



## Plants as a source of new antimicrobials and resistance modifying agents against multi drug-resistant (MDR) strains-A short review

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### Abstract

Antibiotic resistance has restricted the usage of reasonably-priced and vintage antibiotics, has necessitated to used better magnificence antibiotics. The want of better magnificence antibiotics wants a endured look for new antimicrobial compounds. Understanding the mechanisms of resistance is vital withinside the improvement of techniques to fixing the hassle. Active efflux of drugs, alteration of goal web web sites and enzymatic degradations are the techniques with the aid of using which pathogenic microorganism collect or broaden intrinsic resistance to antibiotics. Multi-drug resistance (MDR) pumps, able to spotting and expelling a number of structurally unrelated compounds from the bacterial mobileular and conferring resistance to a huge variety of antibiotics have on the grounds that been characterized in lots of Gram advantageous and Gram terrible pathogens like *Staphylococcus au reus*, *Pseudomonas ae ruginosa*, *Escherichia coli* and, extra recently, in mycobacteria. The cap potential of a few chemical compounds (known as MDR inhibitors or resistance editing agents) to regulate the resistance phenotype in microorganism with the aid of using operating synergistically with antibiotics in vitro has on the grounds that been observed. The look for such compounds which may be mixed with antibiotics withinside the remedy of drug resistant infections can be an opportunity to overcoming the hassle of resistance in microorganism. Crude extracts of medicinal flora stand out as veritable reasserts of ability resistance.

**Keywords:** MDR, plant extract, resistant modifying agent

### Introduction

Infectious sicknesses because of microorganism and fungi have an effect on tens of thousands and thousands of human beings global. Throughout the records of mankind, infectious sicknesses have remained a main purpose of dying and disability. Today, infectious sicknesses account for one-1/3 of all deaths Withinside the world; the World Health Organization estimates that almost 50,000 human beings die every day during the arena from infectious illnesses. The discovery of antibiotics become an crucial element in preventing bacterial infections that when ravaged humankind. Different antibiotics workout their inhibitory pastime on distinct pathogenic organisms. The improvement and unfold of resistance to presently to be had antibiotics is a global concern <sup>[1]</sup>. The growing phenomenon of acquisition of resistance amongst microorganisms to antimicrobial pills is attributed to the indiscriminate and unsuitable use of cutting-edge antimicrobial pills. Today, clinically vital microorganism are characterized now no longer best with the aid of using unmarried drug resistance, however additionally with the aid of using a couple of antibiotic resistance – the legacy of beyond a long time of antimicrobial use and misuse. Drug resistance offers an ever growing international fitness hazard that includes all foremost microbial pathogens and antimicrobial pills. These are hard to deal with and are accountable for a number of infectious illnesses. For over a decade, the tempo of improvement of recent antimicrobial sellers has bogged down whilst the superiority of resistance has grown at an astronomical charge. The charge of emergence of antibiotic resistant microorganism isn't matched with the aid of using

the charge of improvement of recent antibiotics to fight them <sup>[1]</sup>.

Antibiotics that paintings these days might not paintings tomorrow. It is crucial to research more recent pills to which there may be lesser resistance. As resistance to antique antibiotics spreads, the improvement of recent antimicrobial sellers needs to be expedited if the trouble is to be contained.

However, the beyond report of rapid, vast emergence of resistance to newly added antimicrobial sellers suggests that even new households of antimicrobial sellers could have a quick existence expectancy <sup>[2]</sup>.

The gradually growing bacterial resistance to current pills is a extreme trouble, and consequently there may be a dire want to look for new training of antibacterial substances, particularly from herbal sources. Unlike artificial pills, antimicrobials of plant beginning aren't related to aspect outcomes and feature a superb healing capability to heal many infectious illnesses. Sometimes the usage of unmarried antibiotic does now no longer produce the preferred powerful inhibitory outcomes and to triumph over this, a aggregate of medicine frequently physical games their synergistic impact which surpasses their man or woman performance. The synergistic impact can be because of sure complicated formation which will become extra powerful with inside the inhibition of a specific species of microorganisms both with the aid of using inhibiting the mobileular wall synthesis or with the aid of using inflicting its lyses or dying <sup>[2]</sup>.

The international emergence of multi-drug resistant bacterial lines is an increasing number of restricting the

effectiveness of cutting-edge pills and extensively inflicting remedy failure of infections examples consist of methicillin-resistant Staphylococci, Pneumococci proof against penicillin and macrolides, vancomycin-resistant Enterococci in addition to multi drug resistant Gram – negative organisms. [2] As resistance to antique antibiotics spreads, the improvement of recent antimicrobial sellers needs to be expedited if the trouble is to be contained. However, the beyond report of rapid, vast and emergence of resistance to newly added antimicrobial sellers suggests that even new households of antimicrobial sellers could have a quick existence expectancy [2]. According to the World Health Organization, infectious illnesses are the 1/3 maximum sizable motive of mortality round the arena. The burden of infectious illnesses is Excessive in growing countries, as is the emergence of MDR pathogens because of bad health-care facilities, and over the counter availability and misuse of antimicrobial agents. The frequency of resistance is located similarly amongst Gram-poor and Gram-nice organisms, even though Gram-poor microorganism are at risk of expand a MDR phenotype. The excessive occurrence charge of MDR Pseudomonas and Acinetobacter infections in significantly sick sufferers in addition to the presence of MDR Salmonella and Staphylococcus aureus in regular groups are conventional examples of microbiological demanding situations posed in those geographic locations [3].

