Review Article

Therapeutic Potentials of Phytochemicals in Combatting Antimicrobial Resistance (AMR)

ABSTRACT

Antimicrobial resistance (AMR) is a grave threat to global health that is made worse by the abuse and excessive use of antibiotics. This review looks into the processes of this bacterial resistance, particularly efflux pump systems, and calls for the consideration of alternative approaches. The antimicrobial plant derived bioactive compounds, rich in phytochemicals, are of significance as they can serve to mute the resistance mechanisms.. Some of the core active compounds such as flavonoids, alkaloids, phenolics, and essential oils have been proven to work on some multi-drug resistant pathogens Among other things, this review also discusses how phytochemicals interact with ordinary antibiotics to improve drug effectiveness while minimizing the chances of resistance. The case studies emphasized suggest that plant derived antimicrobials are potent tools in the fight against AMR. In conclusion, the results emphasize the need for the incorporation of phytochemicals within modern treatment approaches in order to curb the problems of AMR in the world.

Keywords: {Antimicrobial Resistance, Phytochemicals, Antibiotics, Multi-drug Resistance}

1. INTRODUCTION

Antimicrobial resistance (AMR) represents a critical global health challenge, diminishing the efficacy of antibiotics and posing a serious threat to the treatment of infectious diseases [1]. The escalation of resistant strains, fueled by antibiotic misuse and microbial adaptability, necessitates the exploration of alternative approaches. Major multidrug-resistant pathogens, including Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, and Klebsiella pneumoniae, now contribute significantly to morbidity, mortality, and economic strains on healthcare systems worldwide. Bacteria employ diverse resistance mechanisms such as β-lactamase production, alterations in drug targets, efflux pumps, and biofilm formation, particularly emphasizing the crucial role of efflux pumps in expelling antibiotics from bacterial cells and biofilms in shielding pathogens from antimicrobial agents [2]. These adaptations underscore the urgency for unconventional strategies to combat resistance effectively.

Phytochemicals, bioactive compounds sourced from plants, have emerged as promising tools in the battle against AMR. These compounds, encompassing a variety of secondary metabolites like alkaloids, flavonoids, phenolics, terpenoids, and essential oils, exhibit a broad spectrum of biological actions [3]. Traditionally utilized in herbal medicine, phytochemicals are renowned for their antimicrobial, anti-inflammatory, and antioxidant properties. Recent research has illuminated their potential to combat bacterial resistance through mechanisms such as inhibiting efflux pumps, disrupting biofilms, and interfering with quorum sensing. Furthermore, synergistic effects have been observed when phytochemicals are combined with conventional antibiotics, escalating their effectiveness and combating resistance development [4].

The review aims to comprehensively explore the role of phytochemicals in addressing AMR, delving into their mechanisms of action, potential applications, and challenges in clinical deployment [5]. By investigating the synergy

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between natural compounds and antibiotic resistance, this study underscores the therapeutic promise of phytochemicals and their integration into contemporary antimicrobial strategies. As the global healthcare sector confronts the mounting AMR crisis, phytochemicals offer a sustainable and potent avenue to counter this pressing challenge effectively.

2.0 Mechanism of Phytochemical In Combating Antimicrobial Resistance

Several mechanisms have been identified in the microbial pathogens involved in their self-defense machinery active against the antimicrobial drugs, antibiotics and pesticides [6]. These systems frequently function in tandem with antibiotic-resistant pathogenic microorganisms in particular traits, providing them with defense against an array of antimicrobials [7]. Each time a therapeutic option is used, the lower chance of working against both intended and when employed later, other targets increase [8], as the Antimicrobial antibiotic applications start a complicated interplay between these drug-resistance factors. Interestingly, the same mechanisms have also been noted in bacteria that produce antibiotics and their genetic makeup Clusters containing the defense machinery's coding genes involved in antibiotic biosynthesis. These controlled mechanisms mediate a variety of pathogen defense mechanisms and may be a primary source of antibiotic resistance. [9]. Two types of antibiotic resistance evolution can be distinguished: molecular redundancy, in which organisms attempt to modify their physiology to fit into more complex and novel surroundings, and obtaining the signals and molecular infidelity comes in second where microbial cells under stress become more susceptible to foreign.

DNA can also cause rapid mutations under specific conditions. Microbes are incredibly versatile biological things with enormous capacity to change in reaction to their surroundings [8]. These altered bacterial species create populations with drug-resistant traits and can transmit medication resistance transferring genetic components and genes to other non-resistant microorganisms in the environment through trans generational inheritance systems [9].

2.1 Mechanisms of Bacterial Resistance

2.1.1 Bacterial Efflux System

On bacterial cells, membranes contain proteins called efflux pumps that control the flow of toxic materials from the internal cellular environment to the exterior cellular environment. Bacterial efflux pumps are the quickest acting and most efficient resistance mechanism for bacteria in response to stress, and they are present in almost all bacteria [10].

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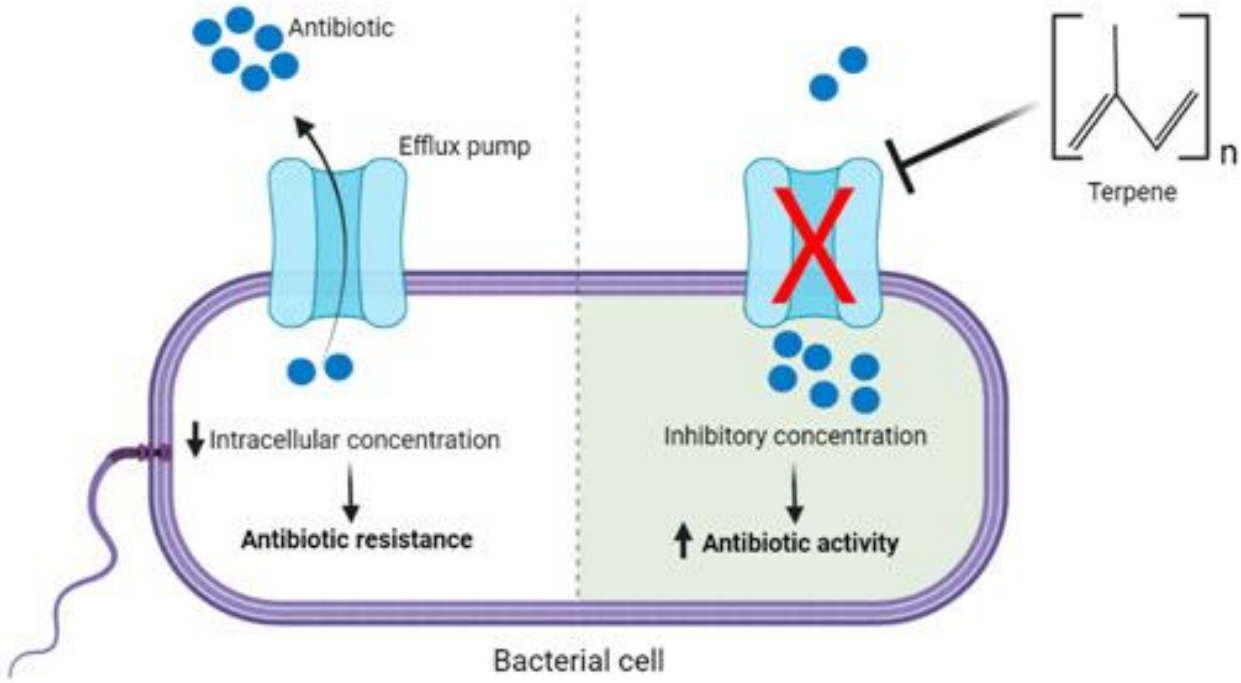

Figure 1. Illustration of the inhibition of bacterial efflux pumps by terpenes and its impact on antibiotic resistance [7].

