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REVIEW ARTICLE

Herbal drugs – an alternative to antibiotics in controlling human skin infection

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ABSTRACT

Herbs have great potential to cure different kinds of skin diseases. The administration of herbs in combination with other therapeutic drugs raises the chances of potential pharmacokinetic and pharmacodynamic herb-drug interactions. *Pseudomonas aeruginosa*, the major causative organism for skin infection, is a prime problem. It is a ubiquitous Gram-negative and environmental bacteria, which affect immune compromised patients, thus reflecting it's opportunistic nature. *P. aeruginosa* infections vary in severity from mild to fatal. Herbal products prove to be more beneficial than allopathic medicines as they show very less to no side effects. The traditional methods have used herbal products extensively in the past for treating many diseases. The major herbal products taken under this study are *Lawsonia inermis* (henna), *Camellia sinensis* (green tea), and *Coriandrum sativum* (coriander). These herbal products are chosen due to their prominent antibacterial properties. Another interesting technology, quorum sensing (QS) is a system used by bacteria to synchronize genetics in agreement with population density by employing signal fragments. This mechanism plays an important role commonly used by pathogens in the infection and disease progression through biofilm formation. The combinatorial study of QS with the herbal extracts can be explored for different biosensor developments and these can restructure the detection methods.

Keywords: Herbal products, *Pseudomonas* sp., Quorum sensing, Skin infection

INTRODUCTION

In the course of one's life, microbes, immune cells, and keratinized skin cells communicate to preserve the skin's immune and physical barrier in both stressful environments and homeostatic situations. The stratum corneum is the skin's outermost layer, and it acts as a barrier to keep foreign matter out, and allowing vital elements like moisture and water in. Infection, irritants, and allergens are all susceptible to a weakened or diseased skin barrier.[1] This review paper discusses skin infections that are caused by *Pseudomonas aeruginosa*. *Pseudomonads* are Gram-negative, aerobic bacteria quantifying 0.5–0.8 μm by 1.5–3.0 μm. Motion is through a solo polar flagellum. The cell envelope of *P. aeruginosa* embodies three coatings: The inner or cytoplasmic membrane, the peptidoglycan layer, and the outer membrane.[2] The outer membrane comprises lipopolysaccharide (LPS), protein, and phospholipid. These bacteria show a differentiating blue-green color on solid media, which is due to the presence of water-soluble pigments pyocyanin and pyoverdin. It gives rise to indophenol oxidase, a biocatalyst that causes them to yield positive results in the "oxidase" test. This allows them to be distinguished from other Gram-negative bacteria. *Pseudomonads* have very low nutritional needs as a group and can get their nutrients from a variety of sources in the environment. *P. aeruginosa*, for example, hardly requires acetate and ammonia as sources of carbon and nitrogen.[3] It transits between a mobile and immobile way of life. A variety of transcription factors, two-component systems, non-coding

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RNAs, and quorum-sensing networks can control the secretion of virulence effectors.[4] Accumulation of genes that code for a specific agent on the resistance plasmids (R plasmids) leads to multidrug resistance (MDR) through multidrug efflux pumps. Chromosomes concerning environmental bacteria show some of these resistance genes.[5]

Antibiotic-resistant infections are now a global health challenge to society. Hundred years ago, the launch of a new antibiotic into the market was comparatively faster and less complicated. It now takes around 10–12 years for the launch of the new antibiotic from the time of discovery. A perfect antibiotic is the one that inhibits or kills the growth of bacteria (harmful) in the host irrespective of the site of infection. It neither affects the gut flora nor causes undue toxicity in the host. However, most antibiotics are no more effective since it was sensed that the bacteria could evolve, obtain, and spread resistance mechanisms.[6] Thereby, calling for an urgent need to find ways to combat these pathogens which cause skin infections. One promising way in which this can be achieved is by the use of herbal products. The connection between man and his quest for drugs in nature dates back to thousands of years. Evidence such as written records, preserved temples, and original plant medicines were discovered. There are many herbal products for resisting the infection of bacteria. This review paper is aimed at an investigative study on seizing the bacterial cell cycle using herbal bioactive substances as antibiotics, and its inhibitory mechanism on bacterial colonization. The major herbal products that are taken under this study are *Lawsonia inermis* (henna), *Camellia sinensis* (green tea), and *Coriandrum sativum* (coriander). *L. inermis* leaf extracts show antibiotic action on the bacteria liable for the trivial skin infections. Its core chemical component is 2-hydroxy-1,4-naphthoquinone (lawsone).[7] Epigallocatechin gallate (EGCG), which is the most copious catechin in *C. sinensis*, has a bactericidal effect.[8] *C. sativum* is a popularly used spice worldwide in culinary. The main compound, linalool, is present in high amounts in seeds and is noted for its abilities to modulate many important pathogenesis pathways of diseases.[9]