Plants are traditionally used to deal with infectious diseases. In in advance days humans used to find out treatments from the nearby herbs. People first used flowers as meals and if effects of ingestion had been favorable, the flowers had been connected with a few sedative and healing properties. For instance, stays of the hollyhock plant, which continues to be an vital herb in phytomedicine, are located withinside the historical civilization of the Neanderthals. Scientific proof helps the speculation that numerous flowers are composed of biologically energetic chemical entities and numerous capsules in contemporary-day day remedy are definitely analogues of plant foundation substances. [3]

### Antibiotic history, developments and mechanism of actions:

Before the 20thcentury, drug treatments consisted specially of herbs and potions. It changed into now no longer till the mid19th century that the primary critical efforts had been made to isolate and purify the energetic standards of those treatments. Since than many evidently taking place capsules were received and their shape determined [4].

There is proof of antibacterial herbs or potions getting used for lots centuries. For instance, the Chinese used mouldy soybean curd to deal with carbuncles, boils, and different infections. Greek physicians used wine, myrrh and inorganic salts. In the center ages, sure sorts of honey had been used to save you infections following arrow wounds. [4] Bacteria are unmarried mobile ular microorganisms which had been first recognized with inside the 1670s via way of means of Van Leeuwenhoek. French scientist Paster, who validated that unique bacterial lines had been vital to fermentation and that those and different microorganisms had been greater great than changed into formerly thought. The opportunity that those microorganisms is probably answerable for disorder started to take hold [4]. Lister introduce ‘germ idea of disorder’ and additionally delivered Carbohic acid as an

antiseptic and sterilizing agent for working theatres and wards. [4]

During the latter ½ of of the 19th century, scientists which include Koch had been capable of discover the microorganisms answerable for the disorder which include tuberculosis, cholera and typhoid. Methods of vaccination had been studied and studies changed into carried. [4]

Paul Ehrlich- father of chemotherapy, delivered the ‘precept of chemotherapy’ changed into that a chemical ought to immediately intervene with the proliferation of microorganisms, at concentrations tolerated via way of meanof the host. This idea changed into popularly called the ‘magic bullet’. The procedure is one of the selective toxicity, wherein the chemical indicates more toxicity to the goal microorganism than to the host cells. Such selectivity may be represented via way of means of a ‘chemotherapeutic index’. He had effectively advanced the primary instance of simply Synthetic antimicrobial drug salvarsan in 1940 [4]

Over the next 20 years, advances were made against a wide variety of protozoal diseases, but little progress had been made in the search for antibiotics until the introduction of proflavin in 1934. Unfortunately, it was too toxic to be used against systemic infections. In 1935, Prontosil was effective in vivo against streptococcal infections. The discovery of sulfonamides, or sulfonamides, was a breakthrough, as they were the first effective drugs against systemic bacterial infections. [4]

Penicillin was discovered in 1928, but was effectively isolated by Florey and Chain in 1940. Penicillin was more effective than sulfonamides, but not against all types of infections, and the need for new antibacterial agents persists. Penicillin is an example of a toxic fungal metabolite that kills bacteria and allows the fungus to compete for nutrients. The understanding that fungi could be the source of new antibiotics. [4]

In 1944 the antibiotic streptomycin was discovered during a systemic search for soil organisms. This compound was the first in a series of antibiotics known as aminoglycosides, which are effective against a wide variety of bacterial infections caused by Gram-ve. The search led to the discovery of chloramphenicol (1947), peptide antibiotics (eg, bacitracin; 1945), tetracycline antibiotics (eg, chlortetracycline; 1948), macrolide antibiotics (eg, erythromycin; 1952), antibiotics cyclic peptides (eg valinomycin) and in 1955 the first example of a second major group of β-lactam antibiotics, cephalosporin C. [4]

In 1952, isoniazid was found to be effective against human tuberculosis. And in 1962, nalidixic acid (the first quinolone antibiotic) was discovered. The second generation of this class of drugs was introduced in 1987 with ciprofloxacin. [4]

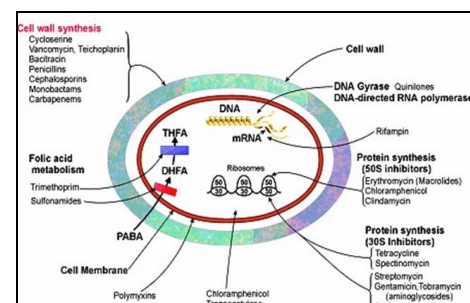


Fig 1: Bacterial targets of current antibiotics used in the clinic [5]

### Mechanism of Action

There are five main mechanisms by which antibiotics work.

