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Benefits of Crude Antimicrobial Delivery of Pharmaceutical: A Traditional Yet Upcoming Era

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KEYWORDS

Antimicrobial, Crude, Skin disease, Antimicrobial resistance, Traditional

ABSTRACT:

Almost 90% of the population suffers from skin diseases, including atopic dermatitis, which is caused by S. aureus. Because synthetic skin infection treatments are expensive and have a number of side effects, drugs produced from natural sources can be used. These drugs are widely available, inexpensive, safe, and effective, with minimal side effects. Saponins, alkaloids, tannins, flavonoids, and steroids were among the phytochemical components found in the herbs investigated. Alkaloids have antibacterial properties due to their ability to inter-chelate with the DNA of Gram positive and negative bacteria and interfere with cell division. Kaempferol, chlorogenic acid, and kaempferol-3-O-D-glucoside are active bio-components of oleander flower extracts with potent anti-inflammatory properties. Synthetic magnetite nanoparticles or an aqueous extract of *Calotropis procera* inhibit Gram-positive bacteria. Antimicrobial chemicals identified in MpEO, *Lawsonia inermis*, IL-6, *Tagetes erecta*, and other plants can be used in topical drug delivery methods as formulations.

1. Introduction

The skin serves as the body's first line of defence, preventing potentially harmful substances or microorganisms from entering. Once cellular immunity is compromised and the barrier of the skin is compromised, pathogens can enter skin tissues and cause illnesses. Staphylococcus aureus (S. aureus), a relatively common human pathogenic bacteria that is ubiquitous in the natural environment, is a leading cause of skin infections in humans. According to research, S. aureus colonises 90% of people with skin illnesses such as atopic dermatitis and 10%-20% of the skin flora of healthy people [Zhu *et al.,* 2022]. Skin tissue infections caused by bacterial pathogens are the most commonly reported illnesses in humans, with 500 to 10,000 cases recorded each year. Pyoderma is the most frequent skin condition among adolescents. It is a term used to describe skin irritation produced by a bacterial infection, the most frequent of which being Staphylococcus aureus and Staphylococcus pyogenes. Pus-producing illnesses include tropical ulcers, cellulitis, folliculitis, furuncles, impetigo, and carbuncles, to name a few [Lucy, Divinah, 2023]. The skin's defensive system against microbial infection is well-organized. When S. aureus enters the skin, immune system effectors such as keratinocytes, resident immune cells, and endothelial cells recognise it and initiate an inflammatory response that activates vascular endothelial cells [Kwiecinski, Kratofil, Parlet, 2021; Nguyen, Soulika, 2019]. The formation of abscesses is the body's defence mechanism over microbial infection. When bacteria invade skin tissue, neutrophils from the blood are pulled in and secreted, resulting in suitable abscesses and the removal of bacteria from the skin [Gonzalez *et al.*, 2019]. Despite the body's ability to create an immune response, antibiotics persist as essential to speed up healing. However, the increase of antibiotic-resistant bacteria has made treating such illnesses harder, and this is an urgent issue that must be addressed [Herman, Herman, 2019].

Antimicrobial peptides (AMPs) have a broad antibacterial spectrum, excellent thermal stability, strong water solubility, and are unlikely to generate drug resistance. They come from several sources and are believed to be the best antibiotic alternatives available

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[Manniello *et al.*, 2021]. Since ancient times, plants' therapeutic properties have been used to treat an extensive variety of human illnesses. Because modern drugs are expensive and can have a range of harmful side effects, traditional medicines are still employed to cure ailments in developing countries. In addition to the various major metabolites, plant secondary metabolites such as alkaloids, terpenoids, flavonoids, quinones, tannins, and others are frequently what make plants medicinally useful. These compounds defend plants from illnesses, pests, herbivores, and environmental hazards. Alkaloids, saponins, flavonoids, tannins, sterols, and phenolic compounds are the most important bioactive compounds found in plants, and they are responsible for the majority of a plant's antibacterial action [Faye, Birhanu, Belete, 2021].