Bacteria

P. aeruginosa is a non-fermentative bacterium. The optimum temperature required for the growth of the bacteria ranges from 25°C to 37°C, but at the same time, it can also survive at temperatures above (42°C) or below the optimum temperature with slow growth.[5]

Growth and reproduction in bacteria

P. aeruginosa is known best genetically among all *Pseudomonads*. In most *Pseudomonas* species, the genetic systems are either nonexistent or undeveloped. Whereas in *P. aeruginosa*, it consists of conjugation, transduction, and transformation, which are the three known phases of gene recombination. There are more than 500 regulatory genes involved in channelization of nutrient import, antibiotic efflux, various protein secretion and chemical sensing components are present. This is of utmost clinical importance since the genetic information exchange is involved in the development of antibiotic resistance.[10]

MDR

Antibiotics are present in very low concentrations in the soil. Despite that, the recent studies show that the microorganisms which utilize antibiotics as nutrients hint the developmental ancestry of antibiotic resistance genes.[5] The size of the genome being larger, the organism is highly adaptable to frequent physiological conditions and thrives between 16 and 24 h and responds to resistance to antibiotics.[22]

MDR in case of *P. aeruginosa*

It was found in many studies that *P. aeruginosa* showed the highest resistance amongst other bacteria. It is resistant to various β-lactams which include ceftriaxone and amoxicillin. This happens due to AmpC β-lactamase that leads to increased levels of resistance when depressed. One of the chief causes for the development of

resistant strains of *P. aeruginosa* is the overuse or misuse of the anti-pseudomonal or antibacterial drugs. The increasing multidrug-resistant strains of *P. aeruginosa* have devastating effects on the burn units. The various risk factors included in hospitalized burn patients that acquire *Pseudomonas* infections are, increased duration of hospitalization, using previous broad-spectrum antibacterials such as carbapenems.

Virulence of P. aeruginosa

The environmental iron concentration regulates the production of endotoxin. Repression in the synthesis of the toxin occurs when there are sufficient iron levels for the optimal growth of organisms.[10]

A few products of *P. aeruginosa* strains are as follows (Table 1):

Phospholipase C: It is synthesized by 70% of all clinically isolated strains of *P. aeruginosa.* It hydrolyses lectin, but is of unknown toxicity.

Leukocidin: It is a thermolabile protein which is the cause of lysis of leukocytes. This is a cytotoxin that is capable of damaging many tissue culture cells as well as lymphocytes.[2]

Table 1: Structure and its functions

Structures	Mechanism
Polar flagella	It is essential for motility in the early phase of pulmonary infection. By attaching to the toll-like receptor (TLR) on the epithelial cells, it activates IL-8 production Pile/non-piling adhesions make it easier to adhere to epithelial and eukaryotic cells (polar pili)
LPS adhesion moiety	It mimics a signal through TLR. It is divided into three sections, namely, core oligosaccharide, lipid A, and O-antigen side chains
Exotoxin A	Causes necrosis and damage of the tissues
Extracellular proteases(alkaline protease, LasA and LasB)	Are involved in the degradation of the elastin
Injecting virulent proteins	The host cell functions can be manipulated that are allowed by Type III secretion
Leukocidin	Destroys neutrophils
Antibiotic resistance genes	By transformation, transduction, and conjugation, these are readily acquired from other bacteria