- Inhibition of cell metabolism: Antibacterial agents that inhibit cell metabolism are called antimetabolites. These compounds inhibit the metabolism of microorganisms but not the metabolism of the host. They can do this by inhibiting an enzyme-catalyzed reaction that is present in bacterial cells but not animal cells. Example; Sulfonamides. [4]
- Inhibition of bacterial cell wall synthesis: Inhibition of cell wall synthesis leads to lysis and death of bacterial cells. Agents that work in this way include penicillins, cephalosporins, and vancomycin. Since animal cells do not have a cell wall, these agents do not affect them. [4]
- Interactions with the plasma membrane: some antibacterial agents interact with the plasma membrane of bacterial cells and influence the permeability of the membrane. This has fatal consequences for the cell. Example; Polymyxins and tyrothricin [4].
- Disruption of protein synthesis: Disruption of protein synthesis means that essential proteins and enzymes that are necessary for cell survival can no longer be produced. Active ingredients that disrupt protein synthesis include rifamycin's, aminoglycosides, tetracyclines, and chloramphenicol [4].
- Inhibition of nucleic acid transcription and replication: Inhibition of nucleic acid function prevents cell division and / or synthesis of essential proteins. The active ingredients that work in this way are nalidixic acid and proflavine. [4]

Antibiotics are the main basis for the therapy of microbial (bacterial and fungal) infections. Since the discovery of these antibiotics and their use as chemotherapy drugs, the medical community has believed that this would ultimately lead to the eradication of infectious diseases. However, the excessive use of antibiotics has become an important factor for the emergence and spread of multi-resistant strains of multiple groups of microorganisms. The worldwide emergence of *Escherichia coli*, *Klebsiella pneumoniae*, *Hemophilus*, and many other  $\beta$ -lactamase producers has become a major therapeutic problem. Multi-resistant strains of *E. coli* and *K. pneumoniae* are widespread in hospitals and increasingly isolated from community-acquired infections. *Candida albicans*, also a nosocomial pathogen, has been reported to be responsible for 50-70% of invasive candidiasis cases. It is alarming that the incidence of nosocomial candidemia has increased considerably during the last decade. All of this had serious consequences, including rising drug costs and patient mortality. [6]

### Antibiotic resistance and its development history

Antibiotic resistance is a form of drug resistance in which some (or less often all) subpopulations of a microorganism, usually a species of bacteria, can survive after from exposure to one or more antibiotics; Pathogens that are resistant to various antibiotics are considered multidrug resistant (MDR) or colloquially as superbugs.

Antibiotic resistance is a serious and growing phenomenon in modern medicine and has become one of the most important health problems of the 21st century. A World Health Organization report published on April 30, 2014 states: "This serious threat is no longer a prediction of the future, it is now happening in all regions of the world and

has the potential to affect anyone, regardless. his age, in any country. "if bacteria changing so that antibiotics no longer work for people who need them to treat infections is a major public health threat today. [8]

In the past fifty years, only two new classes of antimicrobial compounds, such as oxazolidinone and cyclic lipopeptides, have passed clinical trials and are available for clinical use. These active principles have undergone a similar development, and in the last decade six drugs have been introduced on the market; however, they are not useful for MDR pathogens due to the rapid development of resistance mechanisms in bacteria. Most of the other compounds are not included in clinical trials due to their lack of sustained activity and higher rates of toxicity. It is clear that advances in drug discovery lag far behind what is required to meet current needs. The situation calls for the rapid development of new antimicrobial agents. [3]

For most strains of MRSA, glycopeptide-type drugs, such as vancomycin, are the only effective antimicrobial agents. However, vancomycin-resistant *S. aureus* (VRSA) has been reported [10]. As resistance to old antibiotics spreads, the development of new antimicrobial agents must be accelerated to contain the problem. However, the rapid, widespread and emerging resistances to recently introduced antimicrobial agents in the past indicate that even new families of antimicrobial agents will have a short life expectancy. [2]

As resistant clinical isolates are spreading rapidly around the world, finding new antimicrobial agents is of utmost importance. However, the rapid and widespread resistance to recently introduced antimicrobial agents in the past indicates that even new families of antimicrobial agents will have a short life expectancy. For this reason, researchers are paying increasing attention to herbal products and seeking new approaches to develop better drugs against MDR microbes. (6)

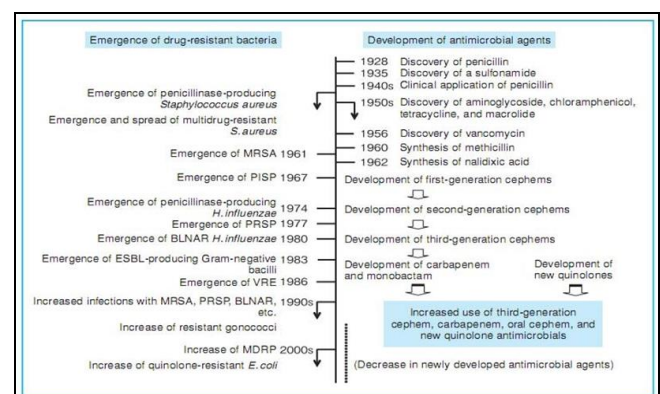


Fig 2: Trend of development of antimicrobial agents and emergence of drug- resistant bacteria [9]