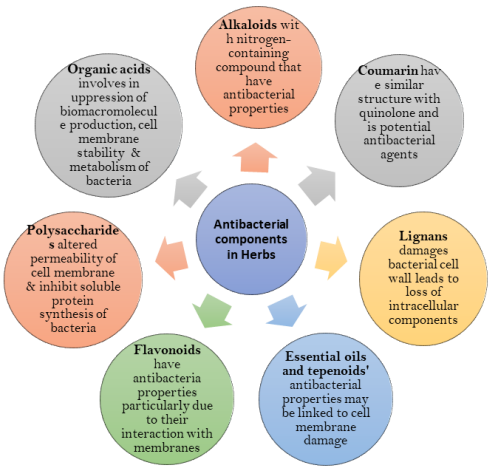

Figure 1: Antimicrobial secondary metabolites present in herbal plants

Drug resistance is becoming a major concern to world health, affecting all major microbial diseases as well as antimicrobial treatments. It causes a variety of infectious disorders and is difficult to treat. Pathogenic microorganisms have developed a number of antibacterial defence mechanisms and are treatment resistant. In recent years, there has been an upsurge in scientific interest in herbal medicines due to the improved effectiveness of novel plant-derived drugs [Levy, Marshall, 2004]. Drug resistance, which affects all main microbial diseases and antimicrobial treatments, is currently a serious danger to global health. It causes a variety of infectious disorders and is difficult to treat. Pathogenic microorganisms have developed a number of antibacterial defence mechanisms and are treatment resistant. In recent years, there has been an upsurge in scientific interest in herbal medicines due to the improved effectiveness of novel plant-derived drugs [Fatahi Bafghi *et al.*, 2022]. The prevalence of multi-drug resistant microbial strains, as well as the emergence of bacteria with low antibiotic resistance, is steadily growing. This rise has been linked to unrestricted use of broad-spectrum antibiotics, immunosuppressive medication, intravenous catheters, organ donation, and persistent HIV infection epidemics. Synthetic medications are frequently contaminated and have serious repercussions in developing nations, as well as being expensive and ineffective for illness management. Novel infection-fighting techniques must be developed to manage microbial infections [Aly, 1996].

Plants contain a diverse spectrum of active chemicals, many of which have been found to have antibacterial and antioxidant properties. Many phytochemical substances found in medicinal plants have a variety of physiological effects on the body and could be used to develop new antibacterial medications. Phenolic compounds, flavonoids, alkaloids, diterpenes, triterpenes, naphthoquinones, and sesquiterpene lactones are examples of bioactive chemicals [Al-Snafi, 2019]. Numerous plants have a variety of chemically active ingredients together, which gives them their medical benefits. *Lawsonia inermis*, *Tagetes erecta*, *Nerium oleander* and *Cascabela thevetia*, *Calotropis procera*, and *Mentha piperita* were discovered as antibacterial crude medicines in the current study. The phytochemicals and antibacterial capabilities of the organic extracts of the aforementioned medicinal plants are described in this study.

1. APPICATION OF CRUDE DRUGS

Several studies have been published on the biological activity of extracts derived from medicinal herbs, including their antibacterial, anti-inflammatory, and antioxidant properties. Antimicrobial compounds generated from botanical products, in addition to potentially being beneficial in combating resistant microbial strains, may suppress the growth of bacteria, fungus, viruses, and protozoa by ways other than those

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utilized by commonly employed antimicrobials. Even while some of those active substances do not have the same potency as antibiotics on their own, when taken with medications, they can aid in reducing the level of antibiotic resistance that microbes have developed. Some of these active compounds have the ability to modify antibiotic resistance as well as have intrinsic antibacterial activity.

Table I- Plant species used in the management of skin conditions with its active parts are follows:

