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Phytochemicals as weapons against drug resistance

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Abstract

Phytochemicals are plant-based products with high medicinal value. These metabolites effectively target disease-causing microbes. Drug-resistant pathogens have developed mechanisms to sustain themselves even with inhibitors. Drug resistance has emerged as a global giant, causing all available treatment options to fail. The solution to this problem is in the phytochemicals of plants with antibacterial and drug resistance modulation properties. Phytochemicals might be able to get rid of efflux pumps, drug-modulating enzymes, resistance genes, quorum sensing, and biofilm, all of which cause pathogens to be resistant to drugs. Moreover, anti-obesogenic and cardioprotective properties are also observed in phytochemicals. Additionally, studies show the success of phytochemical-based nanoparticles in drug resistance regulation. This review emphasizes phytochemicals' different mechanisms of action and their derivatives in curbing drug-resistant pathogens and cancer cells.

Keywords

ABC transporters; efflux pump modulation; Gram-negative bacteria; MDR; nano-biotics; PDR; uro-pathogens

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Introduction

Phytochemicals are non-nutritive substances that have a protective function in plants against pathogenic attacks and environmental stress (1). Phytochemicals participate in secondary metabolism and do not have a role in the survival of plants. Plant secondary metabolites, i.e., phytochemicals, are divided into carotenoids, phenolics, alkaloids, N-containing compounds, and organosulfur compounds based on their biosynthetic origin (2) (Fig. 1.). Phytochemicals are featured by structural diversity and prominently act as antioxidant, antidiabetic, anticarcinogenic, antimicrobial, and anti-inflammatory. These chemicals efficiently disrupt disease causing signaling pathways.(3). Interestingly, phytochemicals have also been investigated for anti-obesogenic and cardioprotective properties (4,5).

Drug resistance is a significant threat in the treatment of diseases (6). The pressure to survive drives the appearance of drug resistance. Any pathogen or cancer cells capable of evolving and diversifying can develop resistance under the influence of inhibitors (7). Many drug-resistant bacterial strains, such as *Mycobacterium tuberculosis, Pseudomonas aeruginosa,* and *Staphylococcus aureus*, have failed all the available treatment options, making it impossible to control the disease (8). Along with bacterial infections, drug resistance is also seen in cancer cells (9). Cancer cells become resistant to chemotherapeutic drugs and continue to proliferate