In the simplest case, drug-resistant organisms may have acquired resistance to first-line antibiotics, requiring the use of second-line agents. Typically, a first-line agent is selected based on several factors, including security, availability, and cost; a second-line agent tends to have a broader scope, a less favorable risk-benefit profile, and is more expensive or, in severe cases, may not be available locally. In some MDR pathogens, resistance to second and even third line antibiotics is acquired sequentially, a case that in some nosocomial situations is usually illustrated with *Staphylococcus aureus*. Some pathogens, such as

*Pseudomonas aeruginosa*, also have high intrinsic resistance. 4,444 antibiotic resistance genes, like antibiotics themselves, are ancient. However, the increasing prevalence of antibiotic resistant bacterial infections in clinical practice is due to the use of antibiotics in both human and veterinary medicine. Any use of antibiotics can increase selection pressure in a bacterial population so that resistant bacteria can thrive and susceptible bacteria can die. As resistance to antibiotics becomes more common, there is a greater need for alternative treatments. Despite the push for new antibiotic therapies, the number of newly approved drugs has steadily declined. Antibiotic resistance is therefore a major problem. [4, 7] Certain classes of antibiotics are more strongly associated with colonization of "superbugs" than other classes of antibiotics. A superbug, also known as multi-resistant, is a bacterium that carries several resistance genes. If superbugs are not susceptible (resistance) to the antibiotic used and if there is high tissue penetration and a broad spectrum effect against "good bacteria", the risk of colonization increases. In the case of MRSA, increased rates of MRSA infections are seen with glycopeptides, cephalosporins, and especially quinolones. If *Clostridium* is difficult to colonize, high-risk antibiotics include cephalosporins and, in particular, quinolones and clindamycin [4, 7].

#### MDR Source

- Although there were a small number of bacteria resistant to pre-existing antibiotics before the widespread use of antibiotics, evolutionary pressures arising from their use have influenced the development of multi-resistant strains and the spread of resistance between bacterial species. The widespread use of antibiotics in and outside of medicine plays an important role in the development of resistant bacteria.
- In some countries, antibiotics are sold without a prescription, which also leads to the formation of resistant strains.
- The use of antibacterial agents in soaps and other household products is also discouraged, although they do not clearly contribute to resistance (as they are not effective in controlling infection).
- Unhealthy practices in the pharmaceutical industry can also contribute to the likelihood of formation of antibiotic resistant strains.
- Procedures and clinical practice during drug treatment are often flawed - steps are normally not taken to isolate the patient to prevent reinfection or infection with a new pathogen, which is the goal of complete destruction. Cancel the end of the course.

#### Antibiotic resistance mechanism in pathogenic bacteria

Antibiotic resistance is the result of three main strategies, namely, enzyme inactivation, modification of target sites, and efflux extrusion. While chemical modifications may be important in antibiotic resistance, exclusion of unchanged antibiotics from the cell is the main strategy for denying the antibiotic access to its targets and is believed to increase resistance even in cases where the that modifications are the main mechanism. [2]

#### Drug Target Modification

Chemical modifications of the antibiotic target can result in reduced affinity of the antibiotic for its binding site. This is

a mechanism used by a number of pathogenic bacteria to avoid the effects of antibiotics. The modifications are usually mediated by constitutive and inducible enzymes. Resistance to the macrolide antibiotics, lincosamide, and streptogramin B (MLS<sub>B</sub> resistance) in pathogenic *Streptococcus* species is the result of the N6 amino group methylation of an adenine residue in 23S rRNA. This is believed to cause conformational changes in the ribosome, resulting in a decrease in the binding affinity of these antibiotics to their binding sites on the 50S ribosomal subunit. Beta-lactam antibiotics work by binding to penicillin-binding proteins (PBPs) and inhibiting their biosynthetic activity, thus blocking cell wall synthesis. In the. *aureus* and *S. pneumoniae* resistance to  $\beta$ -lactams may be the result of mutations that lead to the production of PBP2a and PBP2b, respectively. The two proteins have a reduced affinity for  $\beta$ -lactams and yet assume the functions of normal PBPs in the presence of inhibitory levels of  $\beta$ -lactams. This resistance mechanism is also responsible for resistance to  $\beta$ -lactams in non- $\beta$ -lactamase-producing *Hemophilus influenzae*. [2] It is now widely recognized that constitutive expression of efflux pump proteins encoded by housekeeping genes that are widespread in bacterial genomes are largely responsible for the phenomenon of intrinsic antibiotic resistance. Several studies have shown that active efflux can be a mechanism of resistance for almost all antibiotics. The majority of the efflux systems in bacteria are nondrug specific proteins that can recognize and pump out a broad range of chemically and structurally unrelated compounds from bacteria in an energy dependent manner, without drug alteration or degradation. The consequence of this drug extrusion is that it leads to a reduced intracellular concentration of the antimicrobial such that the bacterium can survive under conditions of elevated antimicrobial concentration. The MIC of the drug against such organisms will be higher than predicted. [2]

