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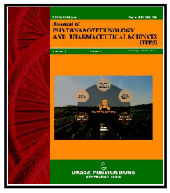

Review Article : Open Access

Mechanism to combat pan drug-resistant *Acinetobacter baumannii* using the traditional system of medicinal plant extracts

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Abstract

The number of fully active antibiotic options that treat many infections due to multidrug resistant, *Acinetobacter baumannii* (*A. baumannii*) is extremely limited. *A. baumannii* is an opportunistic bacterial pathogen, grouped under ESKAPE pathogens that are linked to a high degree of morbidity, mortality, and increased treatment costs (Infectious Disease Society of America). Predominantly causes respiratory infection, pneumonia, wound infections, and urinary tract infections. Resistance to the antibiotics such as amikacin, ampicillin, and aminoglycosidic drugs was revealed; thereby, the mortality and morbidity rates increasing in the infected persons. Carbapenem-resistant, *A. baumannii* has currently emerged as a major threat leaving behind no antibacterial treatment options. Pathogens acquire different mechanisms of antibiotics resistance like production of enzymes that lyse antibiotics, metal chelators, confirmation, alteration in receptor site of antibiotics, *etc*., which ensures drug resistance. Therefore, current research has been focused on finding effective and alternative medicine from plants with antibacterial activity against these bacteria. Herbal medicinal plants contain active herbal elements, such as flavonoids, tannins, phenolics, steroids, *etc*. These ingredients combat pathogens by enhancing the antibacterial activity of antibiotics or decreasing lytic activity of bacterial enzymes on antibiotics or inhibiting the expression pattern of antibiotics resistance genes, *etc*. More than one mechanism operated simultaneously to control such pathogens efficiently. This review article discusses the different types of herbal plants and plant parts which were selected to study their efficacy against *A. baumannii*.

1. Introduction

Acinetobacter baumannii is a gram-negative, short, round or rod shaped (coccobacillus), non-spore forming, non-capsulated bacteria. Typically, opportunistic pathogen in humans, affecting people with compromised immune systems, and is becoming increasingly important as a cause of nosocomial infection. Such as urinary tract infections, surgical site infections, meningitis, ventilator associated pneumonia, bacteremia, and very rarely intra-abdominal infections and infections of skin and central nervous system (*Zarrilli et al*., 2009). *A. baumannii* can cause significant morbidity and mortality, has emerged as a worldwide problem. *A. baumannii* bacteremia is associated with a high mortality rate, ranging from 29% to 46.9%. A diverse spectrum of comorbidities has been investigated as potential risk factors for mortality in many patients such as previous severity of organ failure, neutropenia, malignancy, inappropriate antimicrobial treatments, pneumonia as the source of bacteremia, and septic shock. The morbidity of this organisms is related to the patients underlying medical conditions and immune status. Today, no one single fully active antibiotic options available to treat nosocomial infection due to multidrug resistant, *A. baumannii*.

A. baumannii can cause infections in the blood, urinary tract and lungs or in wounds in other parts of the body. It can also colonize or live in a patient without causing infections or symptoms, especially in respiratory secretions (sputum) or open wounds. Antibiotic resistance occurs when the germs no longer respond to the antibiotics designed to kill them. If, they develop resistant to the group of antibiotics called carbapenem-resistant. When resistant to multiple antibiotics, they are multidrug resistant. *A. baumannii* can live for long periods of time on environmental surfaces and shared equipment, if they are not properly cleaned. The germs can spread from one person to another through contact with these contaminated surfaces or equipment or though person-to-person spread, often *via* contaminated hands. *Acinetobacter* infections are generally treated with antibiotics. To identify the best antibiotic to treat a specific infection, healthcare providers will send a specimen to the laboratory and test any bacteria that grow against a set of antibiotics to determine which are active against the germs. Unfortunately, many *Acinetobacter* germs are resistant to many antibiotics, including carbapenems, which makes them difficult to treat with available antibiotics (Aoife *et al.*, 2012).

A. baumannii can survive for prolonged periods in unsuitable environmental conditions and easily spread to patients in the hospital settings leading to healthcare associated infections. Major risk factors for *A. baumannii* infections are mechanical ventilation, invasive procedures such as central venous catheter or urinary catheter and the use of broad-spectrum antibiotics. The mortality rate of nosocomial *A. baumannii* have been reported between 50-60%, changing due to several factors (Karabay *et al.*, 2012).