Efflux pumps boost an organism's resistance to antibiotics and other antimicrobial agents and increase its ability to survive under harsh conditions [10]. Several bacterial efflux pumps have been identified as a result of the advancement of molecular microbiology. These include those found in *Salmonella spp., Campylobacter jejuni, Acinetobacter baumannii, Pseudomonas aeruginosa, Listeria monocytogenes, Klebsiella pneumoniae, Streptococcus pneumoniae, and methicillin-resistant Staphylococcus aureus* (MRSA) [11]. The ATP-binding cassette (ABC) family, the resistance-nodulation-cytosis (RND) superfamily, the small multidrug resistance (SMR) family, the multidrug and toxin extrusion (MATE) family, the major facilitator superfamily (MFS), and the proteobacterial antimicrobial complex efflux (PACE) family are six bacterial drug efflux pump families that have been found to be involved in the efflux pathway. Only Gram-negative bacteria belong to the RND family. When it comes to secondary active transporters, the ATP-binding cassette (ABC) family employs ATP as a source of energy for transport, while the other five families rely on electrochemical energy captured by transmembrane ion gradients [10]. Bacteria that express efflux pumps are able to exhibit resistance to antibiotics by the excretion of a range of substrates, including antibiotics. Furthermore, excreted by efflux pumps include waste metabolites, dyes, detergents, and poisons [11].

2.2 The Role of Efflux Pump Inhibitors in Reversing Drug Resistance

Efflux pump inhibitors can inactivate drug transport by blocking efflux pumps via one or more mechanisms. Efflux pump inhibitors can be used as adjuvants with antibiotics to improve the activity of antibiotics against bacteria expressing efflux pumps and restore the efficiency of medications that are no longer active against a pathogen [11]. Efflux pump inhibitors increase the amount of antibiotics that accumulate intracellular at one time, increasing the susceptibility of bacteria to antibiotics. An inhibitor's action typically has two effects: first, it re-sensitizes resistant bacteria to the antibiotics that are already in use. Secondly, it will decrease the chance of choosing resistant mutants [12]. One can find bacterial efflux pump inhibitors in a multitude of natural and synthetic sources. The World Health Organization's global priority list of antibiotic-resistant bacteria indicates

which infections are high priority and how urgently and significantly efflux pump inhibitor discovery is needed [13].

2.3 Case Studies and Recent Research on Phytochemicals Combating Antimicrobial Resistance

2.3.1 Plant-Derived Antibiotics as a Solution to Multidrug-Resistant Microbes

Investigating novel medicines made from natural materials is essential for tackling the negative effects multidrug-resistant bacteria have on the environment, society, and human health [14]. The development of novel treatments has increased the significance of plant-derived medicinal compounds and the expanding body of scientific knowledge regarding herbal remedies as substitutes or supplementary therapies [15]. Commercially available plants and plant parts that have antibacterial qualities include Berberis, *Camellia Sinensis* (Green Tea) and *Cannabis Sativa*. Studies reveal that bioactive substances found in medicinal plants; including coumarins, flavonoids, phenolics, alkaloids, terpenoids, tannins, essential oils, lectins, polypeptides, and polyacetylenes, provide the building blocks for the synthesis of antibiotics [16].

For example, unrefined extracts from *Rumex hastatus, P. plebejum, Polygonum persicaria, R. dentatus, Rheum australe, and R. nepalensis* demonstrate antibacterial and antifungal characteristics; preventing the growth of germs like *S. aureus, E. coli, C. frundii, and E. aerogenes* [17]. Additionally, extracts from *Calotropis gigantea* have demonstrated strong antifungal efficacy in Asia against pathogenic fungus such as *Aspergillus species* and *Candida albicans* [18]. Alcohol-based extracts from Strong antibacterial properties of *Plumbago zeylanica* roots are demonstrated against *V. cholerae, E. coli, and P. Fusarium equiseti, Colletotrichum corchori, Curvularialunata, and aeruginosa* [16]. The watery *Euphorbia hirta* and *Erythrophleum suaveolens* leaf extracts, in addition to the methanolic *Thevetia peruviana* leaf extract has antibacterial properties against extended-spectrum bacteria that produce beta-lactamases (ESBLs), such as *K. pneumonia, Pseudomonas, and E. coli Salmonella,* Proteus, and methicillin-resistant *Staphylococcus aureus* (MRSA) [12], [19]. Aqueous and hydro alcoholic extracts from a variety of plants have been the subject of limited investigation; however these extracts have demonstrated antibacterial activity on multidrug-resistant bacteria, such as MRSA and ESBL producers [20]. *Anacyclusmaroccanus Ball and A. radiatus* Loisel methanolic and ethyl acetate extracts have been tested for antibacterial efficacy against a range of bacterial, fungal, and dermatophyte species. Notably, the most sensitive bacteria to these extracts were *T. rubrum and E. coli*. [21]. Aqueous extracts from *Lactuca longidentata's* roots and leaves have been studied for their antibacterial properties against a range of pathogens, including yeast and both Gram-positive and Gram-negative bacteria. As long as the leaf extract content is less than 200 µg/mL and it is biocompatible, showed a strong ability to stop the growth of Trichophyton and *Escherichia coli.* tonsurans, exhibiting less than a 10-µg/mL minimum inhibitory concentration (MIC) [22]. The root and leaf extracts, both aqueous and hydroalcoholic, from female Cannabis sativa cv. Strawberry exhibit significant antibacterial activity against Bacillus subtilis (PeruMycA 6). Both the hydroalcoholic extracts showed high susceptibility to the majority of tested bacterial strains, which shown MIC values of less than 62.99 µg/mL. Additionally, these extracts demonstrated notable effectiveness in preventing the formation of dermatophytes, Arthrodermacurrey (CCF 5207) being the fungal species that are most sensitive, with MIC values less than 6.25 µg/mL [23]. These results are consistent with earlier research on the antifungal properties of aqueous extracts from the the "Futura 75" cultivar of industrial hemp (Cannabis sativa L.) inflorescences [24]. Natural compounds obtained from plants [25],[26], fungi [27], lichens [28], endophytes [29], and diverse marine sources, such as plants [30], [31] seaweeds [32], corals [33], and other marine sources, have been found to have antibacterial properties despite the approval of synthetic drugs in many countries. Microorganisms continue to be a topic of significant research interest [27], [34]. These Natural substances have demonstrated potential in preventing bacterial resistance to antibiotics pathogens [35]. Among the different choices, chemicals originating from plants stand out for their capacity to combat bacterial

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infections. These organic compounds found in plants been shown to offer several advantages, such as antifungal, antibacterial, and antioxidant actions. They can boost the efficiency of conventional antibiotics, helping to prevent the development of resistance [36]. Based on their chemical structures, these compounds can be categorized into major groups such as alkaloids, sulfur-containing compounds, terpenoids, and polyphenols [36].