Multidrug resistance efflux pumps are ubiquitous proteins present in both Gram positive and Gram negative bacteria as either chromosomally encoded or plasmid encoded. Although such proteins are present constitutively in bacteria, the continued presence of the substrate induces overexpression. This increased transcription is responsible for the acquired resistance. In Gram negative bacteria, the effect of the efflux pumps in combination with the reduced drug uptake due to the double membrane barrier is responsible for the high inherent and acquired antibiotic resistance often associated with this group of organisms [1, 2, 4]. The MDR pumps of pathogenic bacteria known so far belong to five families of transporters namely; the major facilitator superfamily (MFS), the adenosine triphosphate (ATP) binding cassette (ABC) superfamily, the small multidrug resistance (SMR) family, and the resistance no dilation cell division (RND) superfamily and the multidrug and toxic compound extrusion (MATE) family. [1, 2, 4]

#### Some characterized efflux proteins of pathogenic bacteria

The Nora protein of *S. aureus* is the best-studied chromosomally encoded pump in pathogenic gram positive bacteria.

It is present in *S. epidermidis* but appears to be absent in *Enterococcus faecalis* or in gram negative organisms, such as *E. coli* and *K. pneumoniae*. Overexpression of the N or A gene in *S. aureus* confers resistance to chloramphenicol and

hydrophilic fluoroquinolone antimicrobials [2]. QA is a member of the major facilitator superfamily of transport proteins, which are involved in the uniport, symport, and antiport of a wide range of substances across the cell membrane. The QA multidrug exporter from *S. aureus* mediates resistance to a wide array of monovalent or divalent cationic, lipophilic, antimicrobial compounds. QA offers resistance to these various compounds through an anti-transport mechanism that depends on the driving force of the proton. [2]. The *S. pyogenes* menD exit protein is a 44.2 kDa hydrophobic transposon-encoded protein of the major facilitator superfamily that mediates macrolide exit, leading to the M phenotype in *S. pyogenes*. It shares 90% amino acid homology with MefE from *S. pneumoniae*, which also mediates macrolide output [2]. For (pneumococcal multidrug resistance protein): *S. pneumoniae* efflux is a chromosomally encoded protein from the family of major facilitators that confers a resistance profile in *S. pneumoniae*. Pneumonia similar to that of N or A in *S. aureus*. The exit protein, which is not constitutively expressed in pneumococcal strains, is responsible for the low resistance to fluoroquinolones in pneumococci. Scientific experiments since the late 19th century have documented the antimicrobial properties of some spices, herbs, and their components. According to the World Health Organization, medicinal plants would be the best source to obtain a wide variety of medicines. Therefore, such plants should be investigated to better understand their properties, Safety and Efficiency. [9]. Plant extracts as antimicrobial agents are currently used only rarely as systemic antibiotics, this may be due to their low activity, especially against gram-negative bacteria. Here we test an alternative approach to of treating bacterial infections by combining antimicrobial agents with raw plant extracts against various pathogens. [10] Synergism is a positive interaction that arises when two active ingredients combine and exert an inhibitory effect that is greater than the sum of their individual effects. Combination therapy can be used to expand the antimicrobial spectrum, prevent the emergence of resistant mutants, minimize toxicity, and achieve synergistic antimicrobial activity, and could be an alternative to monotherapy for patients with difficult-to-treat invasive infections such as: species resistant to medications and for those that do not respond to standard treatment [12].

### **Plants as a source of new antimicrobial agents and resistance modifiers:**

Natural products are rich in biologically active compounds. Many of today's medicines are obtained directly from a natural source or have been developed from a lead substance originally obtained from a natural source. Generally, the natural source has some form of biological activity and the compound responsible for that activity is known as the active ingredient. Such a structure can act as a main compound. Most of the biologically active natural products are secondary metabolites with quite complex structures. This has an advantage in that they are extremely novel compounds [4].

The alkaloid berberine is a common component of a variety of plant species, particularly in the family of Berberidaceae. Berberine alkaloids, which are cationic antimicrobials produced by a variety of plants are readily extruded by MDRs. Berberine was found to synthesize an inhibitor of N or A MDR pump of a human pathogen *Staphylococcus*

*Aureus*. The inhibitor was identified as 5'-methoxyhydnoicarpin, previously reported as a minor component of chaulmoogra oil, a traditional therapy for leprosy [13]. The interaction between water extracts of *Psidium guajava*, *Rosmarinus officinalis*, *Salvia fruticosa*, *Majorana syriaca*, *Ocimum basilica*, *Syzygium aromaticum*, *Laurus nobilis* and *Rosa damascena* alone and then synergy testing of these extracts with known antimicrobial agents of different mechanisms (protein synthesis inhibition: oxytetracycline HCl and gentamicin sulfate; cell wall synthesis inhibition: penicillin G and cephalixin; folic acid synthesis inhibition: Sulfadimethoxine as sodium; and nucleic acid synthesis inhibition: enrofloxacin) using both well diffusion and microdilution method. This study was conducted against five *S. aureus* isolates; one is Methicillin resistant *Staphylococcus aureus* (MRSA) and 4 Methicillin sensitive *Staphylococcus aureus* (MSSA). The results of the conducted experiments using the well diffusion method demonstrate that these plants showed in vitro interactions between antimicrobial agents and plant extracts were additive against the five strains of *S. aureus* while using microdilution method showed synergistic effects between a combination of antibiotics and plant extracts with a significant reduction in the MICs of the test antibiotics against these strains of *S. aureus*. This change in MIC was noticed in all plant extracts against test antibiotics including these plants that showed weak antibacterial activity by well diffusion method. Our results also showed that the synergistic effect between the antimicrobial agent and the plant extract occurred in both susceptible and resistant strains, but the degree of minimal inhibition in resistant strains, especially MRSA strains, was greater than in sensitive strains. [10] Multi-drug resistant (MDR) strains of *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida albicans*. ATCC strains of *Streptococcus mutans*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus bovis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Candida albicans*, of which they showed strong resistance to *Acacia albicans*. *Acacia* resistance. It showed resistance to the extracts of *Terminalia arjuna* and *Eucalyptus globulus*. Community-acquired infections were more sensitive to these extracts than nosocomial infections. The strongest antimicrobial plant was *A. notice*. [6]