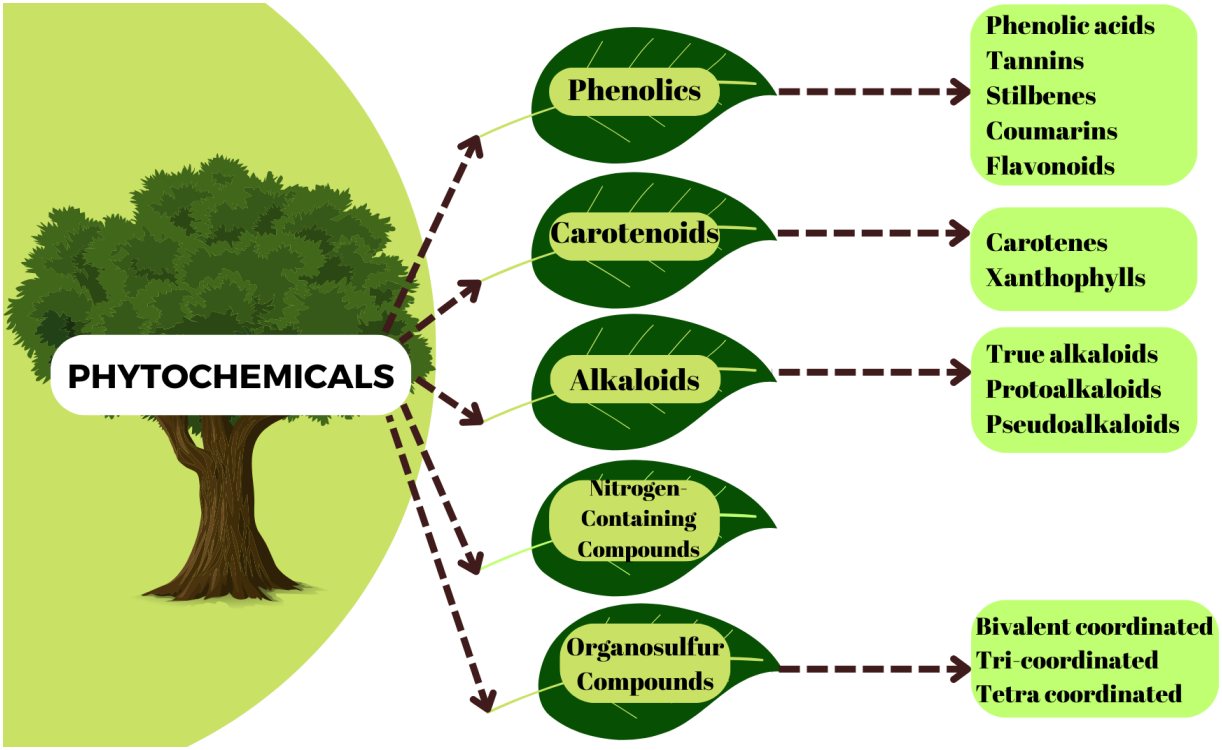

Fig. 1. Classification of phytochemicals

inside the body despite the administration of drugs (10). According to the Centers for Disease Control and Prevention (CDC), antimicrobial resistance is a global public health threat, reporting the death of at least 1.27 million people worldwide and associated with nearly 5 million deaths in 2019(11). Bacteria can either naturally resist some antimicrobial agents or acquire resistance through various mechanisms (Fig. 2.). One such mechanism is accelerating the efflux of antibiotics through bacterial efflux pumps. Many efflux pump families and superfamilies are present namely, the ATP-binding cassette (ABC) superfamily, the resistance nodulation–cell-division superfamily, the major facilitator superfamily, the drug/metabolite transporter superfamily, the multidrug and toxic compound extrusion family, the proteobacterial antimicrobial compound efflux family, and the p-aminobenzoic-glutamate transporter family (12). Other resistance-imparting pathways are plasmid resistance, changes in membrane permeability, alteration of the binding site, destruction of antibiotics, and quorum sensing followed by biofilm formation (13). The unsuitable usage of antibiotics has also resulted in antimicrobial resistance (14,15). European Center for Disease Prevention and Control, Centers for Disease Prevention and Control, and Infectious Diseases Society of America classify drug resistance into the following categories: extensive-drug resistance (XDR), pan-drug resistance (PDR), and multiple-drug resistance (MDR) (14). In XDR, bacteria remain sensitive to only one or two antibiotic categories, whereas in PDR, bacteria are resistant to all antimicrobial agents (16). The biggest threat is MDR, in which bacteria resist at least one agent in three or more antimicrobial classes (17).

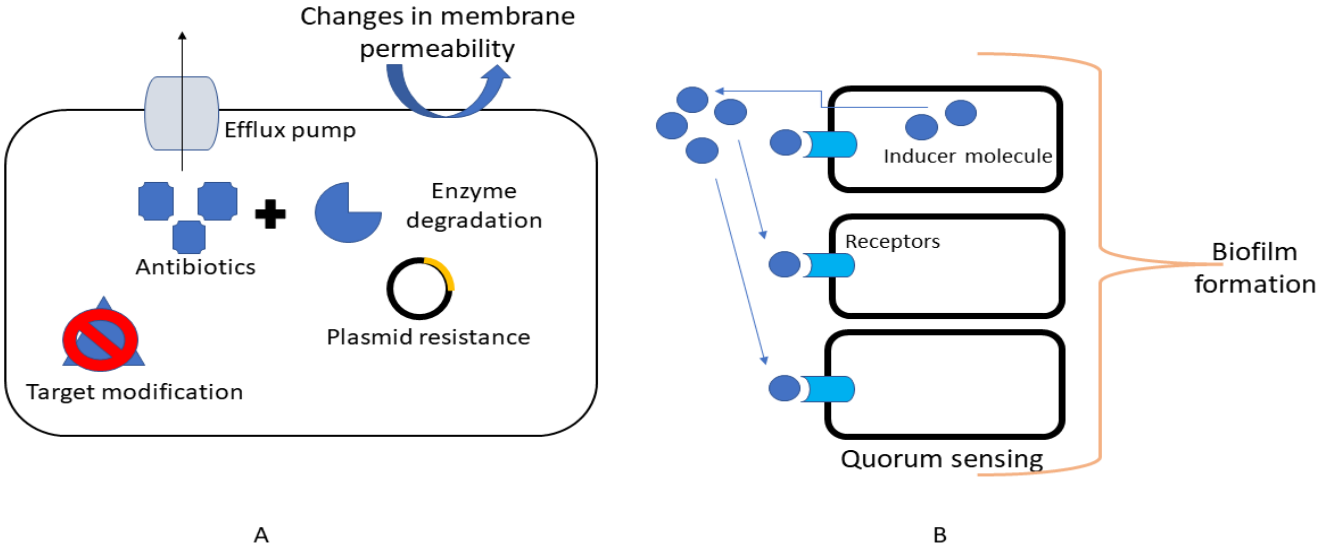

Fig. 2. Mechanism for development of drug resistance in bacteria: A-Efflux pump, target modification, enzyme degradation, plasmid resistance, alteration in membrane permeability; B- Quorum sensing leading to biofilm formation

Multiple-drug resistance is also a significant obstacle in cancer chemotherapeutics. Mechanisms involved in cancer-related MDR can be pump resistance or non-pump resistance (18). Antiapoptotic defense is a non-pump resistance mechanism that utilizes BCL2 proteins. Pump resistance is associated with membrane-bound active efflux pumps. Efflux is majorly conducted by membrane transporters belonging to the ATP binding cassette (ABC) superfamily (19). Many ABC family genes have been identified and subcategorized into seven subfamilies, among which P-glycoprotein also MDR1/ ABCB1, multidrug resistance-associated protein 1, and breast cancer resistance protein are considered as prime factors for induction of MDR (20).

