Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 20; 10(F):305-313.
https://doi.org/10.3889/oamjms.2022.8894
eISSN: 1857-9655
**Category:** *F - Review Articles*
***Section:*** *Meta-analytic Review Article*



# A review of Leaves and Seeds *Moringa oleifera* Extract: The potential Moringa oleifera as Antibacterial, Anti-Inflammatory, Antidiarrhoeal, And Antiulcer Approaches To Bacterial Gastroenteritis

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**Edited by:** Eli Djulejic
**Citation:** Adji AS, Naufizdihar N, Kusbijantoro YB, Billah A, Zakina A, Handajani F. The Potential *Moringa oleifera* Extract as Antibacterial, Anti-inflammatory, Antidiarrheal, and Antiulcer in Treating Bacterial Gastroenteritis. Open Access Maced J Med Sci. 2022 Apr 20; 10(F):305-313. https://doi.org/10.3889/oamjms.2022.8894
**Keywords:** Diarrhea; Gastroenteritis; Antibacterial; Antiulcer; Anti-Inflammation; *Moringa oleifera*
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**Received**: 04-Feb-2022
**Revised:** 06-Apr-2022
**Accepted:** 10-Apr-2022

**Funding:** This research did not receive any financial support
**Competing Interests:** The authors have declared that no competing interests exist


## Abstract

**BACKGROUND:** Bacterial gastroenteritis is a disease in the tropics in the form of inflammation of the stomach and intestines due to several bacteria, such as *Salmonella, Campylobacter, Shigella, Escherichia coli, Vibrio, Yersinia*, and *Listeria* with symptoms of diarrhea without or with vomiting and frequent fever. Gastroenteritis is a global disease with the highest prevalence in the agricultural community, especially farmers and fishermen.

**AIM:** This research is to determine the potential of leaf and seed extract *Moringa oleifera* as an alternative therapy for bacterial gastroenteritis.

**METHODS:** A literature review approach derived from the analysis and synthesis of various related references is used. The author selects journals full text and books published in the last ten years maximum through several databases, namely PubMed, Google Scholar, ScienceDirect, and Cochrane with the keywords: diarrhea, gastroenteritis, antibacterial, antiulcer, anti-inflammation, and *M. oleifera*.

**RESULTS:** Seed and leaf extract *M. oleifera* played a role in preventing some of the effects of the pathogenesis of diarrhea due to bacterial infection. Methanol, N-hexane, ethyl acetate, flavonoids, phenols, saponins, alkaloids, tannins, and steroids from seed and leaf extract *M. oleifera* have antibacterial effects. The content of quercetin has an anti-inflammatory effect. The content of tannins, flavonoids, and alkaloids has antidiarrheal activity. The content of ethanol and tannins has an antiulcer effect. This potential can help cure patients with bacterial gastroenteritis.

**CONCLUSION:** Leaf and seed extract of *M. oleifera* has good antibacterial, anti-inflammatory, antiulcer, and antidiarrheal potential for the treatment of bacterial gastroenteritis.

## Introduction

Gastroenteritis is one of the most serious health problems caused by infectious diseases around the world. It is one of the most common infectious diseases among humans and a leading cause of death in low- and middle-income countries. Diarrhea, vomiting, and abdominal pain are the most common symptoms of gastroenteritis. Patients may also experience fever, fatigue, and lack of energy, depending on the underlying cause [1], [2], [3].

Gastroenteritis can be caused by bacteria, viruses, and parasites [2]. Bacteria, as we will discuss in this review, are responsible for approximately 20%–40% of diarrheal episodes in the UK. However, they are more likely to contribute significantly in developing regions, where the burden of diarrheal disease is associated with higher mortality [3]. Bacteria are also more responsible for severe cases of diarrhea. It was found that among adults diagnosed with severe diarrhea, where the stools were in liquid form for more than three days, 87% of cases were caused by pathogenic bacteria. These bacteria include Salmonella (15.4%), Campylobacter (11.8%), Shigella (4.6%), Shiga toxin produced by *Escherichia coli* (2.8%), Vibrio (0.45%), Yersinia (0.42%), and Listeria (0.26%) [1]. These bacteria can enter the body through contamination of food due to lack of hygiene during food preparation, lack of cleanliness of cutlery, or not washing hands with soap before eating [4].

Gastroenteritis is a global disease with 1.5–2.5 million deaths per year. Based on Indonesia's 2019 health profile, diarrhea is an endemic disease with the potential to become an extraordinary event which is often accompanied by death in Indonesia. Diarrhea and gastroenteritis are the most common diseases that cause hospitalization. The prevalence is most common in rural areas where people work as farmers. Lack of knowledge and concern for healthy living behavior is the reason for the high prevalence of gastroenteritis [2], [3], [4]

According to data from the Indonesian Ministry of Health, the percentage of gastritis in Indonesia is 40.8%. The incidence of gastritis in several areas in Indonesia

itself is quite high, with a prevalence of 274,396 cases among 238,452,952 residents, and gastritis is included in one of the 10 most common diseases among hospitalized patients in Indonesia as much as 4.9%, or 30,154 cases. However, inappropriate antimicrobial usage, poor infection control, and the rise of antibiotic-resistant pathogenic bacteria are making antibiotic therapy increasingly ineffective [3]. The existence of antibiotic resistance is also a problem that must be faced by Indonesia. For this reason, alternative therapies are needed to treat bacterial gastroenteritis. One of them is using plant-derived medicines which are considered relatively safer than synthetic alternatives [5], [6].