3.0 Phytochemicals

Phytochemicals are plant-based bioactive compounds produced by plants for their protection. They can be derived from various sources such as whole grains, fruits, vegetables, nuts, and herbs, and more than a thousand phytochemicals have been discovered to date [37]. From ancient times, plants extracts have been used for treating various diseases because they contain a large number of natural compounds with significant pharmacological properties. They are a rich source of secondary metabolites, commonly known as phytochemicals; these are grouped as alkaloids, polyphenols, flavonoids, saponins, carotenoids, and terpenes, with varying structural and functional properties that have been proven both in animal and human cells [38]. [39], in their research stated that Phytochemicals are low-molecular-weight (LMW) secondary metabolites which are found naturally in plants; they are biologically active molecules which play an important role in the normal cellular metabolic process and enhance health and disease prevention.

Nature is a treasure house of medicinally significant compounds that can be used against various human ailments, including cancer, malaria, inflammatory diseases, and microbial infections [40]. Plants have contributed to the development of drugs against microbial diseases and various human ailments, due to the possession of natural, yet essential compounds. For instance, artemisinin, a sesquiterpene lactone obtained from *Artemisia annua, is* used as a therapeutic agent for the treatment of malaria, caused by Plasmodium falciparum. [41] stated that phytochemicals which include alkaloids, polysaccharides, and terpenoid polyphenols, has low availability because, despite humans consuming various grams of phytochemicals in their daily diet, only a fraction of these compounds is absorbed in the circulation.

Table 1: Common Sources of Phytochemicals

Names of phytochemicals	**Sources**
Carotenoids like α-carotene.	Mango, pear, peach, pumpkin, butternut squash, green bean, okra, avocado, chard, collard greens, tangerine, banana, Pulp of mango, tangerine [42].
Essential Oils	Spices, pulp of watermelon and pumpkin [43].
Isoprenoids like myrcene	Mango, guava, thyme, parsley, bay leaves, lemongrass, cardamom, sweet basil, juniper [44].

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3.1 Natural Antimicrobial from plants as alternatives to antibiotics.

Phytochemicals, although effective as food supplements, herbal medicines, cosmetics as well as antibacterial activities, has also gained relevance in the scientific community; and numerous phytochemicals have been validated for their antimicrobial potentials against MDR strains [45]. Bacterial infections pose a huge threat to human life across the globe. Some of the bacteria which poses threat and have adapted an escape mechansim from antibiotics are grouped as ESKAPE pathogens, which include *E. faecium, S. aureus, Klebsiella pneumoniae, A. baumannii, P. aeruginosa, and Enterobacter spp.*

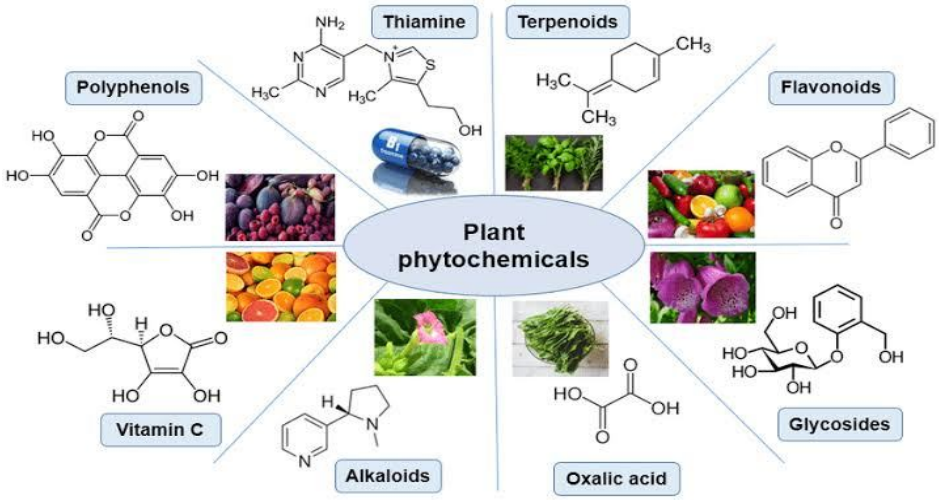

FIGURE 2: Showing the types of phytochemicals [45].

3.1.1 Flavonoids

Naringin is abundantly present in grapefruit and orange, whereas naringenin is an aglycone form of naringin. Naringenin is operative against *Enterococcus faecalis,* a gram-positive bacterium present in the alimentary canal of humans and animals, which can be life-threatening in humans. The synergy of naringenin with oxacillin and cloxacillin showed an antibacterial activity against MRSA [46]. Several studies have displayed the antibacterial and antibiofilm effect of naringin in combination with standard antibiotics that are used in clinics. For example, naringin enhanced the antibiofilm activity of ciprofloxacin and tetracycline on *P. aeruginosa* upon combinational treatment [47].

3.1.2 Alkaloids

Alkaloids are organic nitrogen heterocyclic compounds with a wide variety of chemical structures. Prominent examples like Nicotine, morphine, caffeine, and mescaline which are base-forming water-soluble salts derived from an amino acid [48]. They have shown broad-spectrum antimicrobial activities, and numerous studies have suggested that these compounds could represent an significant role in combating pathogenesis of diverse infection agents [49].

Plant extracts rich in alkaloids from various families, including Amaryllidaceae, Burseraceae, Capparaceae, Mimosaceae, Vitaceae, and Tiliaceae, have shown remarkably antibacterial activity against mycobacteria (*M. fortuitum, M. tuberculosis, and M. smegmatis), E. coli, S. aureus, S. Typhimurium, K. pneumonia and P. aeruginosa* [50]. Berberine, an isoquinoline alkaloid found in the roots and stem bark of Berberis species,

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besides being the main active ingredient in *Cortex phellodendri and Rhizomacoptidis,* has been used in herbal medicine for centuries. This phytochemical possesses antibacterial, antifungal, antiprotozoal, and antiviral properties. Its antibacterial mechanism includes DNA intercalation, targeting RNA polymerase, gyrase, and topoisomerase IV, besides cell division inhibition [51].

3.1.3 Phenolics

Plant phenolics are characterized by an aromatic ring with one or more hydroxyl groups in its structure, and it can be a simple or polymerized molecule. Plant phenolics can be grouped with respect to their structural characteristics, with flavonoids, phenolic acids, and non-flavonoids being the most common [52]. Plant flavonoids are the 2-phenyl-benzo-γ-pyrane nucleus with two benzene ring containing plant phenolic compounds with effective antimicrobial/antimicrobial-potentiator activities. Several classes of flavonoids, such as flavonols, flavanols, flavanones, isoflavonoids, chalcones and dihydrochalcones have been recognized as allelochemicals, which inhibits the microbial growth [53]. The chalcone derivatives such as fluorinated-/ chlorinated-/steroidal-/ferrocene-chalcones have also demonstrated effective antimicrobial activities against various MDR strains [54]. Similarly, the aglycone flavonoids such as myricetin, hesperetin and phloretin were observed to inhibit biofilm formation, which was thought to have resulted from the disrupted functioning of the msrA and norA efflux systems in Staphylococcus strains [55].