Sl No	Scientific name	Family	Phytoconstituents present	Use (s)	Plant part	Reference
1	*Lawsonia inermis* (Henna)	Asteraceae	Terpenoids, Tannins, Quinones, Phenols, steroids, Saponins, alkaloids, glycosides, Flavonoids, Cardioglycosides	antibacterial, antifungal, anticancer, antiparasitic, antioxidant, central nervous, analgesic, anti-inflammatory, wound and burn healing etc.	Roots, fruits, flower, stem, leaves, barks, rhizome, bulbs, latex	Devi *et al.*, 2021; Singh, Gupta, Kannojia, 2020
2	*Tagetes erecta* (Marigold)	Asteraceae	Alkaloids, flavonoids, Thiophene derivative, Benzofuran, carotenoids, essential oils	Antibacterial, anti-inflammatory, Anti-oxidant, Wound healing, Anti-cancer, Mosquitocidal & Anti-fungal activity	Leaves, flower, stem, roots	Khan *et al.*, 2022; Das, Mishra, 2011
3	*Cascabela thevetia* or *Nerium oleander* (Oleander)	Apocynaceae	Alkaloids, Flavonoids, Saponins, Tannins, Carbohydrates, terpenoids, amino acid, glycosides, phlobatanins.	Antimicrobial, antibacterial activity, cardiac glycosides, laticiferous plants	Leaves, flower, seed, stem, root	Kemala *et al.*, 2022; Bogava *et al.*, 2022; Paramasivam *et al.*, 2022
4	*Calotropis procera* (Giant milkweed)	Apocynaceae	alkaloids, saponins, tannins, phenols, steroids, Flavonoids, terpenoids	good stability, and antimicrobial activity	Leaves, stem, fruits, roots	Hamad Al-Mijalli *et al.*, 2022; Gautam, Siddiqui, Jharkharia, 2022
5	*Mentha Piperita* (Mint)	Lamiaceae	Menthol, menthofuran, limonene, menthone, piperitone, terpinene etc.	antimicrobial, insecticidal, antioxidant, anticancer, and anti-inflammatory properties	Leaf, stem, roots	Rastogi, Dwivedi, 2022; Liew *et al.*, 2022

2. ANTIMICROBIAL RESISTANCE (AMR)

The term "antimicrobial resistance" describes the ability of bacteria, virus, fungi and parasite to endure the

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medicinal effects of substances to which they were previously susceptible. Antibiotic Resistance (ABR), which is caused by the widespread use of antibiotics, is an essential element of AMR [Walusansa *et al.,* 2022]. The COVID-19 pandemic is contributing to the global growth in antibiotic resistance, which is extremely dangerous for public health. Today's major global public health risk is mostly caused by a number of causes, including overpopulation, increased global migration, and pressure from rising antibiotic consumption [Alaoui *et al.,* 2022]. The most common type of resistance mechanism appears to be genetically altered medication targets caused by mutations. Mutations affecting membrane permeability, biofilm formation, and efflux pump systems, however, appear to be becoming more and more significant for the emergence of drug-resistant genotypes [Srisuphanunt *et al.,* 2023].

Bacterial resistance frequently results in treatment failure, which can be lethal in critically ill patients. Antimicrobial resistance is a serious threat to human health. The majority of the 4.95 million AMR-related deaths are expected to be caused by six pathogens: Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa [Pei *et al.,* 2023]. Even last-resort medicines are becoming less effective against antibiotic-resistant infections, which are growing more widespread [Frieri, Kumar, Boutin, 2017]. Antimicrobial resistance is on a rise, and how antimicrobial medications will be utilized in the future is unknown. Action should be done to remedy the situation, including the use of medicinal plants as an antibacterial agent [Ibrahim *et al.,* 2019]. Microorganisms have an innate or taught propensity to regularly alter their susceptibility patterns, even in response to the newest medicines. It is imperative to ascertain an organism's antibiotic susceptibility profile promptly following its identification and isolation. This strategy, which makes use of current institutional antibiogram data, not only assists doctors in selecting the most effective antibiotics for patient treatment, but it also directs empirical antibiotic therapy [Salam *et al.,* 2023].

Despite the fact that antibiotics have been extremely effective in treating infectious diseases, bacterial infections and drug resistance remain major challenges in healthcare systems around the world. Antibiotic-resistant Antibiotic abuse or misuse is the primary cause of germs [Azam *et al.,* 2023]. The widespread use of commercial antimicrobial drugs to treat infectious diseases has resulted in drug resistance in human pathogenic microorganisms. Due to the circumstances, researchers were forced to seek out novel antimicrobial chemotherapeutic drugs from a variety of sources, including one of the best: medicinal plants. This is especially relevant given the growing multidrug resistance among newly emerging and re-emerging bacterial illnesses to readily available modern medications or antibiotics [Arbab *et al.,* 2022]. Since the efficacy has decreased, there have been significant attempts made to find new antibacterial agents and create creative treatment plans. Scientists are currently focused on chemically active compounds obtained from plant species traditionally used in herbal medicine, which have the potential to provide antibacterial and antifungal treatments a new identity due to the growing issue of antibiotic resistance [Erfan, Marouf, 2019]. Phytochemicals discovered in several research may hold promise for the finding of lead molecules for the development of innovative and synthetic medicinal medicines. TCM and its constituents have a multi-link, multi-target, and multi-site complicated mechanism of action against bacteria. When it comes to resources, accessibility, medication resistance, active components, bad reactions, and targets, Traditional Chinese Medicine (TCM) outperforms antibiotics. Drug-resistant bacteria may become more susceptible to antibiotics and possibly even regain their susceptibility due to TCM's synergistic action. Drug-resistant bacteria may become more susceptible to antibiotics and possibly even regain their susceptibility due to TCM's synergistic action [Li *et al.,* 2022].

