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A review of natural drugs in the treatment of multidrug resistance microbes

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Abstract

The supreme danger to the life of humans is the microorganisms that are resistant to conventional drugs and cause several life-threatening diseases. Out of them, some are more terrifying as they are resistant to modern antibiotics and cause more complications than normal bacteria and other microorganisms. The resistance among various microbial species (infectious agents) to different antimicrobial drugs has emerged as a cause of public health threats all over the world at a terrifying rate. Due to the pacing advent of new resistance mechanisms and decrease in efficiency of treating common infectious diseases, it fails in microbial response to standard treatment, leading to prolonged illness, higher expenditures for health care, and an immense risk of death. Almost all the capable infecting agents (e.g., bacteria, fungi, viruses, and parasites) have employed high levels of multidrug resistance (MDR) with enhanced morbidity and mortality; thus, they are referred to as superbugs. although the development of MDR is a natural phenomenon, the inappropriate use of antimicrobial drugs, inadequate sanitary conditions, inappropriate food handling, and poor infection prevention, and control practices contribute to the emergence of and encourage the further spread of MDR. Considering the significance of MDR, so to counter the problem we decided to find a solution for this threat and a study should be made to find a proper drug for combating the multidrug-resistant Bacteria.

Keywords: Multidrug-resistant, Antibiotics, Herbal drugs, Essential oil

Introduction

Any organism resistant to one or more classes of antimicrobials is termed multidrug resistance. The aggregation of genes often causes multidrug resistance in bacteria and other microbes, with every gene coding for resistance to every single drug, on R plasmids. The building of resistance genes on an R plasmid is achieved by a mechanism that is provided by transposons, integrons, and ISCR elements. The other mechanism of multidrug resistance is the basic pumping of drugs by multidrug efflux pumps. The Resistant-nodulation-division superfamily pumps in gram-negative bacteria are specifically important because they are

generally coded by chromosomal genes and can be overexpressed easily and because some of them can pump out most of the antibiotics that are currently in use.

Drug resistance is currently recorded for all types of infectious agents. This can restrain the action of antimicrobials. Resistance can occur due to mutation or gene transfer. Multidrug resistance is a vital issue in medical and agricultural advancements. In medicine, the exposure of resistance to multiple drugs usually utilized in therapy is a major hurdle in the treatment of several tumors as well as of various diseases such as tuberculosis, malaria, and other bacterial and fungal infections which often complicate major disabling syndromes like AIDS. In agriculture, the control of resistance of plant pathogens towards natural plant toxins of defense and towards common fungicides, as well as the development of parasite-toxins-resistant crops are economically important. Penicillin was discovered in 1928 followed by many other antibiotics. We presently underestimate that any infectious disease can be cured by antibiotic therapy. Antibiotics and their use had a powerful impact on the life of bacteria. Through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centre for Disease Control and Prevention (CDC) an international expert group comes together to create a uniform international terminology with which to describe obtained resistant profiles in *Staphylococcus aureus (methicillin-resistant), Enterococcus spp., Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp*., these all bacteria are found responsible for infection and susceptible to multidrug resistance. These antibiotics are for humans, animals, and fish, and this resulted in the selection of pathogenic bacteria that are resistant to multiple drugs. Around 500,000 species of plants have been calculated on earth and out of them only 1-10% are utilized as foods by animals and humans. Plants have been another source of medicine for fighting against diseases since earlier times. About 50% of all pharmaceutical products distributed in the United States are of plant origin. The use of natural products derived from plants in medical treatments is gaining more attention due to its potential efficiency and no side effects. Plants are a natural and rich source of precious secondary metabolites. For example, quinines, terpenoids, alkaloids, polyphenols, tannins, and flavonoids are used by plants as a protection mechanism against microorganism predation, herbivores, and insects. Some of the herbs and species that are being used by humans to season foods could give useful medicinal compounds. Multidrug-resistant strains of mycobacterium tuberculosis pose a major threat to universal health. WHO estimates that in 2018, there were new cases of about half a million rifampicin-resistant TB identified universally, of which the larger number have multidrug-resistant tuberculosis which is a form of tuberculosis that is resistant to the two very powerful anti-TB drugs. Isoniazid is a prodrug used in tuberculosis in its first line treatment which works as oxidation by a catalase peroxidase KatG, leading to the formation of an isonicotinoyl radical that then reacts with NAD(H) and forms a functioning metabolite known as the INH-NADH adduct. Multidrug-resistant TB requires treatment courses that are longer, not more effective, and very expensive than those for TB which is non-resistant. Less than 60% of multidrug-resistant TB are successfully cured which were treated.

Antimicrobial resistance

Antimicrobial resistance is a general health and development threat. To attain long-lasting development goals needs urgent multi-sector action. It includes antibiotics, antivirals, antifungals, and antiparasitic and they are the drugs used to prevent and cure infections in humans, animals, and plants.