3.1.4 Essential Oils

Essential Oils are known for their strong antimicrobial potentials and are often used in traditional medicinal practices [56]. They can be extracted from various plant parts, majorly flowers and fruits, and they are by nature lipophilic and volatile plant products. Essential oils have displayed their ability in targeting and/or disturbing the most prevalent drug-resistance, determining the mechanisms of microbes including cell wall, cell membrane and permeability, drug efflux pumps, mobile genetic elements, quorum sensing and biofilm [56]. [57] stated that cinnamon essential oils disrupted the cell microstructure, membrane permeability and integrity, attributed for striking bactericidal potencies against E. coli and Staphylococcus strains.

Biofilm formation and quorum sensing are highly effective approaches evolved by the bacteria for conferring drug-resistance, its persistence and spread. Therefore, targeting bacterial biofilms and quorum sensing are emerging as effective approaches for combating drug resistance. However, inhibiting biofilm is challenging, but there are recent reports on antibiofilm and anti-quorum sensing activities of essential oils. For instance, [58]reported biofilm and quorum-sensing inhibitory activities of essential oils from Eucalyptus globulus against MRSA strains.

4.0 ROLE OF NATURAL ALTERNATIVES IN COMBATING AMR

Antimicrobial Resistance has posed a great threat to the human population; this has result in reduced effectiveness of traditional antibiotics and causes a limitation in the fight against infectious diseases [59]. To fight infections initiated by drug-resistant pathogens, researchers have designed various antimicrobial agents, which include; antibacterial peptides, amphiphiles, and antimicrobial materials like nanoparticles, hydrogels, engineered surfaces, and coatings. Despite these innovations, antimicrobial resistance continues to be a remarkable challenge. Hence, current research is focused on discovering methods to eliminate pathogens without promoting resistance [59].

4.1 Plant-Derived Antimicrobials as a Potential Solution

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A good number of multifaceted medications (such as morphine, penicillin, aspirin, quinine, digoxin) have their sources from natural products and its byproducts. These natural products also called secondary metabolites are chemical compounds that are derived from living organisms [60]. They are called secondary metabolites because they are secondary metabolism derivatives and thus do not have an immediate implication on an organism's growth, development as well as reproduction [60]. From time immemorial, plants have been known to play a very important role in human advancement and health. Extracts from plants have been in constant use in herbal medicine for both disease prophylaxis and therapeutics [61]. These plant extracts possess anti-inflammatory, anti-microbial, and anti-tumor effects and the active ingredients in these extracts are known as "Plant-derived antimicrobials" (PDAs). They occur naturally in plants (Phenolic compounds) and each PDA may have a different mechanism of action though PDAs are generally known for their antimicrobial effects as they disrupt the cytoplasmic membrane, interference of proton motive force, flow of electrons, active transport as well as clotting of cell materials [62].

The study of innovative antibiotics derived from natural products is very important to curb the demographic, economic, and health impacts of multidrug-resistant microbes. Plant-derived therapeutic agents have grown in prominence because of the emergence of novel diseases and the expanding scientific understanding of herbal medicines as replacement or complementary treatments [59]. Many plant extracts and their constituents expend antioxidant activity. Phenolic compounds are specifically potent free radical scavengers. These chemicals can neutralize free radicals by donating hydrogen atoms or electrons to radicals and to chelate metal cations. Apart from neutralizing free radicals, some selected plant extracts and their constituents have been discovered to suppress free radical release, reduce inducible nitric oxide synthase and nitric oxide as well as result in the inhibition of pro-apoptotic proteins and apoptosis [63]. Despite the authorization of synthetic antimicrobial agents in various countries, plant-derived compounds remain a focal point of significant research interest. These natural compounds have demonstrated potential in tackling antibiotic resistance in bacterial pathogens. They are known for their potential in combating bacterial infections and they improve the efficacy of existing antibiotics, thereby preventing the occurrence of resistance [59].

4.2 Importance of Phytochemicals In the Fight Against AMR

Phytochemicals have demonstrated potential in tackling AMR through various mechanisms like inhibition of biofilm formation, modulation of efflux pumps, disruption of bacterial cell membranes, enzyme inhibition (e.g., β-lactamase inhibitors), and interference with bacterial quorum sensing etc. They inhibit the formation of biofilms thereby decreasing the risk of AMR. Formation of biofilm is a strategy employed by pathogens to shield themselves from strenuous situations in their surroundings by the formation of a thick cohesive interstitial matrix containing DNA, proteins, and polysaccharides [64]. As a result of their slow rate of division, biofilm cells diminish the antimicrobial effect meant to target defined cellular activities [64]. They cause resistance to commonly used antimicrobials and disinfectants thereby leading to various human illnesses. PDAs controls the formation of biofilms in major pathogens like; *Listeria monocytogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa,Escherichia coli*, and *Klebsiella pneumoniae* [61].

PDAs like terpenes, flavonoids, phenolics, and alkaloids are protective mechanisms against ecological crises and microbial diseases. These PDAs are capable of tackling virulence factors, target fundamental microbial activities as well cause damage to cell components, all of which reduce the occurrence of resistance [65]. They are also useful in the manufacture of safe, non-toxic, skin-friendly, and environmentally sustainable bioactive textile (goods used for medical and hygiene purposes, including those for surgical, orthopedic, and dental applications) products [66]. Although many natural products are rich in antimicrobial agents, the comparatively lower occurrence of side effects of natural products along with their lower cost, can be leveraged as an

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attractive environmentally friendly alternative to synthetic antimicrobial agents for use in textile applications [66].

4.3 Case studies where phytochemicals enhance the effectiveness of antibiotics

The overuse and misuse of antibiotics in healthcare have led to the rapid development, persistence, and spread of antimicrobial resistance (AMR). This condition occurs when microbes evolve to resist the effects of conventional antibiotics, making treatments less effective or even ineffective. These drug-resistant pathogens, also known as superbugs, are associated with significant illness and death, as well as placing a substantial economic strain on global healthcare systems [67]. The WHO has published the first ever list of antibiotics resistant priority pathogens, describing a catalogue of twelve bacterial families posting the greatest threat to human health [68]. The list covers the resistant pathogens in three tiers as per the urgency of new antibiotics. The first group represents critical priority pathogens, which includes *Acinetobacterbaumannii*, *Pseudomonasaeruginosa* and members of *Enterobacteriaceae* (*Klebsiella*, *Escherichiacoli*, *Serratia* and *Proteus*). The second group is a high priority group with the pathogens including *Enterococcusfaecium*, *Salmonella*, and *Neisseriagonorrhoea*. The last group contains medium priority pathogens such as *Streptococcuspneumoniae*, *Haemophilusinfluenzae*, and *Shigellaspp* [68].