The use of plants in medicine, or known as phytomedicine, is still trusted and widely applied as an alternative in the field of medicine because of its affordable price. Therefore, in developing countries such as Cameroon Africa, 80% of the population uses herbal medicine because plant-based medicines are available and inexpensive for rural communities [7], [8].

According to the World Health Organization (WHO), traditional medicine is used by more than 80% of the world's population for primary healthcare [9]. Moringa plants are widely used by the community as food and also as medicine because the entire tree structure has many benefits. It has earned the nickname "miracle tree" among ordinary people due to its amazing healing abilities for a variety of ailments and even some chronic diseases. *Moringa oleifera* is also used in traditional medicine to treat patients in cases of ulcers, inflammation, and diarrhea. It contains bioactive components found in natural medicinal plants that have anti-infectious properties. Alkaloids, flavonoids, tannins, and phenolic compounds are the most important bioactive molecules found in *M. oleifera* [9], [10]. It also contains glucosinolate and isothiocyanate, which prevent bacterial conjugation and so reduce bacterial pathogenicity. In the removal of microorganisms, niaziminin, kaempferol, rhamnetin, and isoquercitrin had a direct favorable effect [11], [12]. The bacterial activity is summarized in Table 6.

*M. oleifera* plants can grow well in humid tropics or hot dry land, and can survive in less fertile soils, as well as dry. In Indonesia, *M. oleifera* is known as the Moringa plant. *M. oleifera* (*Moringaceae*) is used to treat people with ulcers, inflammation, and diarrhea because it contains a promising source of antibacterial biomolecules. In this study, the authors chose to review articles on *M. oleifera* seed and leaf extract to determine its potential as an alternative treatment for bacterial gastroenteritis [13], [14].

## Methods

This study is a literature review approach based on full-text journals and books related to diarrhea, gastroenteritis, and *M. oleifera* published between 2011 and 2021 in several databases, namely PubMed, Google Scholar, Science Direct, and Cochrane with the keywords: diarrhea, gastroenteritis, and *M. oleifera* using a foreign language other than English. Based on these criteria, we used 36 references in making a literature review of the potential of *M. oleifera* extract to treat bacterial gastroenteritis.

## Results and Discussion

### *Definition and pathophysiology of bacterial gastroenteritis*

Gastroenteritis is derived from the Greek words gastron, which means "stomach," and enteron, which means "small intestine." "Inflammation of the stomach and small intestine" is what the term "gastroenteritis" refers to. Gastroenteritis is a diarrheal condition, or an increase in bowel movement frequency with or without vomiting, fever, and stomach discomfort, according to medical definition. While bacterial gastroenteritis is usually self-limiting, individuals with severe or protracted diarrhea, symptoms suggestive of invasive illness, or a history suggesting a complex course of disease should have an etiological agent identified by bacterial stool culture [15], [16].

Gastroenteritis can be classified into acute, persistent, chronic, and recurrent gastroenteritis. Acute gastroenteritis is a diarrheal condition that develops quickly and may include nausea, vomiting, fever, or abdominal discomfort with a duration of less than fourteen days. Persistent gastroenteritis occurs if the duration is 14-30 days; chronic gastroenteritis occurs with a duration of more than thirty days, and recurrent gastroenteritis occurs when a patient has diarrhea again after seven days of no relapse [17], [18].

Table 1 shows more types of bacterial gastroenteritis that caused gastroenteritis and is divided into 3 parameters secretory, inflammatory, and invasive gastroenteritis [19].

Different methods, such as adhesion, mucosal invasion, and toxin generation, are used by gut bacteria to cause diarrhea. Pathophysiology and the mechanism of these pathogenic strategies can also help with disease evaluation and management. The small intestines primary job is to absorb fluids. Fluid does not get absorbed adequately in the small intestine, and the activity of several toxins causes the intestinal lining to start excreting fluid, resulting in somewhat loose or watery stools [20], [21].

One of the most critical virulence factors that cause pathology is inoculum size. A minimum of 10–100 bacteria are required to infect Shigella and enterohemorrhagic *E. coli*, whereas one hundred thousand or one million Vibrio cholerae bacteria are required to infect Vibrio cholerae. As a result, the

**Table 1: Types of bacterial gastroenteritis**

| Parameter | Secretory gastroenteritis | Inflammatory gastroenteritis | Invasive gastroenteritis |
|---|---|---|---|
| Location | Proximal small intestine | Colon | Distal small intestine |
| Type of illness | Watery diarrhea | Dysentery | Enteric fever |
| Stool examination | No fecal leukocytes | Fecal polymorphonuclear leukocytes | Fecal mononuclear leukocytes (if patient has diarrhea) |
| Mechanism | Enterotoxin or bacterial adherence/invasion causes a shift in water and electrolyte excretion/adsorption | Bacterial invasion or cytotoxins cause mucosal damage that leads to inflammation | Bacteria penetrate the mucosa and invade the reticuloendothelial system |
| Classic pathogens | *V. cholerae*, ETEC, *C. perfringens*, *B. cereus*, *S. aureus* | *Shigella*, STEC, *Salmonella* (not *Salmonella* Typhi/Paratyphi), *V. parahaemolyticus*, *Clostridium diffificile*, *Campylobacter* | *Salmonella* typhi/Paratyphi, *Yersinia enterocolitica* |

*V. cholera*: *Vibrio cholera*, *C. perfringens*: *Clostridium perfringens*, *B. cereus*: *Bacillus cereus*, *S. aureus*: *Staphylococcus aureus*, *V. parahaemolyticus*: *Vibrio parahaemolyticus*, *C. diffificile*: *Clostridium diffificile*, *Y. enterocolitica*: *Yersinia enterocolitica*, ETEC: Enterotoxigenic Escherichia Coli, STEC: Shigatoxin-producing Escherichia Coli.

infective dosages of different pathogens vary greatly and are dependent on both the host and the bacteria [20].