Management of multidrug resistant *Acinetobacter* species, infection is a great challenge for physicians and clinical microbiologists. Its

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ability to survive in a hospital and its ability to persist for extended period of time on surfaces makes it a frequent cause for healthcare associated infections and it has led to multiple outbreaks. Multidrug resistant *Acinetobacter* species vary when referring to a wide array of genotypes and phenotypes. Different terms like multidrug resistant (MDR), extensive drug resistant (XDR), and pan drug resistant (PDR) have been used with varied definitions to describe the extent of antimicrobial resistance among *Acinetobacter* species. However, to date, unlike mycobacterial tuberculosis, internationally, there are no accepted definitions for the extent of resistance in the bacteria. Arbitrarily used term have thus caused great confusions, making it difficult for the available literature to be analyzed. They exhibit resistance through the production of class A, B, C and D beta lactamases, induction of efflux pumps, defects in the permeability of antibiotics, alteration of target antibiotic binding sites, and aminoglycoside group modifying enzymes (Jose *et al.*, 2015).

The organism is not very virulent but due to various innate mechanisms, it has the capacity to acquire resistance. Multidrug resistant isolates of *Acinetobacter* have been described as non-susceptible to at least one agent in all but two or fewer antibiotic classes and non-susceptible to all antibiotic classes.

2. Pathophysiology of *A. baumannii*

Acinetobacter poses very little risk to healthy people. People who have weakened immune system, chronic lung disease, or diabetes are more susceptible to *Acinetobacter* infection. Hospitalized patients, especially those who are very ill, have open wounds, burnt wounds, have an invasive device, are on ventilators, or are in the hospital for a long time is also at greater risk for *Acinetobacter* infection. It is spread by contact with a person or environment that has the bacteria. In healthcare facilities, the bacteria can spread from workers hands or contaminated surfaces or healthcare items. Symptoms of infection can appear from 4-40 days after exposure to the bacteria, but usually appear within about 12 days (Collins, 2008).

Despite extensive research into the virulence potential of this emerging pathogen, little is still known about its true pathogenic potential or virulence. Several factors may contribute to the virulence potential of *A. baumannii* one factor in particular, OmpA, a member of outer membrane protein determine to disease causing potential of the pathogen. *A. baumannii* OmpA binds to the host epithelia and mitochondria and it induces mitochondrial dysfunction and causes it to swell. Followed by the release of cytochrome C, a heme protein, which leads to formation of apoptosome. OmpA being the most abandoned surface protein on the pathogen, involved in resistance to complement and the formation of biofilms. Two key stress survival strategies and potentially important virulence associated factors that helps to promote bacterial survival both inside and outside the host are; the ability of *A. baumannii* to form biofilm allows it to grow persistently in unfavourable conditions and environments. Other factors include nutrient availability, presence of pili and outer membrane protein and macromolecular secretions.

Other key proteins that have been shown to contribute to *A. baumanni* virulence include phospholipase D and C. while phospholipase D is important for resistance to human serum, epithelial cell evasion and pathogenesis, phospholipase C enhances toxicity to epithelial cells. Along with OmpA, fimbria, also expressed on the surface of the bacterial cell, contribute to the adhesion of the pathogen to host epithelia (Aoife *et al.*, 2012).

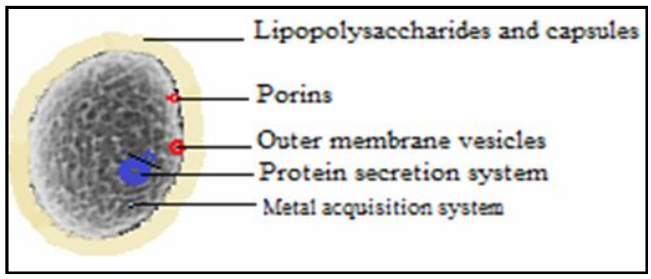

Figure 1: Different virulent mechanism adapted by *A. baumannii*.