*Pseudomonas* are widespread in nature, inhabiting soil, water, plants, and animals (including humans). *Pseudomonas aeruginosa* has become an important cause of infection, especially in patients with compromised host defense mechanisms. Total 5 MDR isolates of *Pseudomonas* sp. were selected for further studies on the basis of their resistance to more than 60% antibiotics. Hot and cold extracts of solvents with increasing order of polarity from petroleum ether, chloroform, acetone, methanol and water were used for study. The combined effect of *Foeniculum vulgare* Miller herbal extracts and antibiotics on the susceptibility of multidrug resistant (MDR) isolates was promising, although individual extracts were not effective against any isolate. The concept of this synergism offers a new idea of antibiotics and bioactive plant extracts in the development of a combined antimicrobial therapy for the effective treatment of *Pseudomonas* MDR isolates. [14]

Studies were conducted to determine the antibacterial activity of 35 aqueous herbal extracts against a total of 20 clinical adhesives *Shiella* s p. isolated. The maximum

antibacterial activity was found in crude extracts of *Syzygium a Romanticismo* (leaf) and *Citrus limon L* at 90%. (Fruit) followed by 85% in *Spondias pinata* (leaf). The sensitivity of these isolates was also evaluated for eight commercial antibiotic discs following disc diffusion assay where most of the isolates were found to develop resistance against multiple commercial antibiotics. 85% of isolates exhibited resistance to chloramphenicol and erythromycin and 80% were resistant to sulfamethoxazole and cephadrine. The isolates showed their resistance between 5560 % to the other four antibiotic discs, viz; gentamycin, streptomycin, ciprofloxacin, and azithromycin. Among 35 herbal extracts tested, 19 herbal extracts were found to possess antimicrobial activity in all multidrug resistant isolates. Therefore these herbal extracts could be used in the future direction as alternative therapeutic agents for the treatment of human diseases caused by *Klebsiella sp* [15].

The emergence of antibiotic resistant bacteria such as *Staphylococcus aureus* calls for inventive research and development strategies. Inhibition of this bacterial pathogenesis may be a promising therapeutic approach. The screening of antimicrobial compounds from endophytes is a promising way to meet the increasing threat of drug resistant strains of human and plant pathogens. In the study, a new endophytic fungus, *Colletotrichum gloeosporioides*, was isolated from the medicinal plant *Vitex n Segundo L*. Extracts of sporozoites of *C. gloeo* were obtained using hexane, ethyl acetate and methanol as solvents. The fungal extracts showed effective antimicrobial activity against bacterial and fungal strains. The extracts were also examined for their antibacterial activity against strains of *S. aureus* resistant to methicillin, penicillin and vancomycin (1-10). The methanol extract showed effective antibacterial activity against *S. aureus* strain 9, with a minimum inhibitory concentration of 31.25 mg/mL. The synergistic effect of an endophytic fungus extract with antibiotics such as methicillin, penicillin and vancomycin against *S. aureus* strain 6. The fractional inhibitory concentration index of methanol extract with methicillin, penicillin, and vancomycin was 1.0, 0.5, and 0.375, respectively. These results clearly indicate that the metabolite of endophytic fungus *C. gloeosporioides* is a potential source of new antibiotics [17]. Some isolated pure compounds of plant origin have been reported to have resistance modifying activities in vitro. Examples of some of the compounds are given in the following table. This has prompted the search for these compounds in a wide variety of medicinal plants. Some of the compounds that have been shown to have direct anti-microbial activity have also been shown to enhance the activity of antibiotics when used at low MIC values.