Antimicrobial resistance occurs when bacteria, viruses, fungi, and parasites change with time and afterward don't respond to drugs making infections hard to treat and building up the risk of disease spread, severe illness, and ultimately death. As a result of resistance to drugs antibiotics and other antimicrobial drugs become ineffective and infections become difficult to treat and sometimes even impossible to treat.

Treatment of MDR

Infection with multidrug resistance *Acinetobacter baumannii* shows a significant expansion in mortality compared to those with multidrug-resistant *Pseudomonas aeruginosa*. Phytochemicals, like essential oils, could be a possible solution to combat multidrug-resistant bacteria. The antimicrobial efficacy of several essential oils such as *Eucalyptus camaldulensis* oil has been known for many years. It is traditionally used to prepare herbal remedies by aborigines in Australia, indicating the plant's antimicrobial properties. *Eucalyptus camaldulensis* leaf extracts have recently been proven to be vital against multidrug-resistant bacteria; including *A. baumannii* likewise its essential oil is accounted to be a good antimicrobial agent against both gram-negative and gram-positive bacteria. The essential oil obtained from this is safer for use when administered alone with a maximal adult oral dose of 300-600 mg and a maximal dermal application level of 5-20%.

Across Australia dried kino was also prepared by mixing fresh kino with water and subsequently dehydrated and they are used in the same way as fresh but previously were softened in water. The small leaves are used as a smoke bath. The smoking medicine was used for fever, flu, cold, and general sickness.

Therapy of herbal drug in combination with antibiotic

Plant products proved as more favorable or challenging antimicrobials even though the antimicrobial activity is lighter than commercially available antibiotics. Essential oils have been used for many years as a curative potential. Herbal drugs are used in combination with antibiotics with amplified activity against bacterial infection. Herbal drugs may act with more energy than drugs to kill microbes, herbs may destroy the enzymes that are produced by bacteria to destroy antibiotics, and herbal drugs may hamper the action of efflux pumps making bacteria unable to remove antibiotics from their body. This combination theory can be used as another therapy against bacterial infections in veterinary and human medicine. It is very important to know the various types of side effects that occur due to the use of different drug combinations. This combined therapy has many advantages which include treatment of mixed infection, or infection caused by specific causative organisms, to enhance antimicrobial activity, stopping the need for long-term antibiotic use, and preventing exposure to multidrug-resistant bacteria. There is one more benefit of using combination therapy which is the use of combination therapy provides a better chance that at least one drug will be

effective in case of intra-abdominal infections that are usually caused by multiple organisms with a variety of aerobic and anaerobic bacteria. Antimicrobial agents such as cephalosporin of the third generation with the drug metronidazole can be used as a possible treatment option in these cases and it can be more cost-effective sometimes than a single agent.

Herbs as antimicrobial

Herbs have been used for many years as food additives and traditional medicine against many infectious agents. The most used herbs that have antimicrobial properties are garlic, black cumin, cinnamon thyme, cloves, mustard, etc. According to WHO herbs can be the best source for a variety of drugs. So it is very important to study herbs in a better way to understand their properties, safety, and efficiency.

Multidrug-resistant microorganisms have been liable for no. of infectious plagues and represent a genuine danger to worldwide wellbeing. There is a prerequisite of earnest exploration here as powerful treatments are absent for these multidrug-resistant microorganisms combined with diminished number of antimicrobial medications in the drug pipeline to treat these contaminations. Resistant of gram-positive microbes, methicillin-resistant Staphylococcus aureus, multidrug-resistant Pseudomonas aeruginosa and multidrug-resistant tuberculosis keep on being the most hazardous, however more as of late there has been expanding reports of vanomycin-resistant Staphylococcus aureus contaminations. For profoundly resistant gram negative microscopic organisms, vanomycin-resistant Enterococci multidrug-safe carbapenemase-producing Klebsiella pneumoniae and multidrug-resistant *Acinetobacter baumannii* are significant as these microorganisms are regularly just powerless to more established antimicrobial specialists, for example, the polymyxins that have a higher unfavorable function profile.

Plant essential oils in the treatment of multidrug-resistant bacteria:

Anti-microbial obstruction is recorded to be a difficult issue that influences the decision of appropriate anti-microbial treatment and builds the likelihood of unfavorable contamination outcomes. One of the proposed techniques to adapt to multidrug-resistant (MDR) microbes is the utilization of elective antibacterial medicines, which incorporate common antimicrobial substances, for example, plant essential oils (EOs). This topic means to survey distributed examinations on the movement of essential oils and their constituents against MDR microbes and to define viewpoints for what's to come. As a rule, distributed investigations show that essential oils can be utilized as successful disinfectants against numerous species, including Multidrug-resistant microorganisms, for example- resistant isolates of *Pseudomonas aeruginosa*, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, Klebsiella pneumoniae, etc. certain essential oils may potentiate the viability of anti-microbials against MDR microscopic organisms; Essential oils can be synergistic with bacteriophages; and polymeric nanoparticles can be utilized for the conveyance of essential oils and upgrade of their action at the site of disease.