2.1 Porins

Porins are outer membrane proteins associated with modulating cellular permeability. OmpA is a β-barrel porin and one of the most abundant porins in the outer membrane. In *A. baumannii*, Omp A is the very well-characterized virulence factor with a variety of interesting biological properties identified in *in vitro* model systems (Mc Connell *et. al*., 2013). Other porins, such as carbapenem associated outer membrane protein (CarO) and OprD-like, are also virulence-related factors associated with attenuated virulence in a mouse model.

2.2 Outer membrane vesicles (OMVs)

OMVs are spherical, 20-200 nm diameter vesicles secreted by the outer membranes of various gram-negative pathogenic bacteria (Kulp and Kuehn, 2010). They are composed of LPS, outer membrane and periplasmic proteins, phospholipids, and DNA or RNA, and are recognized as delivery vehicles for bacterial effectors to host cells. Many *A. baumannii* strains secrete OMVs containing various virulence factors, including OmpA (Moon *et al*., 2012), proteases, and phospholipases. OMVs derived from *A. baumannii* interact with host cells and deliver bacterial effectors to host cells *via* lipid rafts, resulting in cytotoxicity. An *A. baumannii* strain that produces abundant OMVs with more virulence factors induces a stronger innate immune response and is more cytotoxic compared with those of a strain producing fewer OMVs (Li *et al*., 2015).

2.3 Protein secretion systems

Several protein secretion systems have been identified in *A. baumannii*. The most recently described *A. baumannii* secretion system is a type II secretion system (T2SS). The T2SS is a multi-protein complex that is structurally very similar to type IV pili systems, which is an appendage that is commonly found in gram-negative bacteria. *A. baumannii* also has a type VI secretion system (T6SS). Many bacteria use the T6SS to inject effector proteins, providing a colonization advantage during infection of eukaryotic hosts or to kill competing bacteria (Basler *et al*., 2013).

2.4 Capsular polysaccharides and lipopolysaccharides (LPS)

A. baumannii infections express surface capsular polysaccharides and contain a conserved gene cluster, called the K locus, which may determine production of capsular polysaccharides. LPS is the major component of the outer leaflet of the outer membrane in most gram-negative bacteria and is an immunoreactive molecule that induces release of tumor necrosis factor and interleukin 8 from macrophages in a Toll-like receptor 4 (TLR4)-dependent manner. In *A. baumannii*, LPS plays a major role in virulence and survival of *A. baumannii* (Luke *et al*., 2010). Many studies have shown that modifications in LPS decrease the susceptibility of *A. baumannii* to many clinical important antibiotics, such as colistin (Chin *et al*., 2015).

2.5 Phospholipase

Phospholipase is a lipolytic enzyme essential for phospholipid metabolism and is a virulence factor in many bacteria, such as *P. aeruginosa*, *Legionella monocytogenes*, and *Clostridium perfringens*. Three classes of phospholipases, such as phospholipase A(PLA), phospholipase C(PLC), and phospholipase D(PLD) have been defined based on the cleavage site.

2.6 Metal acquisition system

Although, iron is one of the most abundant elements in environmental and biological systems, ferric iron is relatively unavailable to bacteria in the preferred state, because of its poor solubility (10^{-17}M solubility limit for ferric iron) under aerobic and neutral pH conditions as well as due to chelation by low molecular-weight compounds, such as heme, or high-affinity iron-binding compounds, such as lactoferrin and transferrin. To overcome this iron limitation, most aerobic bacteria produce a high-affinity iron chelator known as a siderophore. Siderophores are low molecular weight compounds (400-1,000 kDa) with high affinity for iron. The range of Fe^{3+} siderophore association constants is 1012-1052 (Saha *et al*., 2013).

2.7 Penicillin binding protein 7/8 (PBP7/8) and β-lactamase PER-1

Although, PBPs are commonly involved in resistance to β-lactam antibiotics, PBP7/8 encoded by the pbpG gene is a virulence factor in *A. baumannii*. The pbpG mutant strain grows similar to its wild-type strain in Luria-Bertani medium, but the mutant shows reduced growth in human serum and its survival significantly decreases in rat soft-tissue infection and pneumonia models (Russo *et al*., 2009). An investigation of bacterial morphology using electron microscopy suggested that loss of PBP7/8 may have affected peptidoglycan structure, which may affect susceptibility to host defense factors (Russo *et al*., 2009).