4.4 Phytochemicals for Combating Antibiotics Resistance

Plants are widely recognized for their therapeutic potential, initially utilized as crude extracts or powders and later developed into purified products containing highly potent active phytochemicals [69]. Due to their effective applications as food supplements, herbal medicine, cosmetics as well as antibacterial activities, the phytochemicals have gained interest in the scientific community, and numerous phytochemicals have been validated for their antimicrobial potentials including against MDR strain, [67], [70], [71]. However, despite numerous reports on the therapeutic potential of phytochemicals, only a few have received approval from the Food and Drug Administration (FDA) such as codeine, capsaicin, reserpine, paclitaxel, colchicine [72].

The phytochemicals when applied in form of extracts have been demonstrated to impose inhibitory effects against clinical isolates. For example; [73] test various solvent based extracts of medicinal plant including Lemongrass, Neem, Aloe vera, Oregano, Rosemary, Thyme, Tulsi and Bryophyllum against ten MDR clinical isolates (including Gram positive and Gram negative bacteria). Flavonoids and tannins present in a methanolic extract with antimicrobial activities against methicillin resistant *S. aureus*. Four different extracts of *Lawsoniainermis* were tested successfully against Gram negative (*E. coli*, *S. typhi, Klebsiella spp., S. sonnei*) and Gram positive (*B. subtilis*, *S. aureus*, *S. epidermidis*) clinical isolates.

4.4.1 Alkaloids

Alkaloids have demonstrated broad-spectrum antimicrobial activities, and numerous studies suggest that these compounds could play a significant role in combating the pathogenesis of various infectious agents [74]. Alkaloids are known to target key drug resistance mechanisms, particularly efflux pumps (EPs). For instance, piperine, a piperidine-type alkaloid isolated from *Piper nigrum* and *Piper longum*, has been shown to inhibit the growth of mutant *Staphylococcus aureus*. Additionally, when co-administered with ciprofloxacin, piperine significantly reduced the minimum inhibitory concentration (MIC) required to combat *S. aureus*. Tomatidine, a steroidal alkaloid found in solanaceous plants such as eggplant (*Solanum melongena*), potato (*Solanum tuberosum*), and tomato (*Solanum lycopersicum*), has demonstrated significant antibacterial activity against *Staphylococcus aureus*. This effect is observed both when used alone and when combined with aminoglycosides [75]. Tomatidine can be considered an antibiotic potentiator, enhancing the effectiveness of various antibiotics such as ampicillin, cefepime, gentamicin, and ciprofloxacin. It has shown activity against

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both Gram-negative and Gram-positive bacteria, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis* infections [76].

4.4.2 Flavonoids

Many classes of flavonoids, including flavonols, flavanones, isoflavonoids, chalcones, and dihydrochalcones, have been identified as allelochemicals that inhibit microbial growth [77]. The antimicrobial activities of flavonoids have also displayed the association with nucleic acid synthesis. For examples, the flavonoids such as chrysin and kaempferol restrict the DNA gyrase (essential enzymes in DNA replication) activity in *E. coli* [78]. Apart from the direct antibacterial activities of flavonoids, there are also promising results indicating the role of flavonoids as resistant reversal agents. For instance, [79] demonstrated that pinostrobin-a synergizes with the antibiotic ciprofloxacin to inhibit the growth of resistant strains of *Pseudomonas aeruginosa* and *Escherichia coli*. This synergy is linked to pinostrobin-a's ability to inhibit NorA efflux pumps. Similarly, aglycone flavonoids like myricetin, hesperetin, and phloretin were found to inhibit biofilm formation in *Staphylococcus* strains, likely due to their disruption of the msrA and NorA efflux systems [80].

4.4.3 Essential Oils

The essential oils of *Petroselinum crispum* and *Aocimumbasilicum* were found to be potent antimicrobials against *Vibrio* strains [81]. *Carum carvi, C. sativum, Cuminum Cuminum* essential oils were reported to have notable antibacterial activities against *E. coli* and *S.aureus* [82]. Essential oils have proven their potential in targeting the most prevalent drug resistance determining mechanisms of microbes including cell wall, cell membrane and permeability, drug efflux pumps, mobile genetic elements, quorum sensing and biofilm [67]. Bacterial cell membranes work as the first barrier against antimicrobial agents, which any antibiotics should overcome for its interaction with the target [83].

5.0 CONCLUSION

There is a global and inevitable need to augment the existing arsenal of treatments for infectious diseases due to the rising threat posed by antimicrobial resistance. Indeed, phytochemicals with their broad range of bioactive properties would seem to be an appropriate and eco-friendly answer to the problem. The properties they possess that are said to have disrupted biological resistance including efflux pumps and biofilm forming as well as their combined effects with classical antibiotics all go to their usefulness as therapeutics. However, until such time that their bioavailability and clinical use are sufficiently addressed; including phytochemicals into the mix of antimicrobial measures remains a significant milestone. In the post AMR era, use of phytochemicals in the search for therapies should be the main objectives of the research.

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REFERENCES

1. Flors, Victor, et al. "Enabling sustainable crop protection with induced resistance in plants." *Frontiers in Science* 2 (2024): 1407410.

2. Ugoala, Emeka. "Antibacterial-Resistant Pathogens Mechanisms of Transmission and Strategies for Prevention and Control." (2023).

3. Ivanoff, Andre, Betty J. Blythe, and Tony Tripodi. *Involuntary clients in social work practice: A research-based approach*. Taylor & Francis, 2024.

4. Munita, J. M., and Arias, C. A.. (2016). Mechanisms of Antibiotic Resistance. methicillin-susceptible and methicillin-resistant Staphylococcus aureus. J. Microbiol. Res. 2014, 4, 6–13.Microbiol. 2007, 24, 73–75.

5. Betz, Ulrich AK, et al. "Game changers in science and technology-now and beyond." *Technological Forecasting and Social Change* 193 (2023): 122588.

6. Alara, John A., and Oluwaseun Ruth Alara. "An Overview of the Global Alarming Increase of Multiple Drug Resistant: A Major Challenge in Clinical Diagnosis." *Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders)* 24.3 (2024): 26-42.

7. AlMatar, M.; Albarri, O.; Makky, E.A.; Köksal, F. Efflux pump inhibitors: New updates. *Pharmacol. Rep.***2021**, *73*, 1–16.

8. Jamshidi, S.; Sutton, J.M.; Rahman, K.M. An overview of bacterial efflux pumps and computational approaches to study efflux pump inhibitors. *Future Med. Chem.***2016**, *8*, 195–210.
9. Schindler, B.D.; Kaatz, G.W. Multidrug efflux pumps of Gram-positive bacteria. *Drug Resist. Updat.***2016**, *27*, 1–13.
10. Du, D.; Wang-Kan, X.; Neuberger, A.; van Veen, H.W.; Pos, K.M.; Piddock, L.J.V.; Luisi,B.F. Multidrug efflux pumps: Structure, function and regulation. *Nat. Rev. Microbiol.***2018**, *16*, 523–539.

11. Sharma, A.; Gupta, V.K.; Pathania, R. Efflux pump inhibitors for bacterial pathogens: From bench to bedside. *Indian J. Med. Res.***2019**, *149*, 129–145.

