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A COMPREHENSIVE REVIEW OF ANTIMICROBIALS AND NOVEL OPPORTUNITIES BY TRADITIONAL MEDICINE TO REVERSE ANTIBIOTIC RESISTANCE

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ABSTRACT: An Antibiotic is an infectious disease that is the chief source for treating bacterial & fungal infections. The microbial resistance problem has been increasing daily, and the viewpoint for the usage of antimicrobial drugs is still undefined. Antimicrobial-resistant organisms are found in people, animals, food, plants, and in the environment. Do not use antibiotics to treat viral infections like colds and flu. The leading mechanism for spreading the resistance of antibiotics over bacterial populace is plasmids. Biofilm formation decreases the penetration of antifungal compounds into the population. According to World Health Organization (WHO) medicinal plants would be the best source to attain a variety of drugs. 80% of people from developed countries use traditional medicine derived from medicinal plants. Using plant extracts and phytochemicals with identified antimicrobial properties can be greatly useful in treatments. Several plants rich in a wide variety of secondary metabolites, such as tannins, alkaloids, and flavonoids, have been used for their antimicrobial qualities. They can spread from person to person or between people and animals, including food of animal origin. Quick diagnostics are required for both pathogen identification and resistance testing.

INTRODUCTION: An Antibiotic is an infectious disease that is the chief source for treating bacterial & fungal infections. For now, the findings of these antibiotics as chemo-therapeutic agents have led to the subsequent eradication of infectious diseases. The development of *Escherichia coli, Klebsiella pneumoniae, Haemophilus*, and may other β-lactamase has become a main therapeutic problem. Multi-drug resistant strains of *E. coli* and *K. pneumoniae* are gradually being isolated from community-acquired infections. 50-70% cases have stated to account for invasive candidiasis.

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The microbial resistance problem has been increasing each day, and the viewpoint for the usage of antimicrobial drugs is still undefined [1]. Therefore, steps must be taken to decrease this problem. For example, to control the use of antibiotics, we need to understand the genetic mechanism of resistance. Final goal is to provide suitable and efficient antimicrobial drugs to the patient. For a long time, plants have been a valued origin of natural products for sustaining human well-being.

According to World Health Organization (WHO) medicinal plants would be the best source to attain various drugs. 80% of people from developed countries use traditional medicine derived from medicinal plants. Thus, these plants should be inspected for their properties, safety, and effectiveness. In treatments, use of plant extracts

and phytochemicals with identified antimicrobial properties can be of great implication. Several plants rich in secondary metabolites, such as tannins, alkaloids, and flavonoids, have been used for their antimicrobial qualities. Various plants have been found to treat urinary tract infections, gastrointestinal disorders, respiratory diseases, and cutaneous infections [2].

Mechanism of Antibacterial Activity & Resistance: Antibacterial activity is mostly attributed to two mechanisms, which include interfering chemically with the synthesis of vital components of bacteria and evading the predictable mechanisms of antibacterial resistance.

