indicating that M. oleifera is a better source of bioactive compounds. Among other bioactive substances, phenolic compounds consist of at least 4 lignans, 4 flavonoids, and 3 phenolic acids; their derivatives are shown in Figure 1.[95]

Carbohydrates

Several scientific reports state that vegetative structures have been used to extract carbohydrates from moringa plants.[96] Plants containing carbohydrates can be consumed to prevent or treat various diseases. Moreover, dietary fiber, the indigestible part of the plant cell wall, has antihyperlipidemic and antihypertensive properties. The dietary fiber content in moringa seed flour is very high.

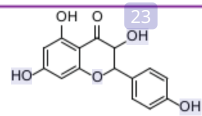
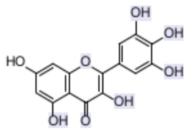
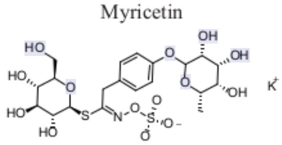
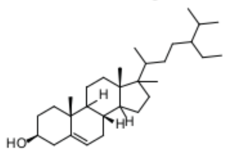
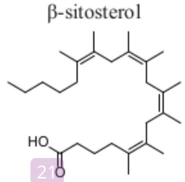
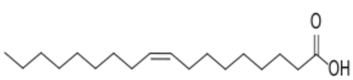
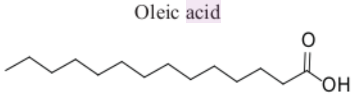
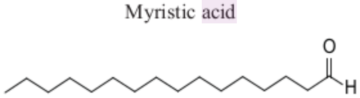
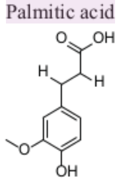
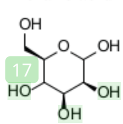
Fat and Protein

It has been reported that moringa seeds and leaves have protein content ranging from 22 to 36.7 grams per 100 grams of dry weight. Previous research has found that moringa seeds and leaves had the highest protein content of all plant parts, with the protein content of moringa stems and leaves being 29.4 and 7.8 grams per 100 grams of dry weight, respectively.[97,98] Studies have documented the presence of protein-based bioactive compounds obtained from moringa plants. These include alkaline peptides ranging in size from 6 to 16 kDa and lectins that exhibit water filtrating binding properties.[99]

Table 1. ***Moringa oleifera*** **Applications in Dentistry**

No.	Object of Study	Applications	References
1	To evaluate the antibacterial activity of *M. oleifera* compounds against oral bacteria	Compounds isolated from *M. oleifera* were active against *Streptococcus mutans* (MTCC 497), *Streptococcus salivarius, Lactobacillus fermentum, Streptococcus anginosus, Streptococcus gordonii,* and *Lactobacillus acidophilus*.	[71]
2	Assessing the antibacterial effect of *M. oleifera* extract as an irrigation solution against *E. faecalis*	*M. oleifera* extract at concentrations of 75% and 100% were as effective as 5.25% NaOCl against *E. faecalis*.	[77]
3	Making a safe mouthwash using *M. oleifera*	*M. oleifera* extract has demonstrated antibacterial and antiplaque properties.	[78]
4	To study the effectiveness of an *M. oleifera*-based paste to increase human dental calcium levels	The results of this study showed that an *M. oleifera* paste induced higher calcium levels post- versus pre-test and that an *M. oleifera* paste was thus effective for increasing calcium levels in human teeth.	[79]
5	To examine and compare the effects of *M. oleifera*, black tea, and green tea on artificially demineralized dentin and enamel	*M. oleifera* had the highest mean value on dentin. According to the research findings, moringa enhances the remineralization process and can therefore be a useful natural remineralizing agent.	[80]
6	To show that *Azadirachta indica* and *M. oleifera* are useful for treating gingivitis and oral health.	The authors stated that accumulative reduction percentages of *Staphylococcus* spp. and *Candida* spp. were found, demonstrating that the herbal mouthwash reduced gingival index and plaque, and indicating the possibility of using the herbal mouthwash as an oral health care product.	[81]
7	To evaluate the antimicrobial properties of *M. oleifera* leaf extracts	The extract showed antibacterial activity against *S. mutans* and prevented cariogenic biofilm formation.	[82]

Table 2. ***Moringa oleifera*** **pharmacology**

Compound structures	Bioactivity	References
 Isorhamnetin	Antioxidants	[87]
 Myricetin	Antioxidants	[88]
 Glucomoringin	Anti-inflammatory, antioxidant, antihypertensive	[89]
 β-sitosterol	Anti-inflammatory	[90]
 Arachidic acid	Increases milk production	[91]
 Oleic acid	Lowers blood pressure and reduces free radical damage to cells	[91]
 Myristic acid	Anxiolytic effect, used in membrane localization of enzymes	[14]
 Palmitic acid	Anti-leukemic	[92]
 Ferulic acid	Cardioprotective, anticancer, anti-inflammatory, antioxidant	[93]
 D-mannose	Treatment for acute urinary tract infection	[94]