Another virulence element for intestinal infections is adhesion. Some bacteria require an initial adhesion to the mucosal lining of the gastrointestinal tract. They create a variety of adhesins and other cell-surface proteins that aid in their attachment to intestinal cells. Specific surface adhesins, such as the toxin-coregulated pilus and other supplementary colonization factors, help V. cholerae stick to the brush boundary of small-intestinal enterocytes. The adherence protein colonization factor antigen is produced by enterotoxigenic *E. coli*, which causes watery diarrhea. This is required for the organism to colonize the upper small intestine before producing enterotoxin, which causes disease [22], [23].

Dysentery can be caused by cytotoxin generation as well as bacterial invasion and destruction of intestinal mucosal cells. Infections caused by Shigella and enteroinvasive *E. coli* are defined by the organisms' invasion of mucosal epithelial cells, intraepithelial proliferation, and subsequent dissemination to neighboring cells [23].

**Table 2: *Phytoconstituents* of *Moringa oleifera***

| Phytoconstituents | Part of tree | References |
|---|---|---|
| Flavonoids and flavanol glycosides | | |
| Rutin | Leaves | [24,25] |
| Kaempferol | Leaves | [26] |
| Kaempferol-3-O-glucoside (Astragalin) | Leaves | [24] |
| Kaempferol-3-O-malonylglucoside | Leaves | [25] |
| Quercetin | Leaves | [27] |
| Quercetin-3-O-glucoside (Isoquercetin) | Leaves | [22] |
| Quercetin-3-O-(6″-malonyl-glucoside) | Leaves | [28] |
| Quercetin-3-O-(X″-malonyl) glucoside | Leaves | [27] |
| Myricetin | Leaves | [24] |
| Glucosinolate and isothiocyanate | | |
| Benzyl isothiocyanate | Leaves | [25] |
| 4-hydroxybenzyl (sinalbin) | Leaves | [25] |
| 4-(α-L-rhamnopyranosyloxy)-benzyl glucosinolate | Leaves, seed | [22,24,25] |
| 4 - [(2′ - O - acetyl - α - L - rhamnosyloxy) benzyl] glucosinolate | Leaves | [24,25] |
| 4 - [(3′ - O - acetyl - α - L - rhamnosyloxy) benzyl] glucosinolate | Leaves | [25,26] |
| 4-[(4′-Oacetyl-α-L-rhamnosyloxy) benzyl] isothiocyanate | Leaves | [25,26] |
| 4 - [(2′ - O - acetyl - α - L - rhamnosyloxy) benzyl] isothiocyanate | Leaves | [26] |
| 4-O-(α-L-acetylrhamnopyranosyloxy)-benzyl isomer 1 | Leaves | [26] |
| 4-O-(α-L-acetylrhamnopyranosyloxy)-benzyl isomer 2 | Leaves | [26] |
| 4-O-(α-L-acetylrhamnopyranosyloxy)-benzyl isomer 3 | Leaves | [26] |
| Phenolic acid | | |
| Salicylic acid | Leaves | [25] |
| Gentisic acid | Leaves | [25] |
| Syringic acid | Leaves | [25] |
| Caffeic acid | Leaves | [25] |
| Ortho-Coumaric acid | Leaves | [25] |
| Cryptochlorogenic acid | Leaves | [23] |
| Alkaloid and sterol | | |
| Pterygospermin | Seed, leaves | [26] |
| Niazimicin | Leaves | [26] |
| 3-O-(6′-oleoyl-β-D-glucopyranoyl)-β-sitosterol | Seed | [23,25] |
| β-sitosterol-3-O-β-D-glucopyranoside | Seed | [23] |
| β-sitosterol | Seed | [22] |

**Table 3: Qualitative phytochemical screening of ethanol and aqueous leaf extract of *Moringa oleifera***

| Solvents used for extraction | Alkaloid | Flavonoid | Saponin | Steroid | Tannin | Glycoside | Reducing sugar | Volatile oil |
|---|---|---|---|---|---|---|---|---|
| Ethanol | + | + | + | + | + | ± | − | − |
| Water | + | + | + | + | ± | ± | − | − |

Another significant virulence factor is toxin generation. Enterotoxins, which cause watery diarrhea by directly acting on secretory systems in the intestinal mucosa, and cytotoxins, which damage mucosal cells and cause inflammatory diarrhea, are examples of these toxins [22].

### *Nutrition and phytochemical analysis of Moringa oleifera*

Some of the phytochemical contents of *M. oleifera* were found to be different in each part of the plant, as shown in Table 2 [11], [22], [23], [24], [25], [26], [27], [28], [29]. Table 3 shows the qualitative phytochemical screening result of both aqueous and ethanol extract of *M. oliefera* leaves [28]. It is also important to note that the phytochemical constituent has a role in determining the antibacterial activities of the leaf extract [17], [18]. In another study using qualitative and quantitative phytochemical analysis, *M. oleifera* leaf extract also contains tannins, saponins, phenols, alkaloids, and phlobatannins [26].