3. ANTIMICROBIAL ACTIVITY OF MEDICINAL PLANT

Scientists are currently focused on chemically active compounds obtained from plant species traditionally used in herbal medicine, which have a chance to provide antibacterial and antifungal treatments a new identity due to the growing issue of antibiotic resistance [Bhoyar, 2021]. However, the architecture and structure of gram-negative bacteria's cell wall may explain this resilience

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[Zaid *et al.*, 2022]. This bacteria's cell wall is composed of three distinct layers that operate as an envelope and a barrier to some physiologically active substances. These layers are made up of a peptidoglycan layer, an outer polysaccharide membrane, and an interior or cytoplasmic membrane [Dardona, Shahabuddin, 2022]. This outer membrane responds positively in gram-negative bacteria but adversely in gram-positive bacteria. It acts as a permeability-restricted barrier, prohibiting some chemicals from entering the bacterial cell, such as medications and antibiotics. Aqueous extracts of the red and pink *Nerium oleander* flowers displayed the most powerful and obvious anti-S. aureus effects, however ethanolic extracts of the white flowers also demonstrated similar effect [Balkan *et al.*, 2018]. Oily or alcoholic preparations of *Nerium oleander* flowers were traditionally used to treat inflammatory conditions. In vitro, an ethanolic extract of oleander flowers was found to have potent anti-inflammatory effects. The extract's active biocomponents were determined to be kaempferol, chlorogenic acid, and kaempferol-3-O-D-glucoside [Subba *et al.*, 2021].

Table II: Methods of preparation and microbe inhibition with different plants

Sl no.	Plant name	Plant part	Method of extract preparation	Microbes which shows inhibition	Reference
1.	*Lowsonia inermis*	Leaves	Dried leaves in distilled water with Soxhlet apparatus	Pseudomonas spp	Liew *et al.*, 2022
		Seed and leaves	Cold maceration technique using methanol and water	MDR related infectious bacteria	Olaitan, Nwadike, 2022
		Leaves	Formation of nano particles with water and 0.5 M magnesium acetate.	S. aureus, B. subtilis, E. coli and P. vulgaris	Akshaykranth *et al.*, 2021
		Leaves	Hydroalcoholic extract with maceration	Pseudomonas, Basilus sabtilis, P. vulgaris, and Candida albicans.	Bafghi *et al.*, 2022
		Leaves	Leaves soaked in ethanol for 20 hours	S. aureus	Elebeedy *et al.*, 2022
2.	*Cascabela thevetia* (yellow oleander)	Leaves	Dried leaves immersed for 4 days in ethanol and methanol, maintaining a 1:10 (w/v) ratio	Klebsiella pneumonia, S. aureus, Vibrio cholerae (C6706)	Mozibullah *et al.*, 2023
		Leaves	Ethanolic extract	Bacillus subtilis, S. aurens, Pseudomonas anuginosa, and E. coli	Gaur *et al.*, 2023
		Flower	Dried, crushed leaves was placed in flask with methanol for 10 days	S. carpae, Listeria monocytogenes, Shigella dysenteriae and Salmonella spp.	Saeed *et al.*, 2023
	Nerium oleander	Flower	Ethanolic extract	Gram-negative isolates	Shafiq *et al.*, 2021
		Leaves	Copper nanoparticles	Staphylococcus aureus, also Candida albicans	Srivastava, Dwivedi, 2018