Under such conditions, plant-derived compounds have always been the prime focus for a solution. Phytochemicals majorly target protein, DNA/RNA, lipids, and bio-membranes, causing inhibition of target pathogens. These secondary metabolites quench biofilm and quorum sensing and modulate efflux pumps, which are significantly involved in antimicrobial drug resistance (21). Anticancer drug resistance can also be tackled through phytochemicals by inhibiting proteins and signal transduction involved in anticancer drug resistance (22). The effectiveness of phytochemicals is improved through nanoparticles through various mechanisms like increasing the compound's bioavailability and improving phytochemical stability. Phytochemical-based nano-formulations have also contributed to combating drug resistance (23).

Collectively, phytochemicals have emerged as an effective way to tackle drug resistance in cancer and bacterial diseases. Drug resistance is challenging the available treatments and increasing the spread of diseases. Phytochemicals also show potential applications as anti-obesogenic and cardioprotective agents. The present review emphasizes different phytochemicals and their mechanisms of action against bacterial and cancer-related drug resistance, along with insights into the success of phytochemical-based nanoparticles in combating drug resistance.

Antimicrobial drug resistance coping through phytochemicals

Different phytochemical compounds have been studied for their drug resistance modulation properties in bacterial drug-resistant strains. The phytochemicals target various mechanisms of drug resistance development, which have been discussed below,

a. Biofilm and quorum quenching mechanism of phytochemicals

Quorum sensing (QS) and biofilm formation effectively participate in drug resistance. Quorum sensing is a density -dependent cell-cell communication system that controls many physiological behaviors in bacteria. Bacteria secrete signaling molecules that can regulate cellular processes involving bacterial luminescence and spore formation. Quorum sensing regulates efflux pump gene expression and biofilm formation, resulting in drug resistance (24). *Camellia sinensis*, commonly called green tea, constitutes phytochemicals that act as quorum-sensing inhibitors (25). Firstly, the fraction with high bioactivity of green tea was characterized and then tested for its antibiofilm and quorum quenching ability on Gram-negative bacteria *Chromobacterium violaceum* ATCC 12472 (ATCC, USA), *Pseudomonas* 138 *aeruginosa*, and *Serratia marcescens* MTCC 97(MTCC, India). The ethyl acetate fraction of green tea was found to have the highest bioactive component, which exhibited antibiofilm production activity by turning off pilus assembly. The quorum quenching also took place due to the binding of phytocompounds to receptor proteins involved in quorum sensing (25). Multiple drug resistance is also seen in wound burn infections; many drug-resistant strains of fungi and Gram-positive and -negative bacteria have been noticed (26). Leaf extracts of *Lycium shawii* were investigated for modulating this resistance. The study conferred potential antimicrobial activities against clinical strains of PDR *Pseudomonas aeruginosa*, *Aspergillus niger, Staphylococcus aureus*, and, *Candida albicans*. Further, toxicological and hemolytic activity determination of the extract suggested that the extract is safe to be used in the subjects (27).

Pseudomonas aeruginosa is a pathogen accounting for 57 percent of nosocomial infections (28). Ethanolic leaf extract of *Syzygium jambos* was confirmed for anti-quorum sensing activity through binding to transcriptional activators of quorum sensing (29). Another study investigated the extract of *Acacia nilotica*, against quorum sensing-related virulence factors of *Pseudomonas aeruginosa* PAO1 and *Serretia marcescens* MTCC 97. Inhibition of biofilm was studied using microtiter plate assay and light microscopy. Extract components interacted with biofilm proteins, thus halting biofilm production. Further in vivo investigation is suggested (30).

b. Modulation of gene

Antibiotic resistance can also be facilitated by the mutation or horizontal transfer of resistance-conferring genes(31). Modulation of resistance gene expressions can happen at transcriptional or translational levels, thus helping the bacteria to cope with the stress (32). Different genes involved here can be targeted to get rid of the infection (33).