Table 4 shows the phytochemical screening result of methanol extract of *M. oliefera* seeds [30]. According to research, medicinal plants with bioactive metabolites such as alkaloids, phenols, and flavonoids have antibacterial capabilities. Several authors have related the existence of bioactive compounds to the antibacterial activities of plant extracts, which explains why medicinal plants are utilized as antimicrobial medications [28], [29].

**Table 4: Phytochemical screening of methanol seed extract of *Moringa oleifera***

| Phytochemicals | Inferences |
|---|---|
| Alkaloids | + |
| Tannins | − |
| Reducing sugar | − |
| Saponins | + |
| Phenols | + |
| Flavonoids | + |

*M. oleifera* extract contains a variety of nutrients summarized in Table 5, including macronutrients, amino acid, and micronutrients [31]. *M. oleifera* are well-known for being a high-protein, easily digestible dietary source.

**Table 5: Nutritional potential *M. oleifera***

| Nutrients | Leaves | Seeds |
|---|---|---|
| Macronutrients *M. oleifera* (g/100 g of plant) | | |
| Proteins | 25.0–30.3 | 29.4–38.3 |
| Lipids | 0.1–10.6 | 30.8–41.2 |
| Carbohydrates | 0.1–43.9 | 0.1–21.1 |
| Fibers | 0.1–28.5 | 0.1–7.2 |
| Amino acids *M. oleifera* (g/100 g) | | |
| Essential | | |
| Arginine | 0.4–1.8 | 4.5 |
| Histidine | 0.1–0.7 | 2.3 |
| Leucine | 0.4–2.2 | 6.7 |
| Lysine | 0.3–1.4 | 1.5 |
| Methionine | 0.1–0.5 | 2.4 |
| Phenylalanine | 0.3–1.6 | 4.0 |
| Threonine | 0.1–1.3 | 3.1 |
| Tryptophan | 0.1–5.2 | 1.6 |
| Valine | 0.4–1.4 | 4.3 |
| Non-Essential | | |
| Alanine | 1.8–3.0 | 6.9 |
| Aspartate | 1.4–2.2 | 5.0 |
| Cysteine | 0.01–0.10 | 2.0 |
| Glutamate | 2.5–2.5 | 20.9 |
| Glycine | 1.3–1.5 | 10.9 |
| Proline | 1.2–1.4 | 4.5 |
| Serine | 1.0–1.2 | 4.4 |
| Tyrosine | 0.01–2.60 | 1.6 |
| Micronutrients *M. oleifera* (mg/100 g of the plant) | | |
| Minerals | | |
| Calcium | 440–3650 | 263.5 |
| Magnesium | 24–1050 | 78.4 |
| Sulfur | 137–925 | Not determined |
| Potassium | 259–20,616 | Not determined |
| Phosphor | 70–300 | Not determined |
| Iron | 0.85–126.20 | 44.8 |
| Zinc | 0.16–3.30 | Not determined |
| Copper | 0.6–1.1 | 1.3 |
| Vitamins | | |
| A | 6.78–18.90 | Not determined |
| B2 | 0.05–20.50 | Not determined |
| B3 | 0.8–8.2 | Not determined |
| B7 | 423 | Not determined |
| B12 | 0.06–2.64 | Not determined |
| C | 17.3–220.0 | Not determined |
| E | 77 | Not determined |

### *Potential of Moringa oleifera as antibacterial*

Gastroenteritis can occur due to infection from various types of bacteria such as Campylobacter, *E. coli*, *Salmonellae, Shigellae, Vibrio cholarae, Bacilus cereus*, and many more. *M. oleifera* has a certain antibacterial response that can be considered for treating bacterial gastroenteritis. Based on the results of the study, the methanol fraction of the seed extract of *M. oleifera* could inhibit the sensitivity of four bacterial species, namely *Salmonella typhi*, *Salmonella paratyphi*, *E. coli* and *B. cereus*. The activity on the target bacterial species is lower than that of gentamicin and metroimidazole, which are commonly used antibiotics [32].

**Table 6: Antibacterial activity of *Moringa oleifera***

| Bacterial causes gastroenteritis (8) | Gram staining | Source of active components |
|---|---|---|
| *S. aureus* | Gram positive | Seed, leaves |
| *E. coli* | Gram negative | Seed, leaves |
| *V. parahaemolyticus* | Gram negative | Leaves |
| *B. cereus* | Gram positive | Seed, leaves |
| *C. perfringens* | Gram positive | Seed, leaves |
| Salmonella typhi | Gram negative | Seed, leaves |
| *S. enteritidis* | Gram negative | Leaves |
| *Y. enterocolitica* | Gram negative | Leaves |
| *V. cholerae* | Gram negative | Leaves |
| *V. vulnificus* | Gram negative | Leaves |
| *S. flexneri* | Gram negative | Leaves |
| *S. sonnei* | Gram negative | Leaves |
| *S. dysenteriae* | Gram negative | Leaves |
| Shigella boydii | Gram negative | Leaves |

*S. aureus*: *Staphylococcus aureus*, *E. coli*: *Escherichia coli*, *V. parahaemolyticus*: *Vibrio parahaemolyticus*, *B. cereus*: *Bacillus cereus*, *C. perfringens*: *Clostridium perfringens*, *S. enteritidis*: *Salmonella enteritidis*, *Y. enterocolitica*: *Yersinia enterocolitica*, *V. cholerae*: *Vibrio cholerae*, *V. vulnificus*: *Vibrio vulnificus*, *S. flexneri*: *Shigella flexneri*, *S. sonnei*: *Shigella sonnei*, *S. dysenteriae*: *Shigella dysenteriae*, *S. boydii*: *Shigella boydii*.