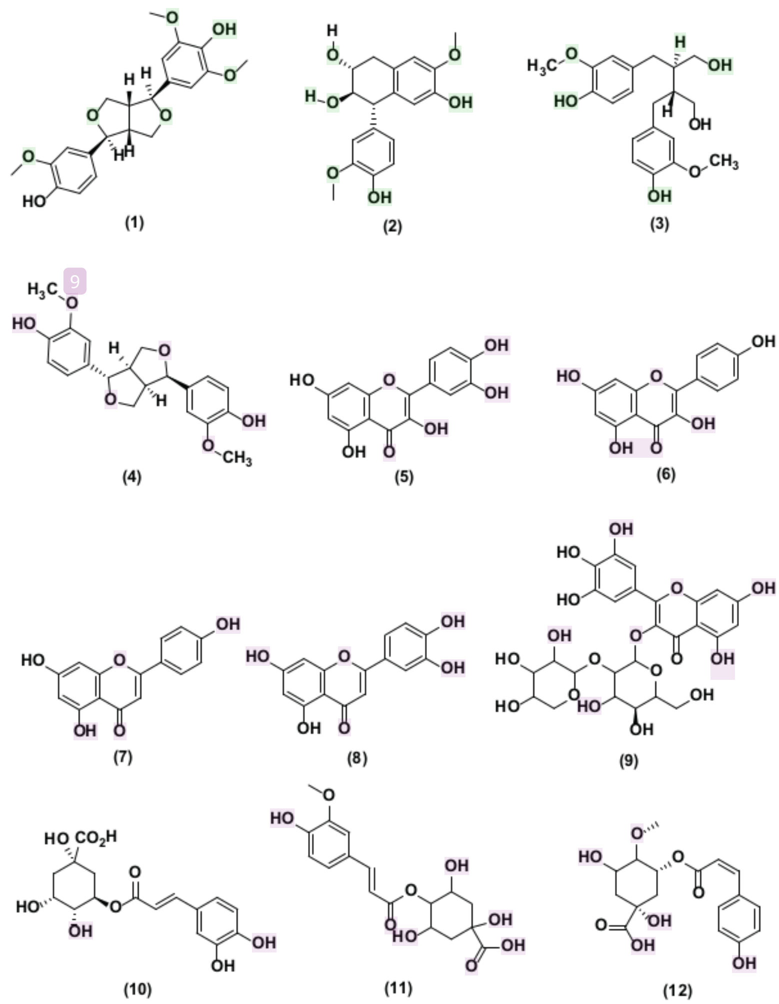


Figure 1. Phenolic compounds: (1) medioresinol; (2) isolariciresinol 9′-β-D-glucopyranoside; (3) secoisolariciresinol; (4) pinoresinol; (5) quercetin; (6) dihydrokempferol; (7) naringenin; (8) 3-O- galactopyranoside ; (9) linariifolioside; (10) chlorogenic acid; (11) 3-feruloylquinic acid; (12) pyridine-3-carboxamide

With moringa plants, it is important to consider protein content and diversity, as this group can include peptides and proteins with a wide range of bioactivities and applications in human nutrition and industrial processes, acting as antioxidants, antidiabetics, antihypertensives, antimicrobials, and caseinolytic agents.[100

Physicochemicals

Moringa seed oil, known for its applications in food manufacturing and its nutritional benefits for human health, has physicochemical characteristics comparable to other vegetable oils. Fatty acids are the main components of moringa oil, especially oleic, palmitic, heptadecanoic, stearic, arachidic, linoleic, linolenic, eicosenoic, and behenate acids.[97,101–103] Unsaturated fatty acids, such as palmitoleic, oleic, and eicosenoic acids, are present in the largest amounts in at least six moringa plant species.[104] Oleic acid is the most abundant unsaturated acid in *M. oleifera* (73.5%) and *M. peregrina* (74.3%) seed oils, which can be a healthy alternative to partially hydrogenated vegetable oils.[102,103]

Antibacterial Activity of *Moringa oleifera L.*

Numerous studies have been conducted to assess the antimicrobial activity of moringa species, yielding the finding that extracts from different parts of the *M. oleif-*

era plant, such as seeds, stem bark, leaves, and root bark, have antimicrobial potential.[71] For example, the growth, survival, and cell permeability of several species of pathogenic bacteria were inhibited by water-soluble lectins derived from *M. oleifera* seed extracts.[105] In addition, it has been reported that *M. oleifera* root extract contains pterygospermin, an active antibiotic with strong antibacterial and fungicidal properties.[71] The antibacterial and antifungal properties of ethanol extract of *M. oleifera* root bark were attributed to deoxy-niazimicin aglycone derived from the chloroform fraction.[106] The active compound components of *M. oleifera* plants have been confirmed to have antimicrobial properties, as they were able to stop the activity of several microorganisms. In a recent study, researchers found that bacteria and pathogens such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* could be inhibited using an aqueous extract of *M. oleifera* plants.[107] The antibacterial activities are shown in Table 3.

Table 3. Antibacterial Activity of Several Active Compounds from *Moringa oleifera*

No	Active Compounds	Bioactivity	References
1	Pterygospermin	Antibacterial and fungicide	[108]
2	4-(4′-O-acetyl-α-Lrhamnopyranosyloxy) benzyl isothiocyanate, 4-(α-Lrhamnopyranosyloxy) benzyl isocyanate, niazimicin, benzyl isocyanate and 4-(α-Lrhamnopyranosyloxy) benzyl glucosinolate, and Sspirochin	Antibacterial	[109]
3	Moringin alkaloids	Antifertility	[110]
4	Nitril, glycoside mustard oil and thiocarbamate glycosides	Anti-hypertension	[111]
5	β-sitosterol	Anti-cholesterol	[112]
6	Polifenol	Hypoglycemic effect	[112]
7	Quercetin and kaempferol	Antioxidant and hepatoprotective	[113]

Conclusion

This review revealed that the *M. oleifera* plant has great potential for drug development applications, both as a candidate for herbal medicines and as a raw material for the production of pharmaceuticals. *M. oleifera* is known to have a large number of secondary metabolites that influence antibacterial activity. It has been researched for use in dental treatment as an irrigation solution against *E. faecalis* and as a mouthwash, and it has been evaluated for its antibacterial effects in vitro. This bioactivity is related to the function of the group of compounds in *M. oleifera* that prevent the growth of bacteria in the oral cavity that cause infection.

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