3. Evolution of multidrug resistance of *A. baumannii*

A. baumannii is labelled as MDR-Ab when it is resistant to more than two of the following five classes of antibiotics:

1. Antipseudomonal cephalosporins (ceftazidime or cefepime).
2. Antipseudomonal carbapenem (imipenem or meropenem).
3. Ampicillin/sullbactum.
4. Fluoroquimolones (ciprofloxacin or levofloxacin) and
5. Aminoglycosides (gentamicin, tobramycin or amikacin).

In the past years, carbapenem where considered as the most important agent for the treatment of infections caused by MDR-*A. baumannii*. Carbapenem resistant *A. baumannii* (CRAB) is now emerging as a potential threat and is usually resistant to all microbial classes except colistin and tigecycline. The most important mechanism of carbapenem resistant in *A. baumannii* is enzyme inactivation by the production of β-lactamases, which hydrolases the carbapenems. The hydrolysing enzyme includes metallo-β-lactamases and class D β-lactamases. The main gene clusters responsible for this resistance are blaOXA-58, blaOXA-23, blaOXA-24/40. They are identified in chromosomes or in plasmids of *A. baumannii* strains.

Another mechanism of reduced susceptibility to carbapenems are:

1. Altered penicillin binding proteins and porins and
2. Upregulation of efflux system.

These factors may together lead to high level carbapenem resistance in these bacteria.

4. General treatment options of *A. baumannii*

Although, carbapenems are effective antibiotics to treat *A. baumannii* infections, the rate of carbapenem-resistant *A. baumannii* isolates has been increasing gradually (Su *et. al*., 2012). Only a few effective antibiotic options are available to treat MDR *A. baumannii* infections. The antibiotics that are usually effective against *A. baumannii* infections include carbapenems, polymyxins E and B, sulbactam, piperacillin/tazobactam, tigecycline and aminoglycosides. Carbapenems (imipenem, meropenem, doripenem) are the mainstay of treatment for *A. baumannii*, though carbapenem-resistant *Acinetobacter* strains have increasingly been reported worldwide in recent years. Different types of drugs are being used which includes;

4.1 Polymyxins

Polymyxins (polymyxin B and colistin (polymyxin E)) are the most commonly used agents for *Acinetobacter* isolates resistant to first-line agents. The dose depends on the formulation of colistin available, which varies by geographic region. They are reserved for use in the setting of highly resistant organisms. Colistin has been used with some success for the treatment of *Acinetobacter* pneumonia, bacteremia, and meningitis.

Both polymyxin B and colistin are rapid-acting bactericidal agents, with a detergent-like mechanism of action. Polymyxins interact with lipopolysaccharide (LPS) of the outer membrane of gram-negative bacteria and are subsequently taken up *via* the 'self-promoted uptake' pathway. The polycationic peptide ring binds to the outer membrane displacing the calcium and magnesium bridges that stabilize the LPS.

4.2 Minocycline

Many resistant strains of *A. baumannii* are susceptible *in vitro* to minocycline, which can be given intravenously, and limited clinical experience suggests favorable outcomes with its use. Minocycline was used for multi- or extensively resistant *A. baumannii* infections, predominantly ventilator-associated pneumonia, but also skin and soft tissue infections, successful clinical and microbiologic outcomes were reported for most patients.The mechanism of action of minocycline involves attaching to the bacterial 30S ribosomal subunit and preventing protein synthesis.This antimicrobial agent has been approved for the treatment of acne vulgaris, some sexually transmitted diseases and rheumatoid arthritis.

4.3 Tigecycline

Tigecycline has activity against some multidrug- and extensively drug-resistant strains of *A. baumannii*, although resistance has been reported and clinical experience is limited. In general, however, tigecycline should not be used in circumstances in which other effective antibiotic choices are available. Tigecycline's antibacterial mechanism of action is similar to that of older tetracyclines. It works by inhibiting bacterial protein synthesis by binding to bacterial 30S ribosomal subunits, ultimately blocking entry of aminoacyl transfer RNA molecules into the A site of the ribosome.

4.4 Cefiderocol

Most isolates of extensively drug-resistant *A. baumannii*, including those possessing OXA-type beta-lactamases, remain susceptible to cefiderocol. However, clinical experience is limited.