*S. typhi* is currently resistant to antibiotics with a nucleic acid target, namely tetracycline; however, *M. oleifera* seeds can inhibit these pathogens. Similarly, *Salmonella* species are resistant to antibiotics with cell wall targets (vancomycin). The leaves and seeds of *M. oleifera* can inhibit pathogens at low concentrations of 0.16 mg/40 L and 0.15 mg/40 L [32], [33].

Ethanol, N-hexane, and Ethyl acetate extracts from *M. oleifera* leaves have antibacterial activity on microorganisms *Staphylococcus aureus*, *E. coli*, *S. typhi*, Mucor, *Candida albican*, which are shown in Table 6 [32]. *M. oleifera* leaf extract has various activities with the highest zone of 10 mm with ethyl acetate extract. The ethanol extract showed an inhibition zone of 9 mm on Staphylococcus, *E. coli* 4 mm, *S. typhi* 6 mm, Mucor 3 mm, and Candida 3 mm. The N-hexane extract had no zone of inhibition (activity) with *S. aureus* and *E. coli*, but showed an inhibition zone with Salmonella typhi 4 mm, Mucor 2 mm, and Candida 2 mm. Ethyl acetate extract had an inhibition zone on all organisms with *S. aureus* and Salmonella typhi having the highest zone of 10 mm, followed by *E. coli* 8 mm, *C. albican* and Mucor having an inhibition zone of at least 4 mm. Salmonella and *E. coli* are pathogens for gastroenteritis.

Dongmo showed that the plant extracts contain phenolic chemicals (phenols, tannins, and flavonoids), as well as alkaloids, triterpenes, sterols, and lipids, according to the phytochemical screening. The crude extracts and methanolic fractions of *M. oleifera* leaves and seeds were active against four bacterial species. The seed extracts of *M. oleifera* have strong activity against four gastroenteritis-causing bacteria (*S. typhi*, *S. paratyphi, E. coli*, and *B. cereus*). *M. oleifera* seed extract had MICs ranging from 2.5 mg/ml (*E. coli* and *S. paratyphi*) to 10 mg/ml (*S. typhi* and *B. aereus*). Calculating the ratio of Minimal Bactericidal Concentration (MBC)/Minimal Inhibition Concentration (MIC) showed that the extract of *M. oleifera* seeds was bactericidal against all susceptible bacterial species (MBC/MIC of between 1 and 2). This activity can be explained by the fact that the extract of *M. oleifera* seeds is high in natural compounds such as pterygospermin, benzyl isothiocyanate, and 4-(L-rhamnopyra nosyloxy) benzylglucosinolate, all of which have strong antibacterial activity [32], [33], [34].

The flavonoids inhibit the synthesis of nucleic acids from bacteria, inhibiting cell membrane function and energy metabolism [32]. The A and B rings of flavonoids cause nucleic acids to accumulate, thereby inhibiting the formation of bacterial DNA and RNA. In ring B, the hydroxyl group located at the 2',4' or 2',6' dihydroxylated position and in ring A located at 5,7 dihydroxylation both play an important role in the antibacterial activity of flavonoids. The result of the interaction between flavonoids and bacterial DNA can also cause damage to the permeability of bacterial cell walls, microsomes, and lysosomes. Flavonoids will inhibit the binding of ATPase and phospholipase enzymes so that the permeability of

cell membranes will be disturbed. Flavonoids will also form compounds with dissolved extracellular proteins, which will cause damage to the bacterial cell membrane so that the function of the cell membrane is inhibited and the intracellular compounds of the bacteria are released [32], [34].

The antibacterial activity of other flavonoids is by inhibiting energy metabolism. Flavonoids will inhibit the use of oxygen by bacteria. Flavonoids will also inhibit cytochrome C reductase so that metabolic processes are inhibited [14]. In other studies, flavonoid compounds have the action of inhibiting the topoisomerase II enzyme in bacteria which can damage the structure of deoxyribonucleic acid (DNA) bacteria and cause death [33].

*M. oleifera* also has phenolic compounds which have antibacterial activity by denaturing cell proteins. Phenol forms hydrogen bonds with proteins, which causes damage to the protein structure and affects the permeability of cell walls and cytoplasmic membranes because proteins make up both of them, after which it will cause an imbalance of macromolecules and ions in cells, resulting in cell lysis [34].

Tannin compounds have antibacterial activity by inhibiting reverse transcriptase enzyme and DNA topoisomerase so that they cannot form bacterial cells, and also have the ability to inactivate bacterial cell adhesion, inactivate enzymes, and interfere with protein transport in the inner layer of cells. These compounds target cell wall polypeptides where the formation of cell walls is less than perfect, which causes bacterial cells to die due to lysis caused by osmotic or physical pressure. Microorganisms that grow under aerobic conditions require iron for various functions, one of which is the reduction of DNA ribonucleotide precursors. Not only that, tannins have a strong ability to bind iron ions. This causes the reverse transcriptase enzyme and DNA topoisomerase to be inhibited, so they cannot form bacterial cells [33], [34].