**Table 1:** some antibiotic resistance modifying compounds from plants [18, 19, 20].

Compound	Plant source	Antibiotics potentiated
Ferruginol 5-Epispiferol	<i>Chamaecyparis lawsoniana</i>	Oxacillin, Tetracycline, Norfloxacin Tetracycline
Carnosic acid carnosol	<i>Rosmarinus officinalis</i>	Erythromycin
Ethyl gallate	<i>Caesalpinia spinosa</i>	$\beta$ -lactams
Epicatechin gallate Epigallocatechin gallate	<i>Camellia sinensis</i>	Norfloxacin, Imipenem, Panipenem $\beta$ -Lactams

Plants that have been used medicinally for thousands of years and most of the world still depends on them. This

study describes the chemical and biological investigations of *Terminalia arjuna*, a plant of the Combretaceae family. Here, the ethanolic extract of *Terminalia arjuna* leaf fruit was used to observe cytotoxicity and antibacterial activity. To determine the bioactivity of the extract, a saltwater shrimp lethality test was performed and it was observed that the LC50 obtained for the T. extract was rich in bioactive compounds. To monitor antibacterial activity, four gram negative and two gram positive bacteria were tested using the agar well diffusion method. The results show that the antibacterial activity of the extract depended on the concentration in the range of 0.510 mg / ml. The striking and characteristic feature of the observed antibacterial activity of the T. arjuna extract is that even at low concentrations (3 mg / ml) it showed good activity against multiresistant gram-negative bacteria *Coliform s pp*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*. The minimal inhibitory concentration (MIC) for the extract was predicted and ranged from 320 mg / ml. [21]

Strength modifying activities of raw plant extracts: the basis for the isolation of potentially useful compounds. If the isolation of resistance modifying compounds from plants is to be realistic, the detection of such activities in crude extracts is the first step in identifying evidence for the isolation of such compounds, and some plants have good indications of these potentials. for use in combination with antimicrobial therapy. Aqueous tea extracts (*Camellia sinensis*) have been shown to reverse methicillin resistance in MRSA and, to some extent, penicillin resistance in beta-lactamase-producing *Staphylococcus aureus*. [22]

*Punica granatum*, *Soymidaf febrifuge*, *Ter Terminalia chebula*, *Tinospora cor defoliata*) and *Tribulus t Terrestris*) was controlled by the agar well diffusion method. This study examines the efficacy of antimicrobial agents for multi-resistant bacteria (MDR) with a view to their possible use in conjunction with common antibiotics. Pathogenic bacteria were isolated from urine samples from patients admitted to the hospital and admitted to the hospital. The isolated bacteria were a florid MDR for most of the day's antibiotics. Methanol extracts from 9 plants were used and extracts from 3 plants, *A. acuminata*, *P. granatum* and *S. febrifuga*, caused at least 25-29 mm as a maximum zone of inhibition in bacterial lawns. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of methanol extracts from 9 plants were recorded. The *A. acuminata* methanol extract had 0.29 mg / ml as the lowest MIC value and 0.67 mg / ml as the lowest MBC value against MDR *S. aureus*, which means efficacy; but it had the highest MIC value. [23]

Extracts from leaves of *Psidium guajava*, *P. Phyllanthus niruri*, *Ehretia microphylla*, and pipe beetle (*P. beetle*) showed antibacterial activity against gram-positive methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. *P. beetle* showed the highest antibacterial activity for these bacteria in the disc diffusion tests (inhibitory diameter 16–33 mm), minimum inhibitory concentration (19–156 mg / ml), and minimum bactericidal concentration (312 mg / ml). Extracts from *P. beetle* leaves showed only remarkable antibacterial activity for all multi resistant gram-negative bacteria (extended-spectrum beta-lactamase-producing, carbapenem-resistant, and metallo beta-lactamase-producing enterobacteria *E. diameter*), Minimum inhibitory concentration tests (312-625 mg / ml) Concentration (312-625 mg / ml). [24]

## Conclusion

Although there is a large body of published data validating the antimicrobial activity of medicinal plants commonly used in folk medicine, this has not led to the identification of commercially viable plant-based antibacterial agents. Most plant-derived antimicrobial compounds generally have MICs greater than antibiotics produced by bacteria or fungi, limiting their therapeutic potential. It has already been established that crude extracts of some medicinal plants and some pure compounds of such plants can enhance the activity of antibiotics in vitro. This search for modulators of antibiotic resistance in plants represents a new dimension in tackling the problem of antibiotic resistance. The chemical diversity present in plants with respect to the potential to enhance the clinical efficacy of antibiotics is still largely unexplored. Most interesting are medicinal plants and food plants that are accidentally used with antibiotics in common community practices and provide opportunities for interaction. Since many medicinal plants are still unexplored, there are enormous opportunities for the discovery of new plant-based compounds that modify resistance. The selection of antibiotic resistance modifying compounds of plant origin is expected to provide the basis for the identification of guidelines for the isolation of therapeutically useful compounds. This could be followed by in vivo evaluations in the future to determine the clinical relevance of such compounds. This represents a potential area for future research.