LPS: Lipopolysaccharide

Pyocyanin and fluorescein: These are the most common strains produced by *P. aeruginosa.* Pyocyanin suppresses the growth of surrounding bacteria and facilitates colonization of *P. aeruginosa*.[2]

Toxin A: It is an extracellular protein. Protein synthesis inhibition in susceptible cells is correlated to toxicity. It is noticed that patients affected by *P. aeruginosa* show increased levels of antitoxin A antibody.[2]

Exoenzyme S: About 90% of the clinically isolated strains of *P. aeruginosa* produce this enzyme which plays a critical role in its infection cycle.[2]

Pathogenesis

P. aeruginosa is an extracellular pathogen. The ability of tissue to resist neutrophil ingestion is crucial for its development. It produces a range of factors which lead to virulence and uses survival strategies, such as:[3]

Antibiotics

Anti-pseudomonal antibiotics are divided into many categories such as monobactams, aminoglycosides, quinolones, and carbapenems. Antibiotics achieve toxic effects on bacteria by either impairing cytoplasmic membrane synthesis and function, impairing cell wall synthesis, or protein and nucleic acid synthesis. Disadvantages of using antibiotics are side effects, hypersensitivity reactions, drug interactions and toxicity, and effect on commensal flora. Misuse of the same leads to antibacterial resistance. Bacteria spontaneously develop resistance to antibiotics and have a firm hold on life, discovering ways of attacking the bacteria without driving resistance rather than just improving the measures to prevent the infection.[10,11] leads to future studies.

Herbal products

Medicinal plants produce substances which are used as precursors in the production of drugs for therapeutic purposes. The industrial revolution and development in the field of medicine have

brought a picture about allopathic medicines and their major advantages. Due to the long-term effects of allopathic medicines for severe diseases resulting in side effects, people have started to use traditional medicines again.[12] A few common herbs with inhibitory activities are provided in Table 2. The ease of availability to common man, feasibility, desired antimicrobial activity, and less to no side effects provide a choice for these plants, that is, *L. inermis*, *C. sinensis,* and *C. sativum*.

L. inermis

This is a flowering plant that grows to be 2–6 m tall. Plant has a dye producing molecule lawsone. The leaf extracts of plants possess good antimicrobial activity against the bacteria which causes skin infections. *L. inermis* can be used as an astringent, cooling agent, antibacterial, and antifungal herb for the skin and hair. The major chemical elements of *L. inermis* are tannic acid, gallic acid, mucilage, lawsone, and mannite.[7] The bioactive characteristic is assumed to be as a result of its high-protein-binding capacity. The important compound

Table 2: Comparison of antibacterial properties of herbs

Herb	Constituents	Bacteria	Property	Mechanism
Melaleuca alternifolia oil	Terpinin-4-ol	*P. aeruginosa*, *S. aureus*, *S. pneumoniae*, *E. coli*	Disorganizing cell respiration	The mechanism to inhibit *E. coli* and *S. aureus* growth is by disorganizing cell respiration by increased leakage of intracellular K+ions and changing cell permeability. The arrangements of polysaccharides molecules, phospholipids bilayers, and dissimilar fatty acids are disrupted due to the passing of essential oils through the cytoplasmic membrane and cell wall. All of this may lead to the coagulation in the cytoplasm of inner cellular components, thereby causing the bonds between protein layers and lipids to break[18]
Azadirachta indica	Flavonoid and phenolic compounds such as ferulic acid and ellagic acid, tannins, rutin	*V. vulnificus*, *P. aeruginosa* Gram-positive and Gram-negative microorganisms	Antioxidant activity against free radicals, healing of wounds	Flavonoid and phenolic compounds such as ferulic acid and ellagic acid have shown to have antioxidant activity by providing protection to host cells against free radicals. Healing of wounds is promoted by tannins. Rutin displays its antioxidant nature by decreasing the free radicals available and promotes effective communication on the skin layers. It binds to the Fe ions and prevents it from binding to hydrogen peroxide, if not it would lead to damage of cells due to free radicals[19]
Curcuma longa	Curcumin, curcuminoids such as bisdemethoxycurcumin, demethoxycurcumin, and curcumin	*S. aureus*, *P. aeruginosa*	Treating inflammation, antimicrobial, and antioxidant activities	Studies show that curcumin is favorably pleiotropic molecule that has capability to interact with molecular targets that are involved in inflammation. Curcumin regulates the responses of inflammation by downregulating lipoxygenase, cyclooxygenase-2 (COX-2), and nitric oxide synthase (iNOS) enzymes. Migration of inhibitory protein, monocyte chemoattractant protein, interleukin, and inflammatory cytokines tumor necrosis factor-alpha productions are inhibited by curcumin. Suppression of NF-κB activation downregulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis.[20]