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		Flower	Ethanol and methanol were used in a Soxhlet device	Staphylococcus aureus and Streptococcus group A	Dardona, Shahabuddin, 2022
3.	*Mentha Piperita*	Leaves	Leaves soaked in water and subjected to Clevenger-type hydro distillation for 3 hours.	S. aureus and Candida albicans	Ilić *et al.*, 2022; Ilić *et al.*, 2019
		Leaves	Essential oil from leaves	E. coli, Bacillus subtilis, Bacillus cereus, S. aureus, S. typhimurium and Proteus mirabilis	Nanda, Jyotirmayee, Mahalik, 2022
		Leaves	Dry leave powder heated at 70°C for 15 min in water	Gram-negative bacterial and fungal pathogen Candida Albicans	Harsha, Jain, Prasad, 2022
		Leaves	Extraction of essential oil using hydro distillation method	Staphylococcus aureus, Bacillus subtilis and Listeria monocytogenes	Al-Mijalli *et al.*, 2022
		Leaves	Extraction of essential oil	P. aeruginosa and fungal pathogens like Candida Albicans	Bogavac *et al.*, 2022
4.	*Tagetes erecta*	Dried Flower	Extraction with water or ethanol using a magnetic stirrer for 30 minutes	Staphylococcus aureus	Burlec *et al.*, 2022
		Fresh Flower	Fresh petals with ethanol were kept for 24 hours at room temperature	S. cerevisiae, S. aureus and E. coli	Gautam, Siddiqui, Jharkharia, 2022
		Dried Flower	Extraction with chloroform, dichloromethane and hexane by maceration at room temperature for 7 days	Gram-positive bacteria, S. aureus and E. coli	Burlec *et al.*, 2019
		Flower	Petals were kept in alkaline solution (sodium hydroxide dissolved in water) and kept at 90°C for 30 minutes	Stephylococcus sp	Paramasivam *et al.*, 2022
5.	*Calotropis procera*	Leaves	Zinc oxide nanoparticles (ZnO NPs)	E. coli, E. fecalicus, Klebsiella sp, Salmonella sp, s. pyogens, S. aureus, Proteus Sp, Pseudomonas sp, and fungal pathogens like candida albicans	Mohideen *et al.*, 2022

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		Leaves	In Silico Molecular Docking Study	Proteus mirabilis and E. coli	Morad *et al.*, 2023
		Leaves	Aqueous and ethanolic extracts	S. aureus, Streptococcus pyrogenes, E. coli, P. aeruginosa and S. typhi	Abegunde, Akinyele, Roseline, 2020
		Leaves	Methanolic extract	Proteus mirabilis, P. aeruginosa, Bacillus cereus, E. coli, Klebsiella pneumonia, S. typhi, and E. faecalis	Bilal, Ali, Uddin, 2020
		Root	Dried roots powder was added to 70% methanol and placed in shaker at 220 rpm at 25 ºC for 48 hrs.	E. coli and S. aureus	Al-Rowaily *et al.*, 2020

The zone of inhibition for S. aureus, E. coli, and K. pneumoniae in the assessment of antibacterial activity for methanolic extracts of *Calotropis procera* leaves and stems, respectively, suggests high to low activity [Abbas *et al.*, 2022]. For gram-positive bacteria, the minimum inhibitory concentration (MIC) is lower than the minimum bactericidal concentration (MBC). Gram-positive bacteria reported lower MIC and MBC values for the methanolic stem extract than gram-negative bacteria [Abegunde, Akinyele, Roseline, 2020]. S. aureus, S. epidermidis, B. subtilis, E. coli, and a variety of other bacteria were efficiently suppressed by synthetic magnetite nanoparticles or an aqueous extract of *Calotropis procera* [Timilsina, Modi, Basnyat, 2020]. The data also revealed significantly higher antibacterial activity against gram-positive bacteria, which is consistent with the findings of this study. S. aureus also displayed stronger antibacterial activity when compared to other microbes [Kalu *et al.*, 2022].

Mentha piperita essential oil (MpEO) has been studied for its antibacterial properties against both gram-positive and gram-negative bacteria. Organic compounds, such as essential oils (EOs), can have either synergistic or antagonistic effects when used with traditional medication. When coupled with amphotericin B, a common antibacterial medicine, MpEO had an antagonistic effect on Candida albicans and a synergistic effect on both Escherichia coli and Candida albicans [Floare *et al.*, 2023]. S. aureus, on the other hand, was only mildly affected. It was also discovered to have an inhibitory effect on clinically dangerous bacteria such as methicillin-resistant Staphylococcus aureus, Streptococcus pyogenes, and Enterococcus faecalis. When Streptococcus mutans was exposed to chitosan polymeric nanogel, MpEO significantly inhibited the pathogen's ability to cause dental caries in humans [Khanal, 2019].