4.5 Eravacycline

This broad-spectrum tetracycline is active *in vitro* against most carbapenem-resistant *A. baumannii*, at MICs that are lower than with tigecycline. However, clinical experience is extremely limited.

The novel beta-lactam-beta-lactamase combinations (*e.g.*, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam) do not have activity against carbapenem-resistant *A. baumannii.*

4.6 Combination therapy

Combination antimicrobial therapy is frequently used in *Acinetobacter* infections as a strategy to increase the likelihood of adequate empiric antibiotic coverage before drug susceptibility testing results are known, to decrease the risk of emergent resistance, and to improve outcomes in multidrug or extensively drug-resistant infections, but there are no definitive clinical data to support its use for these purposes. Several other therapies are also practiced which includes; empiric therapy, directed therapy, *etc.*

A. baumannii has emerged in the last decades as a major cause of healthcare associated infections and nosocomial outbreaks. MDR - *A. baumannii* is a rapidly emerging pathogen in healthcare settings, where it causes infections that includes bacteremia, pneumonia, meningitis, and urinary tract and wound infections. Antimicrobial resistance poses great limit for therapeutic options.

5. *A. baumannii* and traditional medicinal herbs

Medicinal plants, also called medicinal herbs, have been discovered and used in traditional medicine practices since prehistoric times. Plants synthesise hundreds of chemical compounds for functions including defence against insects, fungi, diseases, and herbivorous mammals. Numerous phytochemicals with potential or established biological activity have been identified. However, since a single plant contains widely diverse phytochemicals, the effects of using a whole plant as medicine are uncertain. Further, the phytochemical content and pharmacological actions, if any, of many plants having medicinal potential remain unassessed by rigorous scientific research to define efficacy and safety. In many countries, there is little regulation of traditional medicine, but the World Health Organization coordinates a network to encourage safe and rational usage. Medicinal plants face both general threats, such as climate change and habitat destruction, and the specific threat of over-collection to meet market demand.

Although, no antibiotics with specific cellular targets have been isolated from plants but modified plant natural antibiotics has been more successful such as penicillin (Lewis and Ausubel, 2006). Attempts to develop potent antibiotics from plants have failed by both pharmaceutical and biotech firms. A reason for this may be the use of varying chemical strategy by the plants to control bacterial infection, in order to reduce the selective pressure for developing resistance to antibiotics. For instance, antibacterial active compounds may act quite effectively in combinations and have little potency alone. Plant alkaloid berberine has excellent antibacterial properties, but it is ineffective when acting alone as it is a preferred substrate of bacterial encoded MDRs (multidrug resistance pumps). 52-methoxyhydno carpin, a compound isolated from the same plant as berberine blocks the MDRs, and therefore, enabling berberine to act as a potent antibacterial agent in presence of this compound. So, it is very necessary to first identify the antibacterial mechanism of the plants and then screen pharmaceutically to develop some effective antibiotic (Lewis and Ausubel, 2006). Since there is no new development of antibiotics against the carbapenem resistant strains of *A. baumannii*, therefore, it is necessary to focus on the antimicrobial activity of plant derived substances that are being used in traditional medicine worldwide (Savoia, 2012). Secondary metabolites are responsible for the antimicrobial activity of plants. In this present review, we have explained the various herbal active compounds which have potent activity against *A. baumannii* and other gram-negative bacteria. This will initiate the search for new antibiotics from herbal origin against the resistant strains of *A. baumannii* and this may lead to the development of new antibiotics.

6. Plant parts used for medicinal purposes

Medicinal properties derived from plants can come from many different parts of a plant including leaves, roots, bark, fruit, seeds, flowers. The different parts of plants can contain different active ingredients within one plant. Thus, one part of the plant could be toxic while another portion of the same plant could be harmless.

Medicinal properties can be derived from the following:

6.1 Bark

The protective outer layer of a tree trunk that is formed by layers of living cells above the wood. Active ingredients are often found in higher concentrations in the bark. Examples of bark used for medicinal properties are quinine bark, oak bark, pepperbark, and willow bark (Jane *et al.*, 2011).