P. aeruginosa: *Pseudomonas aeruginosa, S. aureus*: *Staphylococcus aureus*, *S. pneumoniae*: *Staphylococcus pneumonia*, *A. indica*: *Azadirachta indica*, *C. longa*: *Curcuma longa*, *M. alternifolia*: *Melaleuca alternifolia*

present is 2-hydroxy-1,4-naphthoquinone which comprises 5% of the weight in leaves.[13]

Mechanism of action

Oxidation and reduction reactions are responsible for the switching of hydroquinone (diphenol) and quinone. The quinone-hydroquinone pair's individual redox potential is crucial in many biological systems. Polyphenol oxidases are the enzymes, in the presence of which hydroxylated amino acids are made into quinones. Quinones form irreversible complexes with nucleophilic amino acids that are present in proteins that lead to inactivation and loss of function of the protein. Membranous enzymes, cell wall polypeptides, and adhesions that are exposed to surfaces are the mobile targets in the cells of microbes. They also display inhibition of cell growth in the culture. Substrates that are not available to the microorganisms may be rendered by quinones.[14] Many free hydroxyls integrate with carbohydrates and proteins in the cell wall of bacteria, which may explain the antimicrobial activity. They can possibly bind to the enzyme sites making them inactive. The antibacterial efficacy is dependent on the solvent properties.[7]

C. sinensis

C. sinensis cultivated in Asian countries. The leaf extracts contain polyphenolic components which show a wide range of antibacterial properties. (−) EGCG and (−)-epicatechin gallate are phenolic catechins that show inhibition against most Gram-negative and Gram-positive bacteria with moderate potency. Components that are most abundantly found are flavonoids such as catechin gallates, polyphenols, proanthocyanidins, and catechins.[8]

Mechanism of action

C. sinensis extracts are capable of preventing the pathogenic bacteria from attaching onto the host cell membrane. Thus, *C. sinensis* acts as a potential anti-adhesive agent. EGCG interacts with the outer membrane of the bacteria and prevents it from adhering to mammalian epithelial cells (HEp-2) without altering its function. The extracts are also capable of affecting the activity of the enzyme (dihydrofolate reductase [DHFR]) required by the bacteria to synthesize purine and pyrimidine along with increasing the epidermis thickness.[14]

The major property of *C. sinensis* catechins is that it has the ability to incorporate itself into the cell membranes of bacteria. The presence of LPS in the outer membrane of Gram-negative bacteria is made resistant to green tea catechins (GTCs) binding. Hydrogen peroxide leads to the damage in the cell membrane that is generated due to the binding of EGCG to the membrane of the bacterial cell in *P. aeruginosa.* The damage of cell membrane also leads to the loss in mobility of transporter proteins (required for secretion of toxin and efflux of antibacterial agents). GTCs pose a spectrum of effects on the functions of bacteria. One of the important properties is that it can inhibit enzymes that are involved in the fatty acid biosynthetic pathway. Fatty acids play an important role in building cell membranes, production of toxic metabolites from bacteria, and as an energy source. Folate biosynthesis pathway is the other target. DHFR is a vital enzyme in the previously mentioned pathway and is a target for some sulfa drugs. DHFR activity is also inhibited by EGCG. Other enzymes are also inhibited, which play a role in bacterial ATP synthase activity, bacterial DNA gyrase, and bacterial protein tyrosine phosphatase and cysteine proteases. It can be concluded that *C. sinensis* leaf extracts are used to treat multidrug-resistant strains of *P. aeruginosa*-related diseases.