Saponin compounds have a detergent surface that can reduce the surface tension of the bacterial cell wall, causing damage to the bacterial cell membrane, which is very disturbing. Saponins can diffuse through the outer membrane and vulnerable cell walls, which will increase the cytoplasmic membrane and cause cytoplasm to leak out of the cell, resulting in cell death [33].

Antibacterial activity in alkaloid compounds can occur by interfering with the peptidoglycan constituent components in bacterial cells so that the cell wall layer is not perfect, which, in turn, will cause the death of bacterial cells [33]. Another mechanism of antibacterial alkaloids is that the alkaloid component is known as a DNA interchelator and inhibits the bacterial cell topoisomerase enzyme [34].

*M. oleifera* have another compound that has antibacterial activity, namely steroids. The activity of steroids is related to membrane lipids and sensitivity to their components resulting in liposome leakage. This compound can interact with cell phospholipid membranes with permeable properties to lipophilic compounds, which results in decreased membrane integrity and cell membrane morphology changes so that cells will be brittle and lysis [27].

In other studies, it is said that chemical compounds contain secondary metabolites such as flavonoids, alkaloids, and phenols, which can also inhibit bacterial activity. Based on the results of the *in vitro* study of *M. oleifera* leaf extract against Salmonella enteritidis bacteria, it can be concluded that the *M. oleifera* leaf water extract has potential as an antibacterial against S. enteritidis [27], [28].

In their study, Tiania and Krystyna stated that the aqueous extract of *M. oleifera* seeds had antibacterial activity against *S. aureus*, with a minimum inhibitory concentration of 0.25% of the extract (Table 7). The hydroalcoholic extract provided a more effective antibacterial effect by inhibiting the growth of three bacterial species, namely *S. aureus*, *S. typhimurium, and V. cholerae* (Table 7) [27], [34].

**Table 7: Inhibition zone (mm) of pathological bacteria by liquid extract and hydroalcohol extract on seeds**

| Strain | Concentration of *M. oleifera* seed extract (%) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Liquid extract | | | | | Hydroalcohol extract | | | | | |
| | 2.0 | 1.0 | 0.5 | 0.25 | 0.125 | 50 | 25 | 12.5 | 6.25 | 3.12 | 1.56 |
| *S. aureus* | 20 | 16 | 15 | 14 | 0 | 30 | 20 | 15 | 12 | 12 | 12 |
| *T. typhimurium* | 0 | 0 | 0 | 0 | 0 | 20 | 15 | 15 | 15 | 20 | 0 |
| *V. cholerae* | 0 | 0 | 0 | 0 | 0 | 25 | 20 | 20 | 20 | 16 | 14 |

*V. cholera: Vibrio cholerae, S. aureus: Staphylococcus aureus, M. oleifera: Moringa oleifera.*

### *Moringa oleifera potential as anti-inflammatory*

Gastroenteritis bacterial infection can cause inflammation, which shows the involvement of neutrophils and other polymorphonuclear leukocytes which are bactericidal, but can also damage the intestinal epithelium and cause bloody diarrhea. In *Campylobacter jejuni*, inflammation damages the epithelium of the digestive tract [21], [22]. An increase in the number of *E. coli* in the gastrointestinal tract will further cause infection and cause inflammation. *E. coli* will induce regulatory T cells (Treg cells) mediated by chemical mediators such as interleukin 10 (IL-10), ICOS, and butyrate, proliferation of regulatory T cells will cause diarrhea. *S. typhi* infection occurs by attacking the intestinal epithelium; it meets macrophages in the lymphoid tissue associated with the intestine. The interaction between Salmonella and macrophages causes changes in the expression of a number of host genes, such as those encoding pro-inflammatory cytokines (including IL-1, IL-6, IL-8, tumor necrosis factor [TNF]-, INF, granulocyte-macrophage colony-stimulating factor [GM-CSF]), receptors, adhesion molecules and mediators, and anti-inflammatory [23], [24].

Based on several studies, it was found that *M. oleifera* extract has anti-inflammatory effects. Isothiocyanate-enriched *M. oleifera* seed extract had anti-inflammatory activity demonstrated by a reduction

in carrageenan-induced rat paw edema (33% at 500 mg/kg MIC-1) comparable to aspirin (27% at 300 mg/kg). Anti-inflammatory activity occurs in murine macrophages stimulated by Lipopolysaccharide (LPS) by decreasing nitric oxide (NO) production and inflammatory gene expression (iNOS, IL-1β, and IL-6) [25]. In another study, the anti-inflammatory activity was evaluated by determining the production of NO in RAW264.7 macrophage cells. The group given *M. oleifera* leaf extract at a concentration of 100 g/mL gave lower NO production compared to aspirin. In contrast, *M. oleifera* seed extract with the same concentration resulted in higher NO production than aspirin, but without a significant difference. Thus, it turns out that the leaf extract of *M. oleifera* has better anti-inflammatory potential than the seeds [28].