6.2 Bulb

A bulb is defined as a fleshy structure comprised of numerous layers of leaf bases otherwise known as bulb scales. Onion species and garlic bulbs are popular for medicinal uses.

6.3 Essential oil

These are defined as volatile oils that are generally extracted from plants using a steam distillation process. Examples include camphor and peppermint oil.

6.4 Fatty oil

These are defined as non-volatile vegetable oils that are pressed from the seeds or fruits of plants and are insoluble in water. Examples of fatty oils used in medicine are castor oil, olive oil, and safflower oil. Some fatty oils have direct medicinal properties while others are used as carriers in liquid formations and ointments.

6.5 Flowers

The flowers of plants have always been popular in traditional medicine. Examples include clove and chamomile flowers. Flower parts are also used such as saffron stamens, the stigmas of maize, or pollen.

Table 1: Plant extract with active compounds and its mechanism to inhibit *A. baumanii*

Plant name	Antibacterial compounds	Extracted from	Separation methods	Identification method	References
Aloe vera (Indian aloe, GhiKunvar)	p-coumaric acid, ascorbic acid, pyrocatecholcinnamic acid	Leaves	Ethanol, methanol and acetone extracts, thin layer and column chromatography	GC-MS	Tiwari *et al*., 2015
Allium sativum (garlic)	Allyl methyl disulphide, diallylsulfide, diallyltrisulfide, allyl methyl trisulfide, diallyldisulfide	Bulbs	HPLC	GC-MS	Lai *et al*., 2013
Cinnamomum zeylanicum (cinnamic/dalchini	Trans-cinnamaldehyde	Essential leaf oil	N/A	N/A	Pelletier, 2012
Oreganum vulgare (oregano)	Carvacrol	Essential leaf oil	N/A	N/A	Pelletier, 2012
Curcuma longa (turmeric/haldi)	Curcumin	Plant extraction powder	Methanolic extract	N/A	Betts and wareham, 2014
Azadirachta indica (neem)	Stgmasterol, nimbiol,sugiol, 4-cymene,α-terpinene,terpinen-4-ol	Leaves,bark	Methanolic extract	GC-MS	Nand *et al*., 2012
Camellia sinensis (green tea)	Epigallocatechingallate, epicatechin	Plant extract powder	Ethanolic extract	N/A	Betts and Wareham, 2014
Camellia sinensis (black tea)	Theaflavin	Plant extract powder	Ethanolic extract	N/A	Betts *et al*., 2011.
Cinnamomum zeylanicuma,b (cinnamon)	Rans-cinnamaldehyde	Essential leaf oil	N/A	N/A	Saulnier, 2014
Curcuma longa (turmeric/haldi)	**Decrease in ROS due to quenching and** Helps in Downregulation of the QS genes **by** Curcumin	Plant extract powder	Methanolicextract	N/A	Kaur *et al*., 2018
Holarrhenaanti dysenterica	7.8 µg/ml demonstrated remarkable resistant modifying ability against A. *baumanni* in combination with Novobiocin.	Bark	Ethanol extracts (alkaloids, condensed tannins, and triterpenoids)	Phytochemical analysis	Phatthalung *et al*., 2012
Lythrum salicaria	Hexahydroxydiphenoyl ester vescalagin	Flowers and leaves	Methanolic extract	Column chromatography	Guclu *et al*., 2014
Pimentaracemosa essential oils	β-Myrcene, limonene, 1,8-cineole, and eugenol	Leaf	Essential oils	GC/MS	Ismail *et al*., 2020
Pisumsativum	NuriPep 1653, a non-modified peptide which has low propensity to induce bacterial resistance. A novel anti-infective or adjuvant compound capable of reverting resistant phenotypes.	Protein library of plant	Purified compound from MS	GenScript	Mohan *et al*., 2019
Syzygium aromaticuma (clove)	Guanosine, apioline, eugenol, and elemicin binds to Penicilling binding protein 1 & 3 makes it sensitive to antibiotics	Essential leaf oil	Hydroxide solution or ethanolic extract extraction and distillation	N/A	Saulnier, 2014; Mahmoud *et al*., 2021

6.6 Fruit

Fruits have been heavily used for medicinal purposes. Dried whole fruits or portions of fruits can be used. Many members of the carrot family have fruits that are used in medicine including fennel fruit and anise.