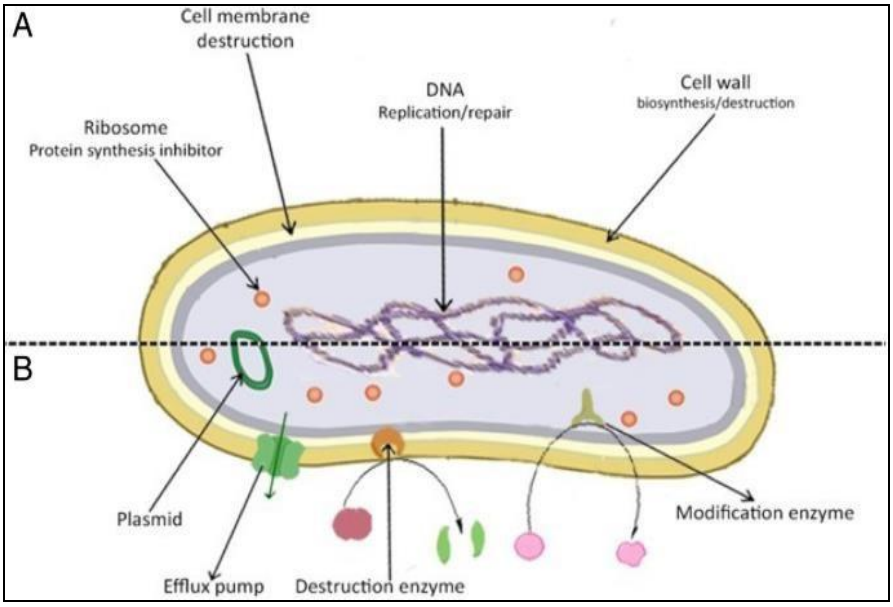

FIG. 1: SHOWS THREE MECHANISMS, MULTIPLE TARGETS FOR ANTIBACTERIAL AGENTS THAT COMPRISE I) BACTERIAL PROTEIN BIOSYNTHESIS II) BACTERIAL CELL-WALL BIOSYNTHESIS III) BACTERIAL CELL MEMBRANE DESTRUCTION IV) BACTERIAL DNA REPLICATION & REPAIR V) INHIBITION OF METABOLIC PATHWAY [3]

Determine targets for antibacterial drugs. Different antibiotics, such as macrolides, aminoglycosides, and tetracyclines, target protein biosynthesis at the ribosome. The cell membrane can be targeted by antibiotics such as Polymixin B. These antibiotics modify bacterial outer membrane permeability & finally destabilize the outer membrane of bacteria. Fluoroquinolone antibiotics hinder DNA replication by trapping a complex of DNA bound to the enzyme DNA Gyrase. Various antibiotic resistance mechanisms in bacteria. Efflux pumps eradicate the antibiotics from bacteria. E.g. Fluoroquinolones. They were repairing enzymes that evolve the antibiotic structure, e.g., Chloramphenicol. The leading mechanism for spreading the resistance of antibiotics over the bacterial populace is plasmids. Each of these mechanisms has been discussed in the following:

Bacterial Protein Biosynthesis: Many steps are involved in the initiation, elongation & termination of protein aggregation. The inhibition of protein synthesis is by targeting the ribosomal subunits an effective approach to fight against bacterial infections. Macrolides, Aminoglycosides, Tetracycline's show antibacterial activity through this particular mechanism.

Cell Wall Biosynthesis: Bacterial cell wall layer stands as a recognized target for antibacterial agents, which consists of a network of peptide & glycan strands that are covalently cross-linked to each other & provide advanced mechanical strength of osmotic lysis. Two types of enzymes have critical roles in the development of this layer, which include Transglucosylases & Transpeptidases. Transglucosylases are suitable targets for bacterial antibiotics, including penicillin & cephalosporins.

Filamenting temperature-sensitive mutant Z (FtsZ) is the first protein that moves towards the division site during the process of cell division. This protein is fundamental for utilizing other proteins that

produce a new cell wall between the segregated bacterial cells.

Inhibiting Nucleic Acid Synthesis: DNA gyrase is the enzyme responsible for performing the supercoiling & uncoiling of bacterial DNA & DNA replication. This enzyme is crucial for synthesis, replication, repair& transcription processes. Gyrase is considered a fine target for antibacterial agents & antibiotics including nalidixic acid and fluroquinolones such as ciprofloxacin.

Destruction of Bacterial Membrane: Destruction of bacterial Membranes has been reported from previous studies which had involved chemical compounds such as local anesthetics or disinfectants. Destruction of the external membrane, cytoplasmic membrane can cause the loss of permeability and leakage of intracellular constituents.[3]

Symptoms of Bacterial Infection: Fever, Chills and sweats, Gastrointestinal disorders, swollen lymphnodes, Headache, Skin flushing, swelling or soreness, Shortness of breath [4].

Prevention and Control of Antibiotics: Individuals follow the following instructions to prevent and control the spread of antibiotic resistance. Antibiotics are used only when prescribed by a certified health professional. When using antibiotics, always follow your health worker's advice. Do not share or use leftover antibiotics. Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practicing safer sex, and keeping vaccinations current. Prepare food hygienically, following the WHO Five Keys to Safer Food (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals [5].

Treatment of Antibacterial: Most bacterial infections require treatment with antibiotics (Gentamicin, Amoxicillin, Azithromycin, ciprofloxacin). The antibiotic prescribed depends on the particular bacterial infection, which usually depends on the type, severity, and location of the infection. If or not the bacterial species is contrary to certain classes of antibiotics. If or not the person has worn the antibiotic before. If or not the person is damaged by antibiotics or any ingredients. Whether or not the person has any other health issues [6].