Silver nanoparticles; the powerful nano weapon against multidrug-resistant bacteria

In the current situation, biomedical &pharmaceutical areas are confronting the difficulties of nonstop expansion in the multidrug-resistant (MDR) human pathogenic microorganisms. Re-emergence of Multidrug-resistant microorganisms is encouraged by drug as well as anti-microbial resistance, which is an acquired method of microorganisms for their endurance and multiplication in awkward conditions. Multidrug-resistant bacterial infections lead to huge increases in mortality, morbidity, and cost of delayed treatment. In this way, improvement, modification, or looking for antimicrobial compounds having bactericidal potential against MDR microscopic organisms is a priority for the research. Silver as different compounds and Bhasma's have been utilized in Ayurveda to treat a few bacterial diseases since time of immemorial. As a few pathogenic microbes are creating anti-biotic resistance, silver nanoparticles are the new hope to treat them. This paragraph examines the bactericidal capability of silver nanoparticles against the MDR microscopic organisms. This multiactional phenomenon can be utilized for the treatment and anticipation of drug-resistant microorganisms. When an individual is infected with MDR microscopic organisms, it is not easy to cure the person. the person needs to invest their time in the medical clinic and requires a numerous therapy of broad-spectrum anti-infection agents, which are less successful, more poisonous, and more costly. Along these lines, advancement of or adjustment in antimicrobial compounds to improve bactericidal potential is a needed territory of exploration in this present scenario. Nanotechnology gives a good platform to alter and build up the significant properties of metal as nanoparticles having promising applications in diagnostics, biomarkers, cell marking, and contrast operators for natural imaging, antimicrobial specialists, drug conveyance frameworks, and nano drugs for the treatment of different infections. Subsequently, analysts are moving towards nanoparticles as a rule and silver nanoparticles specifically to tackle the issue of the rise of multidrug-resistant microbes.

Plants with their constituents and antimicrobial properties

HERBAL DRUG	ACTIVE CONSTITUENTS	THERAPEUTIC ACTION	THERAPEUTIC USE
Ocimum sanctum	Eugenol, urosolic acid	Analgesics, anti-inflammatory, antipyretic, immunomodulatory, Antibacterial	Against enteric organisms and pathogenic microbes.
Cinnamomum cassia	Cinnamaldehyde, 2-Hydroxy Cinnamaldehyde	Antimicrobial	Foodborne pathogens, Skin infection
Curcuma longa	Curcumin	Antimicrobial, Anti-inflammatory, Anti-neoplastic	Detoxification, Insecticidal, wound healing
Piper nigrum	Piperine, Penta-dienyl-piperidine	Antimicrobial (Anti-Mycobacterial)	Asthma, Toxins
Thymus vulgaris	Thymol and carvacrol	Antibacterial, Anticandidal, Antioxidant	Digestive disorders
Withania somnifera	Withanolides, Withaferins, Dimeric-thio withanolides	Analgesic, Anti-inflammatory, Antimicrobial, anti-tumor	Alzheimer's disease, Arthritis
Azadirachta indica	Nimbin, Azadirachtin, gedunin, gallic acid	Antibacterial, Anti-malarial, Anti-leprotic, Anti-tuberculosis	To treat skin conditions, dental tartar and caries, endometritis
Allium sativum and Allium cepa	Allin, allicin, allyl sulfides	Antibacterial	MDR pathogens causing nosocomial infections
Syzgium aromaticum	Eugenol, Eugenol acétate, α& β caryophyllene	Antibacterial, Anti-inflammatory, Analgesic	Periodontal problems
Zingiber officinale	6,8,10-gingerol,	Analgesis, Anti-inflammatory, Antipyretic,	Helicobacter pylori infection

	6- shogaol	antimicrobial	
Morinda citrifolia	Anthraquinones glycosides, flavonoids, Iridoids	Anti-inflammatory, Antimicrobial, Antioxidant, Anti-helminthic, Immunomodulating	Anti-cancer, sickle cell anemia.

Conclusion:

Currently, the pharmaceutical and biomedical sectors are facing difficult challenges due to the continuous increase of multi-drug-resistant bacteria and other microbes. These microbes could multiply even in uncomfortable environments, making them essential but also dangerous. The infections caused by these bacteria not only increase the rate of mortality but also the costs of treatments. However, silver nanoparticles and natural plants and herbs offer a ray of hope for people. Silver nanoparticles are a multi-action weapon used for the prevention and cure of multi-drug-resistant bacteria and other microbes. On the other hand, the use of natural plants and different herbs has been widely accepted in the medicinal and healthcare industries. The extracts obtained from natural products are used as they are accepted in the community as a preventive and curative measure. The different plant-based secondary metabolites are also used as a source of antibiotic resistance. Therefore, plants, different drugs, and natural products are considered preventive and curative measures for multi-drug-resistant bacteria.

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