6.7 Gum

Gums are solids that are mixtures of polysaccharides (sugars). They are water-soluble and are in part digestible by humans.

6.8 Leaf

The leaves of plants, shrubs, and trees can be used for medicinal properties. Leaves can be used alone or can be mixed with twigs, stems, and buds. Examples include maidenhair tree.

6.9 Resins

Resins are a mixture of essential oils and terpenes that are usually not soluble in water. They are excreted by specialized cells or in ducts of plants. Examples include frankincense, myrrh, and mastic.

6.10 Roots

The fleshy or woody roots are used for medicinal purposes. Roots may be solid (ginseng), fibrous (stinging nettle), or fleshy (devil's claw).

6.11 Rhizome

A rhizome is defined as a fleshy or woody elongated stem that usually grows horizontally below the ground. Rhizomes often produce leaves above the ground and roots into the ground. Several medicinal plants are used primarily for their rhizomes including: ginger, wild columbine, and bloodroot.

6.12 Seed

The seeds of many plants are used for their medicinal properties. Seeds may be contained within a fruit or are sometimes used on their own. Juniper berries look like fruits but they are actually seeds surrounded by beautiful woody cones (Subas Chandra Parija and Harithalakshmi Jandhyam, 2018).

6.13 Tuber

A tuber is defined as a swollen, fleshy structure below ground. Tubers are usually of stem origin but can be partly stem and root in origin. Tubers used for medicinal properties include African potato and autumn crocus.

6.14 Wood

Thick stems or the wood of trees or shrubs are used for medicinal properties. Sandalwood and quassia wood are popular examples.

Mountain monardella (*Monardellao doratissima*) is a member of the mint family, whose members are notable for their essential oils. Echinacea species (*Echinacea angustifolia*) were widely used by the North American plains, Indians for its general medicinal qualities (Ekor, 2014).

7. Concenterations

The six most active compounds where identified as: ellagic acid in *Rosa rugosa*; norwogonin in *Scutellaria baicalensis*; and chebulagic acid, chebulinic acid, corrilagin and terchebulin in *Terminialia chebula*. The most potent compound was identified as norwogonin with a minimum inhibitory concenteration of 128 µg/ml, and minimum bactericidal concenteration of 256 µg/ml against clinically relevant strains of *A. baumannii*. In several studies, the conclusion were identified as antimicrobial compound, norwogonin was the most potent against multidrug resistant *A.baumannii* strains (Miyasaki *et al.*, 2013).

8. Active compounds of plants and its identification

Numerous works have been done to isolate and characterize bioactive compounds from plant resources that are active against gram-positive and gram-negative bacteria, fungi and viruses. Miyasaki reported that generally flavones, tannins and phenolic compounds are known to be active against *Acinetobacter* (Miyasaki *et al*., 2013). Many active herbal compounds have been isolated and reported for their activities. These secondary metabolites were extracted using different solvents such as methanol, ethanol, water, hydroxide, acetone, and through various techniques like HPLC, column chromatography from plant materials. The antibacterial components of various plants, their separation and identification techniques are listed below in Table 1. Some of these herbal compounds have the ability to work alone or in presence of the other, *i.e.*, in synergy which are also explained in Table 1. Here, the study aimed to the literature regarding herbal active compounds which are naturally presents against various bacteria, including *A. baumannii.*

9. Conclusion

Like emerging viral mutants, evolution of drug-resistant bacterial pathogens heaves big challenge in treatment of clinical pathogens such as *Tubercle bacilli*. A novel strategy needed to control completely eradicate the pathogen without any side-effects. Currently antibiotics in combinations are recommended for the treatment of bacterial infections, including infections caused by *A. baumannii.* Side effects caused by the antibiotics throws a major constraint in recommendation. So, a biocompatible compound inhibiting pathogens in more than one mechanism needed to overcome the problem. Phytochemicals from various edible plant parts are bio-companionable and inhibit the pathogens by more than a single mechanism. Herbal ingredients in synergistic activity with antibiotics such as colistin found to inhibit the ESKAPE pathogen. So, several similar studies are underway which will pave a promising way or opening-up novel ways to treat XRD pathogens.

Conflict of interest:

The authors declare no conflicts of interest relevant to this article.

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