Mechanism of Antifungal Agent: Bio-film formation decreases penetration of antifungal compounds into the population. Damage of mitochondrial complex I was demonstrated to consequence in azole-resistant segregates.

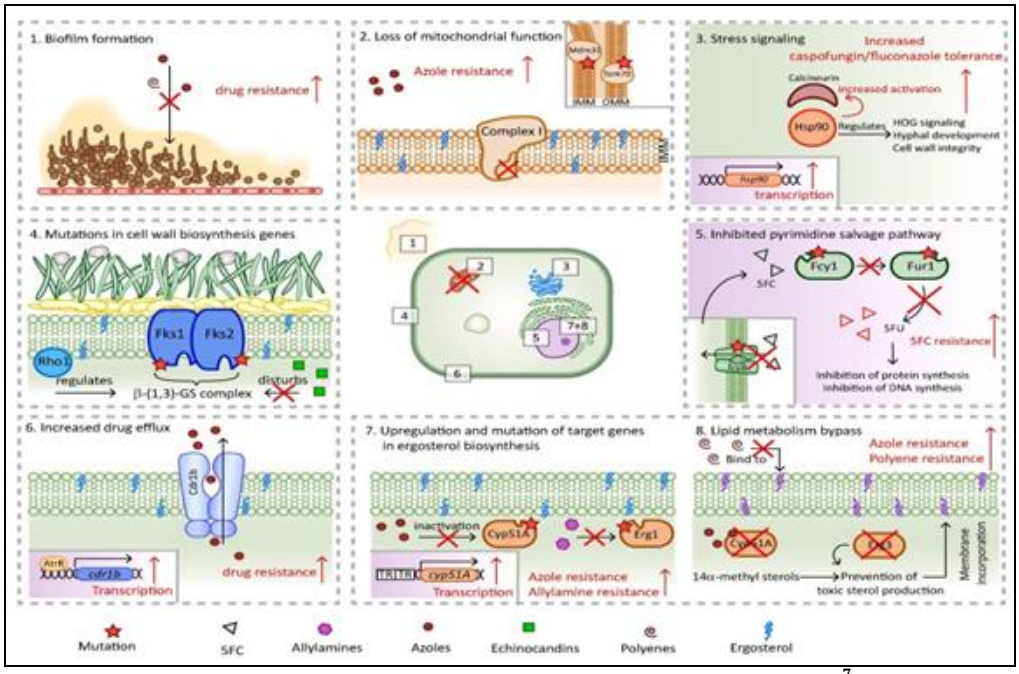

FIG. 2: MECHANISM OF ANTIFUNGAL RESISTANCE [7]

Enhanced production of HSP90 activates stress-signaling pathways & leads to improved tolerance for azoles & echinocandins. Mutations in 1, 3 β-glycan synthase complex catalytic subunits prevent interference in cell wall synthesis by echinocandins. Alterations in the cytosine permease FcyB prevent flucytosine from entering the cell. Mutations in the cytosine deaminase Fcy1prevent conversion of flucytosine to the toxic 5-fluorouracil. Increased activity of drug-efflux transporters results in less intracellular drug accumulation. Mutations in the squalene epoxidase erg1 or 14α-sterol demethylase Cyp51A prevent the activity of allylamines and azoles. No appearance of the sterol desaturase Erg3 halts the production of toxic sterols if Cyp51A is constrained by azole compounds [7].

Symptoms of Fungal Infection: Skin changes such as redness and possibly cracking or peeling skin. Itching and swelling. Redness and soreness on and surrounding the vagina. It was cracking, Flaking or dry peeling of skin in the infected area [8].

Prevention of Antifungal: To prevent infection in immunodeficiency patients, contact to fungal spores must be imperfect with high-efficiency particulate air filters and positive pressure in the patient's room. High-risk patients must avoid contact with soil or tap water. Declining the period of neutropenia or terminating immunosuppressive agents would be considered to avoid fungal infection. Information on the susceptibility pattern of existing fungi in each province and the usage of prophylactic doses of interferon-ϒ and azoles antifungal agents can be beneficial to accomplish infection in high-risk patients, yet after long-term prophylaxis with antifungal agents, infection by resistant etiologic agents needs to be considered. Fungal colonization of different sites in the same patient (mouth, nose, rectum, urinary tract, and vagina) and cutaneous infections should be estimated before antineoplastic therapy and major surgery [9].