12. Sharifi-Rad, J.; Mnayer, D.; Roointan, A.; Shahri, F.; Ayatollahi, S.A.M.; Sharifi-Rad, M.; Molaee, N. Antibacterial activities ofessential oils from Iranian medicinal plants on extended-spectrum β-lactamase-producing Escherichia coli. Cell. Mol. Biol. 2016, 62,

13. Aggarwal, Rupesh, et al. "Antibiotic resistance: a global crisis, problems and solutions." *Critical Reviews in Microbiology* (2024): 1-26.

14. Sasidharan, S.; Chen, Y.; Saravanan, D.; Sundram, L.Y.; Yoga, L. Extraction isolation and characterization of bioactive compoundsfrom plants' extracts. Afr. J. Tradit. Complement. Altern. Med. 2011, 8, 1–10.

15. Valli, M.; Pivatto, M.; Danuello, A.; Castro-Gamboa, I.; Silva, D.H.S.; Cavalheiro, A.J.; Araújo, Â.R.; Furlan, M.; Lopes, M.N.;Bolzani, V.D.S. Tropical biodiversity: Has it been a potential source of secondary metabolites useful for medicinal chemistry? Trop.Biodivers. 2012, 35, 2278–2287.

UNDER PEER REVIEW

16. Rahman, M.S.; Anwar, M.N. Antimicrobial Activity of Crude Extract Obtained from the Root of Plumbago zeylanica. Bangladesh J. Microbiol. Spectr. 4, 481–511. doi:10.1128/microbiolspec.VMBF-0016-2015

17. Batool, K.; Sultana, S.; Akhtar, N.; Muhammad, H.; Naheed, A. Medicinal plants combating against human pathogens: A review. 2014, 2, 47–51.4, 685–688.

18. Parvin, S.; Kader, M.A.; Chouduri, A.U.; Rafshanjani, M.A.S.; Haque, M.E. Antibacterial antifungal and insecticidal activities of methicillin-susceptible and methicillin-resistant Staphylococcus aureus. J. Microbiol. Spectr. 4, 481–511. doi:10.1128/microbiolspec.VMBF-0016-2015

19. Niranjan, P.S.; Kaushal, C.; Jain, S.K. Pharmacological Investigation of Leaves of Polypodium decumanum for Antidiabetic Activity.J. Drug Deliv. Ther. 2017, 7, 2685–2688.

20. Manso, T.; Lores, M.; de Miguel, T. Antimicrobial Activity of Polyphenols and Natural Polyphenolic Extracts on Clinical Isolates.Antibiotics 2021, 11, 46.

21. Sissi, S.; Di Giacomo, S.; Ferrante, C.; Angelini, P.; Macone, A.; Giusti, A.M.; Toniolo, C.; Vitalone, A.; Abdellah, A.; Larhsini, M.;et al. Characterization of the Phytochemical Composition and Bioactivities of Anacyclusmaroccanus Ball. and Anacyclus radiatus Loisel Aerial Parts: Preliminary Evidence for the Possible Development of Moroccan Plants. Molecules 2022, 27, 692.

22. Di Simone, S.C.; Angeles Flores, G.; Acquaviva, A.; Nilofar, M.; Libero, M.L.; Venanzoni, R.; Tirillini, B.; Orlando, G.; Zengin,G.; Lai, F.; et al. Phytochemical and biological properties of the water extract from roots and leaves of Lactuca longidentataanendemicphytoalimurgic (food) species of Central Sardinia (Italy). Plant Biosyst. 2023, 157, 594–604.

23. Serventi, L.; Flores, G.A.; Cusumano, G.; Barbaro, D.; Tirillini, B.; Venanzoni, R.; Angelini, P.; Acquaviva, A.; Di Simone, S.C.;Orlando, G.; et al. Comparative Investigation of Antimicrobial and Antioxidant Effects of the Extracts from the Inflorescencesand Leaves of the Cannabis sativa L. cv. strawberry. Antioxidants 2023, 12, 219.

24. Orlando, G.; Adorisio, S.; Delfino, D.; Chiavaroli, A.; Brunetti, L.; Recinella, L.; Leone, S.; D'Antonio, M.; Zengin, G.; Acquaviva,A.; et al. Comparative Investigation of Composition Antifungal and Anti-Inflammatory Effects of the Essential Oil from Three Industrial Hemp Varieties from Italian Cultivation. Antibiotics 2021, 10, 334.

25. Kauffmann, A.C.; Castro, V.S. Phenolic Compounds in Bacterial Inactivation: A Perspective from Brazil. Antibiotics 2023, 12, 645.

26. Gechev, T.S.; Van Breusegem, F.; Stone, J.M.; Denev, I.; Laloi, C. Natural products from resurrection plants: Potential for medical applications. Biotechnol. Adv. 2014, 32, 1091–1101.

27. Wu, C.; Kim, H.K.; van Wezel, G.P.; Choi, Y.H. Expanding the chemical space for natural products by Aspergillus–Streptomyces co-cultivation and biotransformation. Sci. Rep. 2015, 5, 10868.

28. Youssef, S.; Hassan, M.; Ahmed, S. Lichens: Chemistry and biological activities. In Studies in Natural Products Chemistry;Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 2014; pp. 223–259 .

UNDER PEER REVIEW

29. Deshmukh, S.K.; Verekar, S.A.; Bhave, S.V. Endophytic fungi: A reservoir of antibacterials. Front. Microbiol. 2015, 5, 715.

30. Ng, T.B.; Cheung, R.C.F.; Wong, J.H.; Wang, Y.; Ip, D.T.M.; Wan, D.C.C.; Xia, J.; Chan, W.Y.; Fang, E.F. Antibacterial products of marine organisms. Appl. Microbiol. Biotechnol. 2015, 99, 4145–4173.

31. Mayer, A.M.S.; Glaser, K.B.; Cuevas, C.; Jacobs, R.S.; Kem, W.; Little, R.D.; McIntosh, J.M.; Newman, D.J.; Potts, B.C.; Shuster, D.E. Marine pharmacology in 2009–2011: Marine compounds with antibacterial antidiabetic antifungal anti-inflammatory antiprotozoal antituberculosis and antiviral activities; affecting the immune and nervous systems and other miscellaneous mechanisms of action. Mar. Drugs 2013, 11, 2510–2573.

32. Singh, R.P.; Singh, A.; Arya, M.; Maheshwari, A.; Bhadouria, R.; Pandey, S.; Kharwar, R.N.; Stal, L.J.; Dubey, N.K. Antimicrobial compounds from seaweeds-associated bacteria and fungi. Appl. Microbiol. Biotechnol. 2015, 99, 1571–1586.

33. Hossain, M.A.; Park, H.C.; Park, S.W.; Park, S.C.; Seo, M.G.; Her, M.; Kang, J. Synergism of the Combination of Traditional Antibiotics and Novel Phenolic Compounds against Escherichia coli. Pathogens 2020, 9, 811.

34. , S.; Zhang, Z.; Guo, L. Antibacterial Molecules from Marine Microorganisms against Aquatic Pathogens: A Concise Review.Mar. Drugs 2022, 20, 230.