C. sativum

C. sativum is an Apiaceae family annual plant. The herb is a Mediterranean native that is widely grown and used in countries such as India, Europe, and Argentina. This is an herb popularly known to all and can be used in a variety of ways such as spice, pharmaceutical, folk medicine, and food industries. It shows good antimicrobial activity due to the bilateral effect of bioactive chemicals present. This mechanism of action is unclear and is in the scope of research. *C. sativum* has anti-emetic, lipolytic, anti-inflammatory, antiseptic, antidiabetic, myorelaxant, and nerve soothing

properties. Antibacterial property is said to be found in methanolic leaf extracts of *C. sativum.* Linalool, camphor, a-pinene, and geraniol are the major components of essential oil.[9]

The reducing properties of the methanol extract from *C. sativum* seeds may partly explain the inhibition of bacterial growth when a mixture of phytochemicals is present in the growth medium. Deficiency of vital metal ions in the growth medium could be caused by the metal ion chelating trait of the extract. However, in the presence of extract, increased release of nucleotides occurs. Hence, the main mechanism of the action of *C. sativum* extract is membrane damage, which leads to cell death.

Quorum sensing (QS)

Bacteria employ a mechanism wherein the gene expression is regulated with respect to the density of the population, utilizing the signaling molecules. This mechanism is termed as QS [Figure 1]. Pathogens make use of this technique in the infection and disease process by communication and group behavior in bacterial populations.[4]

Biofilms are microcommunities of sessile bacteria found adhered to a surface. The flagellar-mediated motility helps in biofilm formation largely. Important role in biofilm formation is played by a cell-to-cell mechanism. There are three groups: Acyl homoserine lactones, the LuxS or autoinducer-2, and oligopeptides. A comprehensive work has been done to discover the mechanism by which QS regulates production of biofilm, as it can elucidate the pathway to control the biofilm formation. The Las QS system plays a primary role in creation of mature, differentiated biofilms.[15]

Mechanism of QS

Typical quorum-sensing pathways comprise signal molecules, bacterial populations, and behavioral genes. Autoinducers are signal molecules that are discharged into the environment by the bacteria. The increase in concentration of autoinducers is directly proportional to the growth of the bacterial population. The gene regulation occurs when the concentration reaches the threshold and the bacterial population can detect the molecules. These genes regulate various behaviors such as biofilm formation, horizontal gene transfer, virulence, and competence. Nonetheless, QS is customary among bacteria, for instance, *P. aeruginosa* uses QS to modulate disease mechanisms.[4]

QS control of P. aeruginosa virulence

A minimum of one orphan autoinducer receptor and three interlinked quorum sensing systems to influence the potential of *P. aeruginosa* to induce bacterial disease. Las and rhl (two of these systems) depend on the production of the signaling molecule, *N*-acyl homoserine lactone (AHLs). In the las system, the lasI gene encoded enzyme produces N-3-oxododecanoyl-homoserine lactone (3OC12-HSL). As *P. aeruginosa* attains the threshold, 3OC12-HSL attaches to the transcriptional activator LasR. This then dimerizes and attaches to motors and directs gene expression. In the rhl system, N-butyryl-homoserine lactone (C4-HSL) is produced from an rhlI gene-encoded enzyme. The transcriptional and post-transcriptional levels of the rhl system are restrained by the las system. Along with encoding RhlR and LasR, *P. aeruginosa* also encodes QscR (orphan receptor protein) which is capable of sensing 3OC12-HSL to control its own regulon.[4]

The ability of communication acquired due to QS is extremely useful in bacterial populations to obtain traits from animals, plants, and other higher level organisms. This helps bacterial populations to grow more quickly, procure access to increased resources, and gain stronger possibilities for survival. QS pathways help pathogens infect the host organisms more efficiently which leads to more fatal diseases.[4] Exploiting the above strategy used by bacteria, it could be a potential field for drug target therapy in the future.