Treatment of Antifungal: Localized infection is typically treated with topical antifungal agents. Management of fungal infections is differently liable on the type of infection and etiologic agents. Antifungal agents have a variable spectrum of activity, safety profile, dosing, and costs. The kidney expels Fluconazole and flucytosine in most preparations as active drugs. Itraconazole and Voriconazole metabolism in the liver comprises specific enzymes, mainly CYP3A4, CYP2C9 and CYP2C19. Genetic polymorphisms of enzymes involved and difficulties in the kidney or liver can reflect the serum level of these antifungal agents. The absorption of some antifungal agents involves special conditions. For example: Absorption of Itraconazole from capsule preparations is PH-dependent and requires an acidic environment. Clinical use of flucytosine is inadequate due to its gastrointestinal, hematological and neurological toxicity. Serum Flucytosine concentration should be observed to detect clinical indications, drug interactions and toxicity. Efficacy and safety of antifungal agents are influenced by serum concentrations, clinical aspects and patient's physiological conditions [5].

Diagnosis of Antimicrobial: Quick diagnostics are required for both pathogen identification and resistance testing. Rendering to the present approvals on AST (antimicrobial susceptibility testing), pure culture isolates are used to assess the result of antimicrobial drugs. This is essential as the sample matrix (blood, urine, mucosal) and the number and proportions of different microbial species might differ greatly in polymicrobial samples. Whether the noticed microbe is pathogenic or merely a commensal species may be uncertain. Despite significant progress in diagnostic technologies in current years, maximum patients with infectious diseases are still treated empirically, and therefore antibiotics are heavily overused.

Current diagnostic tests help hospitalized patients well; they are often unavailable in outpatient clinics.

Microbiology laboratories apply EUCAST-recognized breakpoint principles to describe whether the microorganism is susceptible or resistant to tested antibiotics. They need the Disk Diffusion Method or new systems measured to EUCAST standards [10].

Resistance: Antimicrobial Resistance appears when bacteria, viruses, fungi, and parasites change over time and respond earlier to medicines generating infections that are tough to treat &

progressively the liability of disease spread, serious ailment and death. Due to drug resistance, antibiotics and new antimicrobial medicines become indecisive and infections become progressively difficult or preposterous to treat. Antibiotics are becoming increasingly inadequate as drug resistance spreads universally leading to more challenges to treat infections and death [5].

- Some bacteria in the human body are drug-resistant Antibiotics kill bacteria, but not those resistant to drugs.
- Resistant bacteria then have space to multiply.
- Bacteria can even transfer their drug resistance to new bacteria [11].

Overuse of Antibiotics Creating Resistance: Do not take antibiotics without instruction from skilled healthcare authorities**.** Do not use antibiotics to treat viral infections like colds and flu**.** Clean your hands and maintain social hygiene. Identify early symptoms of infection: Severe diarrhea, loss of appetite, abdominal pain and nausea [8].

Herbal Plants:

***Morinda citrifolia L*:** It is also known as Noni, belongs to the family *Rubiaceae*. It can be worn as medicinal element. Noni plants contain antibacterial compounds namely Anthraquinones, alkaloid, Flavonoid, Acubin and Alizarin.

Noni leaves are known as stomachache medicine, antidiabetic, antihypertensive & nourish the body after birth. Fruit is used to treat cough, intestinal worm, and inflammation of the tonsil, high blood pressure and constipation [13].

FIG. 3: *MORINDA CITRIFOLIA L* [12]

Avicennia marina: *Avicennia marina,* a mangrove tree belonging to *Acanthaceae* family. It is mostly found in subtropical and tropical regions of the Indo-West Pacific area. It contains glycosides, tannins, terpenes, steroids, naphtha quinones, alkaloids and flavonoids.

It is used in traditional medicine system for treating malarial fever and food poisoning, used as antimicrobial [15].

FIG. 4: *AVICENNIA MARINA* [14]

***Aegle marmelos* Correa Ex Roxb:** It is commonly known as Bili, belonging to *Rutaceae* family. It is located in India, Bangladesh, Srilanka, Nepal. It consists of flavonoids, rutin, marmesin, alkaloids.