35. Barbieri, R.; Coppo, E.; Marchese, A.; Daglia, M.; Sobarzo-Sanchez, E.; Nabavi, S.F.; Nabavi, S.M. Phytochemicals for humandisease: An update on plant-derived compounds antibacterial activity. Microbiol. Res. 2017, 196, 44–68.

36. Bribi, N. Pharmacological activity of alkaloids: A review. Asian J. Bot. 2018, 1, 1–6

37. Kumar, A., P, N., Kumar, M., Jose, A., Tomer, V., Oz, E., Proestos, C., Zeng, M., Elobeid, T., K, S., & Oz, F. (2023). Major Phytochemicals: Recent Advances in Health Benefits and Extraction Method. Molecules (Basel, Switzerland), 28(2), 887.https://doi.org/10.3390/molecules28020887

38. Dwivedi, S.; Kushalan, S.; Paithankar, J.G.; D'souza, L.C.; Hegde, S.; Sharma, A. Environmental toxicants, oxidative stress and health adversities: Interventions of phytochemicals. J. Pharm. Pharmacol. 2022, 74, 516–536.

39. Yoo, S.; Kim, K.; Nam, H.; Lee, D. Discovering Health Benefits of Phytochemicals with Integrated Analysis of the Molecular Network, Chemical Properties and Ethnopharmacological Evidence. Nutrients 2018, 10, 1042

40. Hegde, M.; Girisa, S.; Naliyadhara, N.; Kumar, A.; Alqahtani, M.S.; Abbas, M.; Mohan, C.D.; Warrier, S.; Hui, K.M.; Rangappa, K.S. Natural compounds targeting nuclear receptors for effective cancer therapy. Cancer Metastasis Rev. 2022, 1–58.

41. Martel, J.; Ojcius, D.M.; Ko, Y.-F.; Young, J.D. Phytochemicals as Prebiotics and Biological Stress Inducers. Trends Biochem. Sci. 2020, 45, 462–471.

42. Zeece, M. Food colorants. In Introduction to the Chemistry of Food; Zeece, M., Ed.; Academic Press: Cambridge, MA, USA, 2020; pp. 313–344

UNDER PEER REVIEW

43. Ballard, C.R.; Maróstica, M.R. Health Benefits of Flavonoids. In Bioactive Compounds; Woodhead Publishing: Cambridge, UK, 2019; pp. 185–201

44. Surendran, S.; Qassadi, F.; Surendran, G.; Lilley, D.; Heinrich, M. Myrcene-What are the potential health benefits of this flavouring and aroma agent? Front. Nutr. 2021, 8, 699666

45. Anand, U., Jacobo-Herrera, N., Altemimi, A., and Lakhssassi, N. (2019). A Comprehensive Review on Medicinal Plants as Antimicrobial Therapeutics: Potential Avenues of Biocompatible Drug Discovery. Metabolites 9, 258. doi:10.3390/metabo9110258

46. Tomar, A.; Broor, S.; Kaushik, S.; Bharara, T.; Arya, D. Synergistic effect of naringenin with conventional antibiotics against methicillin resistant Staphylococcus aureus. Eur. J. Mol. Clin. Med. 2021, 7, 2020.

47. Dey, P.; Parai, D.; Banerjee, M.; Hossain, S.T.; Mukherjee, S.K. Naringin sensitizes the antibiofilm effect of ciprofloxacin and tetracycline against Pseudomonas aeruginosa biofilm. Int. J. Med. Microbiol. 2020, 310, 151410.

48. Compean, K. L., and Ynalvez, R. A. (2014). Antimicrobial Activity of Plant Secondary Metabolites: A Review. Res. J. Med. Plant 8, 204–213. doi:10.3923/rjmp.2014.204.213

49. Casciaro, B., Mangiardi, L., Cappiello, F., Romeo, I., Loffredo, M. R., Iazzetti, A., et al. (2020). Naturally-Occurring Alkaloids of Plant Origin as Potential Antimicrobials against Antibiotic-Resistant Infections. Molecules 25, 3619. doi:10.3390/molecules25163619

50. Omar, F., Tareq, A. M., Alqahtani, A. M., Dhama, K., Sayeed, M. A., EmranBin, T. B., et al. (2021). Plant-Based Indole Alkaloids: A Comprehensive Overview from a Pharmacological Perspective. Molecules 26, 2297. doi:10.3390/ molecules26082297

51. Peng, L., Kang, S., Yin, Z., Jia, R., Song, X., Li, L., et al. (2015). Antibacterial Activity and Mechanism of Berberine against Streptococcus Agalactiae. Int. J. Clin.Exp. Pathol. 8, 5217–5223.

52. de Souza, E. L., dos Santos, A. S., de Albuquerque, T. M. R., Lacerda Massa, N. M.,

53. Górniak, I., Bartoszewski, R., and Króliczewski, J. (2019). Comprehensive Review of Antimicrobial Activities of Plant Flavonoids. Phytochem. Rev. 18, 241–272. doi:10.1007/s11101-018-9591-z

54. Xu, M., Wu, P., Shen, F., Ji, J., and Rakesh, K. P. (2019). Chalcone Derivatives and Their Antibacterial Activities: Current Development. Bioorg. Chem. 91, 103133. doi:10.1016/j.bioorg.2019.103133

55. Lopes, L. A. A., dos Santos Rodrigues, J. B., Magnani, M., de Souza, E. L., and de Siqueira-Júnior, J. P. (2017). Inhibitory Effects of Flavonoids on Biofilm Formation by Staphylococcus aureus that Overexpresses Efflux Protein Genes. Microb. Pathogenesis 107, 193–197. doi:10.1016/j.micpath.2017.03.033

56. Yu, Z., Tang, J., Khare, T., and Kumar, V. (2020). The Alarming Antimicrobial Resistance in ESKAPEE Pathogens: Can Essential Oils Come to the rescue?.Fitoterapia 140, 104433. doi:10.1016/j.fitote.2019.104433

UNDER PEER REVIEW

57. Zhang, Y. B., Liu, X. Y., Jiang, P. P., Li, W. D., and Wang, Y. F. (2015). Mechanism and Antibacterial Activity of Cinnamaldehyde against Escherichia coli and Staphylococcus aureus. Mod. Food Sci. Technol. 31, 31–35.