DISCUSSION

In India, above 50% of skin diseases are effectively treated with extensive low cost. The great benefits of these bioactive compounds formulated, extracted and their preparations have been popular and evident in tribal areas and villages. Records on application of Ayurvedic medicines have been

Table 3: Comparison of Qu activity of bacteria

Bacteria	Infection	Cause for QS	Mechanism
S. aureus	Human infections: Blood stream, skin and soft tissue, skeletal and respiratory system	Agr locus, LuxS	Agr locus regulates QS which, in turn, regulates virulence in addition to the metabolic genes. Agr mutants show increased levels of biofilm formation[21]
Escherichia coli	Intestinal infections, bacteremia, urinary tract infection, cholangitis	Autoinducer substances	Cells of bacteria produce autoinducer substances (AI) to the extracellular layer and when required in high quantities they upregulate the formation of biofilm and its maturation. AI is responsible for secretion of virulence factors, regulating host immune response and genetic changes[22]

QS: Quorum sensing, *S. aureus*: *Staphylococcus aureus*, *E. coli*: *Escherichia coli*

Figure 1: *Pseudomonas aeruginosa*; quorum sensing. https://www.britannica.com/science/quorum

in use since 3000 BC. According to the Botanical Safety Handbook, herbs have been classified based on its safety and use into Class 1 (safe to consume appropriately), Class 2 (safe to consume with restriction), Class 3 (restricted to use only when supervised by an expert), and Class 4 (insufficient data of safety). The adverse climatic changes and change in the ecosystem with the development in the technology have resulted into serious and unlikely types of infections. *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* comprise major therapeutic challenges in the chronic wounds of burns.[16]

Traditional medicine forms; in the form of herbal teas – they are a mix of complete or partial drugs, hence, the effect is minimal, tinctures – they are drug extract, dry extracts – the moisture content is <2%.[17]

Gut bacteria have a substantial impact on the host's metabolic and immunological systems. Bacteria rely on QS to manage their survival and compete for space domination in the gut's loud environment. Bacteria, through their components or bacteria-derived metabolites, are essential in humans for maintaining epithelial barrier integrity and the mucosal immune system. Biofilm formation is linked to the PQS system. The above-mentioned QS signals interact with human cells when *P. aeruginosa* infects the host, causing physiological and functional alterations in immune cells. In inflammatory bowel illness, the wild-type strain harboring 3O-C12-HSL and C4-HSL increased macrophage phagocytosis and led to chronic inflammation indicators.[4] Table 3 for comparison of Quorum Sensing activities of different bacterial species.

CONCLUSION

India has been considered one of the largest producers of medicinal herbs globally also known as "Gold mine of herbs." Over 17,000 species of Indian flora and 7500 species of higher plants have been reported and proven to have effective medicinal value. Almost 25,000 effective plant-based formulations are still used in folk medicines by rural communities in India. This study is in the similar prospects of finding the use of natural antibiotics to manifest the decolonization of bacteria as an infectious agent. The less toxic or highly targeted effective application of herbal compounds as "*wonder drug*" sometimes also named as can protect the human skin from harmful external organisms. Skin infections are commonly caused by the bacteria *P. aeruginosa*. Plants have been long used by traditional healers to prevent or cure infectious diseases. The secondary metabolites present in plants have shown to have antimicrobial properties *in vitro*. *L. inermis* shows

antimicrobial properties by inactivating enzyme sites through the binding of free hydroxyls to the carbohydrates and proteins in bacterial cell walls. *C. sinensis* exhibits antimicrobial activity by avoiding the adhesion of the bacterial cell membrane in mammalian epithelial cells with the help of EGCG. *C. sativum* shows antibacterial properties by reacting with the proteinaceous materials and intracellular nucleotides released from the bacterial cells. From this study, it can be inferred that natural antibiotics could be an effective substitute for Western medicines.

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