The antibacterial and anti-inflammatory properties of henna, or *Lawsonia inermis*, make it a popular treatment for wound and burn wound infections. According to our findings, *Lawsonia inermis* may limit the growth of S. aureus. This is consistent with a literature review that discovered *Lawsonia inermis* has antibacterial properties [Akshaykranth *et al.*, 2021]. Surprisingly, the proinflammatory cytokine IL-6 is linked to skin inflammation and healing. TNF is another proinflammatory cytokine that contributes to the pathogenesis of a variety of inflammatory diseases and wound infections. According to our findings, *Lawsonia inermis* may limit the growth of S. aureus. This is congruent with a survey of the literature, which discovered *Lawsonia inermis* to have antibacterial properties. Surprisingly, the proinflammatory cytokine IL-6 is linked to skin inflammation and healing. TNF, another proinflammatory cytokine, is linked to the

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pathogenesis of some inflammatory disorders [Marimuthu *et al.*, 2012].

A plant extract from *Tagetes erecta* demonstrated a variety of activities on both gram-positive and gram-negative bacteria. The plant extract's broad-spectrum antibacterial activity is attributed to the newly found alkaloids. S. aureus, a Staphylococcus and Streptococcus family member, is one of the most prevalent gram-positive bacteria found in skin microflora [Das, Mishra, 2011]. They can cause minor skin diseases such as abscesses, cellulitis, boils, pimples, scalded skin syndrome, and pimples. They have the potential to cause fatal infections such meningitis, pneumonia, and septicaemia. Streptococcus skin infections include cellulitis, impetigo, perianal dermatitis, and vaginal dermatitis. The inhibitory zones of crude alkaloids were discovered to differ from those of standard antibiotics [Rojas-Sandoval, 2022].

4. MECHANISM OF ACTION OF ANTIMICROBIAL AGENTS

The vast majority of antimicrobial medicines used to treat bacterial infections are classified into several classes based on their basic mechanisms of action. The main mechanisms of action are interference with cell membrane development and destruction, inhibition of protein synthesis, obstructing bacterial efflux pumps, interference with nucleic acid and protein synthesis, restriction of a metabolic pathway, breakdown in energy metabolism, and an increase in intracellular osmotic pressure. The most prevalent antibacterial approach is cell membrane breakdown [Atay Balkan *et al.*, 2018]. Organic acids also have antibacterial properties because they raise intracellular pH. The most efficient antimicrobial agents are flavonoids, which have antibacterial characteristics. While most alkaloids have minimal antibacterial properties, berberine has potent antimicrobial properties. Antimicrobial activities are prominent in some terpenes and partial essential oils [Wanga, Nyamboki, 2023]. Organic acids, such as chlorogenic acid, have antibacterial properties that can be used. Extracts are thought to be particularly active if their MIC values are less than 100 g/mL, moderately active if they are between 100-625 g/mL, and weakly active if they are above 625 g/mL; similarly, pure compounds are thought to be significantly active if they are less than 10 g/mL, moderately active if they are between 10-100 g/mL, and weakly active if they are above 100 g/mL [Alaoui Mdarhri *et al.*, 2022].

5. DISCUSSION

The goal of this study was to evaluate the antibacterial activity of numerous medicinal plants employed in traditional medical systems to treat symptoms caused by microorganisms. This study's five herbs—*Lawsonia inermis*, *Tagetes erecta*, *Cascabela thevetia*, commonly known as yellow oleander, *Nerium oleander*, *Calotropis procera*, and *Mentha piperita*—contain a variety of phytochemical components, primarily saponins, alkaloids, tannins, flavonoids, and steroids. The chemical composition of these herbs differs from that of other countries and plants grown in other regions. Secondary metabolite concentrations were high in all of the plant extracts analysed, although activity is also influenced by secondary metabolite concentration and potential interactions with other components [Dzotam, Touani, Kuete, 2015; Abdel Halium *et al.*, 2019; Mohammed *et al.*, 2019]. Apart from the existence of these compounds in plant extracts. Steroids' antibacterial properties derive from their capacity to mix with membrane lipids and cause leakage, whereas flavonoids' action stems from their ability to bind with intracellular and soluble proteins, as well as bacterial cell walls. Antibacterial action is caused by alkaloids' ability to bind with the DNA of both Gram-positive and Gram-negative bacteria and interfere with cell division [Bukar *et al.*, 2015; Hemeg *et al.*, 2020].

As a result, it was discovered that the plants mentioned above possess antimicrobial agents in addition to other agents. To use those herbs as formulations in topical drug delivery systems, more research must be conducted.

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