In another study, the anti-inflammatory effect of *M. oleifera* leaf extract and its active component (quercetin) was investigated in rats fed a high-fat diet. The results showed that short-term treatment of *M. oleifera* extract and quercetin inhibited the release of TNF-, IL-6, and the expression of nuclear factor kappa B (NF-kB), iNOS, IFN-γ, and C-reactive protein in mice fed a high diet. Fat compared to mice fed a high-fat diet. In another study, it was found that *M. oleifera* can eliminate the production of monocyte-derived macrophage factors, such as TNF-α, IL-6, and IL-8. *M. oleifera* exerts some of its immune-related effects mainly through direct pathogen removal or modulating the balance of pro- and anti-inflammatory mediators released from various types of immune cells by regulating the activity of signaling pathways, such as the NF-B pathway (Figure 1) [25], [26], [27].

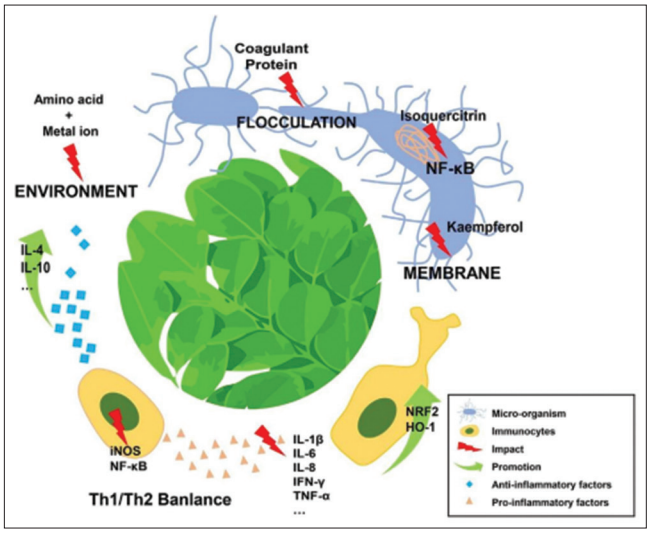


*Figure 1: Schematic diagram of Moringa oleifera in treating immune disorders [27]*

### *Moringa oleifera potency as antiulcer*

The ethanolic extract of *M. oleifera* was found to have an antiulcer effect. In Manoj *et al.*'s study, the administration of *M. oleifera* ethanol extract to gastric ulcers in albino wistar rats showed an improvement. *M. oleifera* reduced free acidity, total acidity, and ulcer index better than the control group given omeprazole (30 mg/kg, p.o.) and salt (NaCl, 0.9%) [29].

Tannins are also known to have antiulcer activity by affecting the integrity of the mucous membrane and forming a protective film to prevent the absorption of toxic substances [30].

### *Potency of Moringa oleifera as antidiarrheal*

Vibrio cholera, when it reaches the intestine, is propelled by a sheathed flagellum and then penetrates the mucus barrier to attach to the small intestinal mucosa. V. cholerae will invade the middle small intestine to the distal small intestine, where it forms microcolonies in the villous crypts. All strains of V. cholerae that cause cholera harbor ToxR regulation and secrete both TCP (toxin-coregulated pilus) and cholera toxin (CT). TCP on pilus type IV is required for colonization of V. cholerae. CT consists of an enzymatically catalytic A subunit (CtxA) and a pentamer of a B subunit (CtxB). The pentamer subunit B binds to the monosialoganglioside GM1 via cell surface receptors on the apical surface of the epithelium. The toxin is endocytosed, and CtxA exits the endosome for G-protein-regulated adenyl cyclase ribosylation on the basolateral membrane of the cell. This results in loss of chloride (Cl–) and massive secretion of fluid into the small intestine, the diarrhea produced by V. cholerae being a means of transmission [31], [32].

### *Toxicity of Moringa oleifera evaluation*

*M. oleifera* is a multifunctional plant with both nonmedicinal and therapeutic properties. Even though this herbal mixture is widely used for the treatment of a variety of diseases, there is only a little evidence for its safety. However, herbal preparations are typically thought to be reasonably safe and free of numerous side effects due to their "natural" origin (2). Previous studies on the acute and sub-acute toxicity of aqueous leaf extract in male Sprague-Dawley rats found no toxicity up to a dose of 5000 mg/kg body weight. Although the aqueous leaf extract of *M. oleifera* did not cause any mortality when given orally at doses ranging from 400 mg/kg to 6.4 g/kg, some animals treated with higher doses of 3200 and 6400 mg/kg 2 h after treatment showed reduced mobility and dullness. At higher doses of 1000 and 2000 mg/kg, the intraperitoneal (i.p.) route resulted in 20% and 80% mortality, respectively. Using a probit analysis method, the LD50 was calculated to be 1585 mg/kg. Another study used data from leaf, and seed extracts to perform one-way analysis of variance, with statistically significant differences considered at $p<0.05$, $p<0.01$, and $p<0.001$. At all doses tested, histopathological changes were observed in the heart, liver, lungs, spleen, and kidneys of rats treated with the extracts. At the highest dose tested (1000 mg/