## Reference

- Chanda S, Rakholiya K. Combination Therapy: Synergism Between Natural Plant Extracts And Antibiotics Against Infectious Diseases. Science Against Microbial Pathogens: Communicating Current Research And Technological Advances, 2011, 520-529.
- Sibanda T, Okoh AI. The Challenges of Overcoming Antibiotic Resistance: Plant Extracts As Potential Sources of Antimicrobial And Resistance Modifying Agents. African Journal of Biotechnology, 2007;6(25):2886-2896.
- Farooqui A, Khan A, Borghetto I, Kazmi SU, Rubino S, Paglietti B. Synergistic Antimicrobial Activity Of Camellia Sinensis And Juglans Regia Against Multidrug-Resistant Bacteria. Plos One, 2015;10:E0118431.
- Patrick, Graham L. An Introduction To Medicinal Chemistry (First Edition, Part B Chapter 9 And Part D Chapter 16). Oxford University Press, 2006.
- Sumitra chandra, Kalpana Rakholiya. Combination therapy: Synergism between natural plant extracts and antibiotics against infectious diseases. Science against microbial pathogen s: communicating current research and technological advances A. mendez-vilas (Ed.), 2011, 520-529.
- Khan R, Islam B, Akram M, Shakil S, Ahmad A, Ali SM, Khan AU. Antimicrobial Activity Of Five Herbal Extracts Against Multi Drug Resistant (Mdr) Strains of Bacteria And Fungus Of Clinical Origin. Molecules, 2009;14:586-597.
- Antibiotic resistant. retrieved from <http://wikipedia/antibiotic-resistance>, retrived date, 2015.
- WHO. Fact sheet N°194. Retrieved from <http://www.who.int/drugresistance/publications/infographic-antimicrobial-resistance-2014043>
- Tomoo Saga, Keizo Yamaguchi. History of Antimicrobial Agents and Resistant Bacteria. Japan medical association journal (JMAJ), 2009;52(2):103-108.
- Ghaleb Adwan, mohammad Mhanna. Synergic effects of plant extracts and antibiotics on Staphylococcus aureus strains isolated from clinical specimens. Middle-East Journal of scientific research, 2008;3(3):134-139.
- Sevil Toroglu. In-vitro antimicrobial activity and synergistic/antagonistic effect of interactions between antibiotics and some spice essential oils. Journal of Environmental Biology, 2011;32(1):23-29.
- Aiyegoro Olayinka, Afolayan Anthony J, Okoh Anthony. Synergistic interaction of Helichrysum pedunculatum leaf extracts with antibiotics against wound infection associated bacteria. Biol Res, 2009;42:327-338.
- Frank stermitz, Peter Lorenz *et al.* Synergy in a medical plant: Antimicrobial action of berberine potentiated by 5'-methoxyhydnocarpin, a multidrug pump inhibitor. Proceedings of the National Academy of Sciences, 2000;97(4):1433-1437.
- Vijay N Charde, Pratik M Bezalwar, Ashok V Gomash. In Vitro Management of MDR Pseudomonas Sp. By Combined Activity of Antibiotics and Foeniculum Vulgare Miller Extract. International Journal of Research Studies in Biosciences (IJRSB), 2014;2(11):62-70.
- Rehnuma Sharmeen. Md. Nazmul Hossain *et al* In-vitro antibacterial activity of herbal aqueous extract against multi-drug resistant Klebsiella sp. isolated from human clinical samples. International Current Pharmaceutical Journal, 2012;1(6):133-137.
- Bassam abu-shanab, ghaleb adwan, dahood abu-safiya antibacterial activities of some plant extracts utilized in popular medicine in palestine. Turk j biol, 2004;28:99-102.
- U.S. Ezhil Arivudainambi, Thangarajan Durai Anand *et al.* Novel bioactive metabolites producing endophytic fungus Colletotrichum gloeosporioides against multidrug-resistant Staphylococcus aureus. FEMS Immunol Med Microbiol, 2011;61:340-345.
- Smith ECJ, Williamson EM *et al.* Antibacterial and modulators of bacterial resistance from the immature cones of Chamaecyparis lawsoniana. Phytochem, 2007;68(2):210-217.
- Oluwatuyi M, Kaatz GW, Gibbons S. Antibacterial and resistance modifying activity of Rosmarinus officinalis. Phytochemistry, 2004;65(24):3249-3254.
- Shibata H, Kondo K *et al.* Alkyl Gallates, Intensifiers of  $\beta$ -Lactam susceptibility in Methicillin-resistant Staphylococcus aureus. Antimicrob. Agents Chemother, 2005;49(2):549-555.
- Abdullah-Al-Emran, Farzana Ahmed *et al.* Investigation of Antimicrobial Activity of Ethanolic Leaf- Fruit Extract of Terminalia arjuna against Multi-Drug Resistance (MDR) Bacteria in Bangladesh. Journal of Applied Environmental and Biological Sciences, 2011;1(5)90-95.
- Stapleton PD, Shah S, Anderson JC, Hara Y, Hamilton-Miller JMT. Modulation of  $\beta$ -lactam resistance in Staphylococcus aureus by catechins and gallates. International Journal of Antimicrobial Agents, 2004;23(5):462-467.
- Monali P Mishra, Sibanarayan Rath, Shasank S. Swain *et al* In vitro antibacterial activity of crude extracts of 9

- selected medicinal plants against UTI causing MDR bacteria. Journal of King Saud University – Science. Retrieved, 2015. from <http://dx.doi.org/10.1016/j.jksus.2015.05.007>
24. Demetrio L Valle Jr, Jeannie I Andrade *et al.* Antibacterial activities of ethanol extracts of Philippine medicinal plants against multidrug-resistant bacteria. Asian Pacific Journal of Tropical Biomedicine, 2015;5(7):532-540.