58. Merghni, A., Noumi, E., Hadded, O., Dridi, N., Panwar, H., Ceylan, O., et al. (2018). Assessment of the Antibiofilm and Antiquorum Sensing Activities of Eucalyptus Globulus Essential Oil and its Main Component 1,8-cineole against Methicillin-Resistant Staphylococcus aureus Strains. Microb. Pathog. 118, 74–80. doi:10.1016/j.micpath.2018.03.006

59. Angelini, P. (2024). Plant-derived antimicrobials and their crucial role in combating antimicrobial resistance. *Antibiotics, 13*(8), 746.https://doi.org/10.3390/antibiotics13080746

60. Eze, A. A., Ogugofor, M. O., & Ossai, E. C. (2022). Plant-derived compounds for the treatment of schistosomiasis: Improving efficacy via nano-drug delivery. *Nigerian Journal of Clinical Practice, 25*, 747–764.https://doi.org/10.4103/njcp.njcp_1322_21

61. Upadhyay, A., Upadhyaya, I., Kollanoor-Johny, A., &Venkitanarayanan, K. (2014). Combating pathogenic microorganisms using plant-derived antimicrobials: A minireview of the mechanistic basis. *BioMed Research International*, Article ID 761741.https://doi.org/10.1155/2014/761741

62. Johnson, E. J., Duan, J. E., Srirattana, K., Venkitanarayanan, K., Tulman, E. R., & Tian, X. C. (2022). Effects of intramuscularly injected plant-derived antimicrobials in the mouse model. *Scientific Reports, 12*, 5937.https://doi.org/10.1038/s41598-022-09705-9

63. Merecz-Sadowska, A., Sitarek, P., Zajdel, K., Kucharska, E., Kowalczyk, T., & Zajdel, R. (2021). The modulatory influence of plant-derived compounds on human keratinocyte function. *International Journal of Molecular Sciences, 22*(12), 12488.https://doi.org/10.3390/ijms222212488

64. Cappiello, F., Loffredo, M. R., Del Plato, C., Cammarone, S., Casciaro, B., Quaglio, D., Mangoni, M. L., Botta, B., &Ghirga, F. (2020). The revaluation of plant-derived terpenes to fight antibiotic-resistant infections. *Antibiotics, 9*(6), 325.https://doi.org/10.3390/antibiotics9060325

65. De Fazio, R., Oppedisano, F., Caioni, G., Tilocca, B., Piras, C., &Britti, D. (2024). Plants with antimicrobial activity against *Escherichia coli*: A meta-analysis for green veterinary pharmacology applications. *Microorganisms, 12*(9), 1784.https://doi.org/10.3390/microorganisms12091784

66. Reta, B. A., Murugesh Babu, K., & Tesfaye, T. (2022). Studies on healthcare and hygiene textile materials treated with natural antimicrobial bioactive agents derived from plant extracts. *AATCC Journal of Research, 14*(10), 1–17.https://doi.org/10.1177/24723444231215444

67. Yu Z , Tang J , Khare T., Kumar V. (2020). The Alarming Antimicrobial Resistance in ESKAPEE Pathogens: Can Essential Oils Come to the rescue? Fototerapia 140, 104433. 10.1016/j.fitote.2019.104433 [DOI] [PubMed] [Google Scholar]

68. World Bank (2017). Drug-Resistant Infections: A Threat to Our Economic Future. Available at: https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

69. Samy R. P., Gopalakrishnakone P. (2010). Therapeutic Potential of Plants as Anti-Microbials for Drug Discovery. Evid. based Complement. Altern. Med. 7, 283-294. 10.1093/exam/nen036

UNDER PEER REVIEW

70. Anand U., Jacobo-Herrera N., Altemimi A., Lakhssassi N. (2019). A comprehensive Review on Medicinal Plants as Antimicrobial Therapeutics: Potential Avenues of Biocompatible Drug Discovery. Metabolites 9, 258. 10.3390/metabo9110258

71. Mohammad M. J., Anand U., Altemimi A.B., Tripathi V., Guo Y., Pratap-Singh A. (2021). Phenolic Composition, Antioxidant Capacity and Antibacterial Activity of White Wormwood (*ArtemisiaHerbalba*). Plants 10, 164. 10.3390/plants10010164

72. Kongkham B., Prabakaran D., Puttaswamy H. (2020). Opportunities and Challenges in Managing Antibiotics Resistance in Bacteria Using Plant Secondary Metabolites. Fototerapia 147, 104762. 10.1016/j.fitote.2020.104762

73. Dahiya P., Dahiya P., Purkayastha S. (2012). Phytochemical screening and Antimicrobial Activity of Some Medicinal Plants against Multi-Drug Resistant Bacteria from Clinical Isolates. Indian J. Pharm. Sci. 74, 443-450. 10. 4103/0250-474X.108420

74. Casciaro B., Mangiardi L., Cappiello., Romeo I., Loffredo M. R., Iazzetti A., et al. (2020). Naturally Occuring Alkaloids of Plants Origin as Potential Antimicrobial against Antibiotics-Resistant Infections. Molecules 25, 3619.10.3390/molecules25163619.

75. Jiang Q.-W., Chen M.-W., Cheng K.-J., Yu P.-Z., Wei X., Shi Z. (2016). Therapeutic Potential of Steroidal Alkaloids in Cancer and Other Disease. Med. Res. Rev. 36, 119-143. 10.1002/med.21346

76. Soltani R, Fazeli H., Bahri Najafi R., Jelokhanian A. (2017). Evaluation of the Synergistic Effect of Tomatidine with Several Antibiotics against Standard and Clinical Isolates of *Staphylococcus aureus, Enterococcus faecalis, Pseudomona aeruginosa and Escherichia coli*. Iran. J. Pharm. Res. IJPR 16, 290-296.

77. Gorniak I., Bartoszewski R., Kroliczewski J., (2019). Comprehensive Review of Antimicrobial Activities of Plant Flavonoids. Phytochem. Rev. 18, 241-272. 10.1007/s11101-081-9591-z

78. Wu T., Zang X., He M., Pan S., Xu X. (2013). Structure-Activity Relationship of Flavonoids on Their Anti-*Esherichiacoli* Activity and Inhibition of DNA Gyrase. J. Agric. Food Cherm. 61, 8185-8190. 10.1021/jf402222v

79. Christena L. R., Subramaniam S., Vidhyalakshmi M., Mahadevan V., Sivasubramanian A., Nagarajan S. (2015). Dual Role of Pinostrobin-A Flavonoids Nutraceutical as an Efflux Pump Inhibitor and Antibiofilm Agent to Mitigate Food Borne Pathogens. RSC Adv. 5, 61881-61887. 10.1039/C5RA07165H

80. Lopes L. A.A., dos Santos Rodrigues J.B, Magnani M., de Souza E. L., de Siqueira-Junior J. P. (2017). Inhibitory Effect of Flavonoids on Biofilm Formation by Staphylococcus aureus that Over expresses Efflux Protein Genes. MicrobPathogensis 107, 193-197. 10.1016/j.micpath.2017.03.033

81. Snoussi M., Dehmani A., Noumi E., Flamini G., Papetti., A. (2016). Chemical Composition and Antibiofilm Activity of *Petroselinumcrispum* and *OcimumBasilicum* Essential Oils against *VibrioSpp*. Strains. MicrobPathogensis 90, 13-21. 10.1016/j.micpath.2015.11.004

82. Khalil N., Ashour M., Fikry S., Singab A. N., Salama O. (2018). Chemical Composition and Antimicrobial Activity of the Essential Oils of Selected Apiaceous Fruits. Future J. Pharm. Sci. 4, 88-92.10.1016/j.fjps.2017.10.004

UNDER PEER REVIEW

83. Martinez de Tejada G., Sanchez-Gomez S., Razquin-Olazaran I., Kowalski I., Kaconis Y., Heinbockel L., et al. (2012). Bacterial Cell Wall Compounds as Promising Targets of Antimicrobial Agents I. Antimicrobial Peptides and Lipopolyamines. CDT 13, 1121-1130. 10.2174/138945012802002410

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