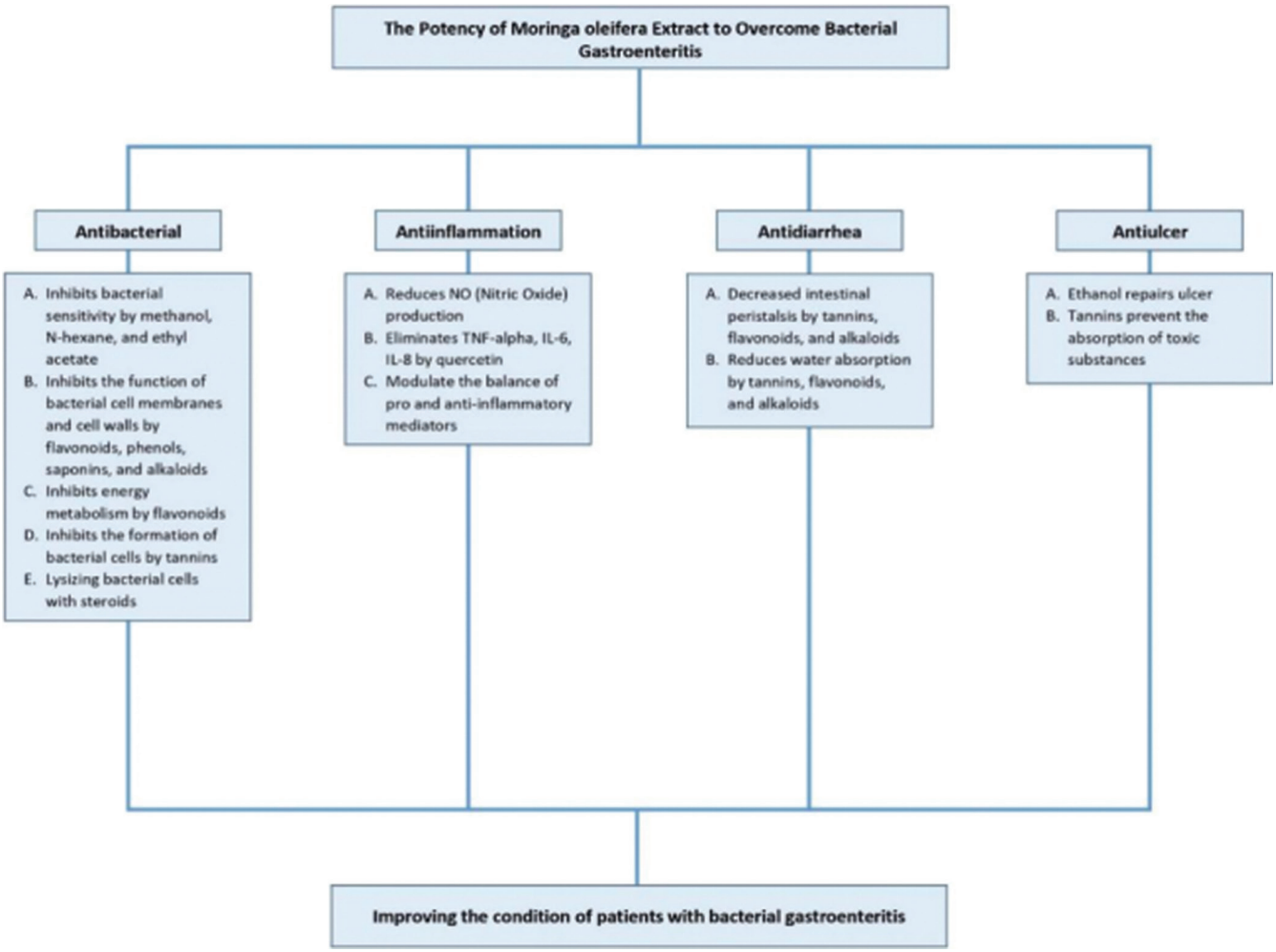


*Figure 2: The potency of Moringa oleifera leaf and seed extract framework*

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kg) of the seed extract, other physical changes such as agitation, confusion, and disorientation were observed. There was a significant increase ($p<0.05$) in neutrophils, white blood cells (WBC), and platelets. The findings suggest that *M. oleifera* leaf and seed extracts may boost immunity and have hepatoprotective properties. *M. oleifera* can be concluded to be relatively safe for human consumption. However, long-term administration, on the other hand, necessitates caution [33], [34].

*M. oleifera* extract contains tannins, flavonoids, and alkaloids, which have antidiarrheal effects. Tannins, flavonoids, and terpenoids reduce intestinal peristalsis by blocking muscarinic receptors and acting on -opioid receptors in the muscles of the small intestine. Tannins also denature proteins in the intestinal mucosa and cause the pores and intestinal mucous membranes to narrow. This action can reduce the absorption of water by the intestine. Different roles of flavonoids and ethanol have different roles in restraining intestinal motility. Based on the explanation above, extracts of leaves and seeds of *M. oleifera* have good potential to help treat gastroenteritis caused by bacteria (Figure 2). The utilization of leaf and seed extracts of *M. oleifera* will be very useful considering the ease with which *M. oleifera* lives in the tropics and that public trust in alternative herbal medicine is still high [35].

## Conclusion

Gastroenteritis is the result of inflammation in the digestive organs, namely the stomach and intestines, which is characterized by symptoms of diarrhea, vomiting, fever, and abdominal pain. This disease is characterized as a result of bacteria, viruses, and parasites.

Leaf and seed extract of *M. oleifera* has good antibacterial, anti-inflammatory, antiulcer, and antidiarrheal potential for the treatment of bacterial gastroenteritis. Making extracts with certain active ingredients is a challenge in exploiting the potential of *M. oleifera* leaves and seeds. Based on this literature review, further research can be carried out regarding the therapeutic effects of clinically tested *M. oleifera* seed and leaf extract.

It is hoped that further research will be carried out on the content and therapeutic effects of clinically tested *M. oleifera* seed and leaf extract, so that this

extract can eventually be used as an alternative therapy for patients with bacterial gastroenteritis.

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