It is used as anti-oxidant (fruit), anti-diabetic (leaf and seeds), anti-cancer (leaf), anti-inflammatory (leaf), anti-diarrheal activity (unriped fruit) activity [16].

FIG. 5: *AEGLE MARMELOS* CORREA EX ROXB [16]

***Annona squamosa* L.:** It is commonly known as Sitaphal, belonging to *Annonaceae* family. It contains diterpenoid alkaloid, oxophoebine, reticuline, isocorydine, methylcorydaldine and flavonoid quercetin-3-O-glycoside.

It is used as antibacterial (leaf), antimicrobial (leaf), anti-tumor (seed), cytotoxic (defatted seed), anti-inflammatory (leaf) activity [16].

FIG. 6: ***ANNONA SQUAMOSA*** **L**[16]

Citrus limon **L.:** It is commonly known as Limbu, belonging to *Rutaceae* family. It consists of vitamin C, polyphenols, terpenes and tannins. It is used as antimicrobial (peel), cytotoxic effects (peel), anti-ulcer, anti-urolithetic (juice), and anti-oxidant activity [16].

FIG. 7: ***CITRUS LIMON*** **L**[16]

Azadira ctaindica **A. Juss:** It is commonly called Limbdo, belongs to the family *Meliaceae.* It contains azadirachtin, glycerides, polyphenols, nimbolide, triterpenes, beta-sitosterol, catechins. It is used as antibacterial (seed), antimicrobial (fruit rind) and anti-oxidant (bark), anti-diabetic (leaf), anti-ulcer activity (leaf) [16].

FIG. 8: ***AZADIRA CTAINDICA*** **A. JUSS** [16]

Piper betle **L:** It is generally known as Nagarvel, associated to the family *Piperaceae.* It contains eugenol, chavicol, phytosterols, alkaloids, oleanolic acid, terpinolene, cardinene and 3- carene. It is used as anti-fertility, anti-ulcer, antimicrobial, anti-cancer, anti-filarial activity [16].

FIG. 9: ***PIPER BETLE*** **L**[16]

Cassia fistula**:** It is generally known as golden shower, associated to the family *Fabaceae.* It contains oxalic acids, tannins, glycosides, anthraquinones, flavonoid, Rhein, sennosides A B. It is used as antifungal, anti-oxidants, antimicrobial, anti-inflammatory, anti-tumor, hepatoprotective and hypoglycemic activity [18].

FIG. 10: ***CASSIA FISTULA*** [17]

Clitoria ternatea**:** It is generally known as Asian pigeonwings, associated to the family *Fabaceae*. It contains triterpenoids, flavonol, glycosides, anthocyanins, steroids. It is used as antimicrobial, anxiolytic, anti-depressant, anti-convulsant, sedative, anti-stress [20].

FIG. 11: ***CLITORIA TERNATEA*** [19]

Cynodon dactylon is commonly known as Bermuda grass, belonging to the family *Poaceae*. It contains flavonoids, alkaloids, glycosides, terpenoids, triterpenoids. It is used as anti-microbial, laxative, coolant, expectorant, carminative, used to treat all types of bleeding and skintroubles [22].

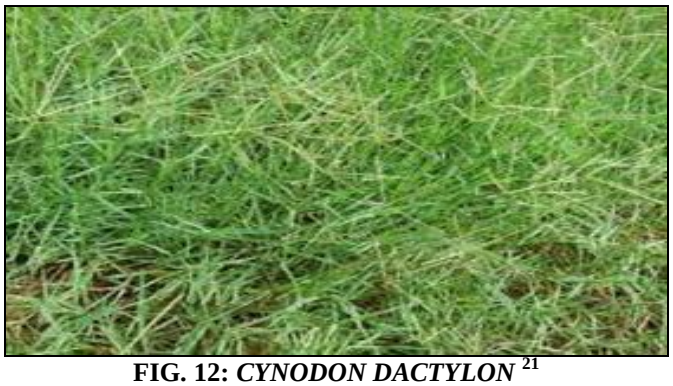

FIG. 12: *CYNODON DACTYLON* [21]

CONCLUSION: There are many medicinal plants that are scientifically proved for Antimicrobial activity. This article reviewed the list of medicinal plants having an antimicrobial activity. However, future study must to be carried out to explore the plants having higher efficacy and no side effects for the treatment of antimicrobial activity.

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CONFLICTS OF INTEREST: NIL

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