Gallic acid showed antimicrobial activity against *Shigella flexneri*, which invades colonic epithelium. Gallic acid regulates the expression of the mdoH gene and OpgH protein, which inhibits biofilm formation and controls its growth (34). Transcription profiling of Aloe-emodin, a phytochemical, showed an antibacterial effect by changing the genes involved in metabolism, membrane biosynthesis, and biofilm formation (35). Another Gram-negative bacteria, *Helicobacter pylori*, causes gastritis in humans and has also been reported as a carcinogen. Vacuolating cytotoxin (VacA) and cytotoxin-associated (CagA) genes confer pathogenicity to these bacteria. *Syzygium aromaticum* extracts were reported to modulate the CagA gene, in turn affecting PDR. The major constituent of the methanolic extract of *S. aromaticum* was found to be eugenol, a phenolic compound(36).

Genes responsible for enzyme synthesis can also be targeted for combating drug resistance. Versatile

mechanisms are involved in the development of resistance through enzymes. Enzymes target the antibiotic and prevent its action. Enzymes undergo structural changes which are the target of the antibiotic and thus surpass the effect of antibiotics (37). Nosocomial infections are a rising concern in the world, and one of the pathogens causing such infections is *Klebsiella pneumoniae*. Production of Carbapenemase and extended-spectrum beta-lactamase (ESBL), metallo beta-lactamase or ampicillinase (AmpC) enzymes causes drug resistance in this species. The research evaluated the inhibitory effect of crude ethyl extract (CEA) of *Andrographis paniculata* on the gene encoding AmpC beta-lactamase. It was observed that CEA stops the growth and biofilm production of the drug-resistant bacteria along with suppression of the AmpC gene (38).

c. Efflux pump modulation

An efflux pump is a bacterial system capable of excluding the toxins outside the cell. Using the exact mechanism, antimicrobial substances are thrown out of the cell, allowing the cell to survive. A large family of protein pumps is involved in this mechanism (39). AcrAB-TolC efflux pump confers MDR to *Salmonella enterica*, which is responsible for foodborne infections(40). A total of 71 phytocompounds derived from plants in Mexico, were tested for inhibition action against these pump proteins using molecular docking and molecular dynamics simulation techniques. Three compounds, 5-methoxypsoralen, licarin A, and naringenin (Fig. 3.), showed efflux pump inhibition activities. Licarin A showed the highest inhibition activity, supporting further research on its antimicrobial activities (41). Another investigation of catharanthine extracted from *Catharanthus roseous* showed its potential to reverse the drug resistance. The study was done in silico, which revealed the MexA, MexB, and OprM pump protein inhibition mechanism of the catharanthine (42).

Anticancer drug resistance modulation using phytochemicals-

One of the world's challenges is to tackle drug-resistant cancer cells. Studies done using phytochemicals in cancer focus on two aspects: to reverse the drug's effect by affecting the expression of ABC transporter proteins and to exert combined interactions with anticancer drugs (43). A study revolving around the cytotoxicity check of phytochemicals against MDR bladder cancer cells suggested, that capsaicin has a synergistic cytotoxic effect against drug-resistant cancer cells (44). The gemcitabine drug, resistant cell line, T-24 GCB, was used in the study. In bladder cancer cells, drug resistance is caused due to membranous ABCC2 (ATP binding cassette subfamily C member 2), cytoplasmic DCK (Deoxycytidine kinase), and TKs (thymidine kinases) expression. Many phytochemicals such as curcumin, capsaicin, resveratrol, and quercetin, along with gemcitabine, were assessed through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Also, capsaicin and quercetin alone and combined with gemcitabine reduced the expression of resistant-causing factors (45).

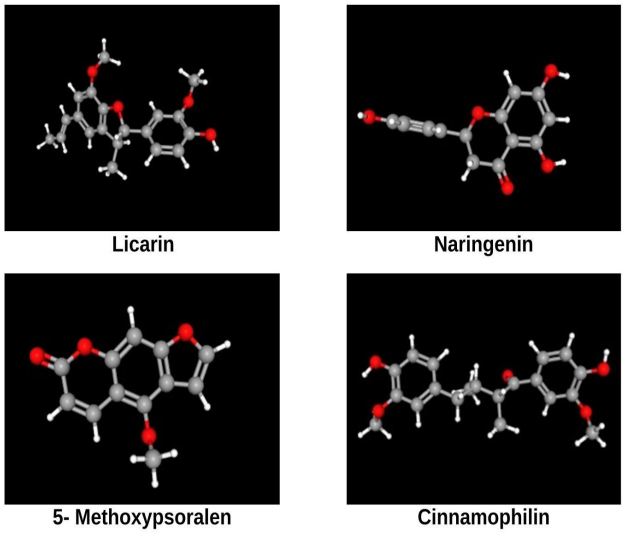

Fig. 3. Phytochemicals which have potential to tackle drug resistant pathogens

P-glycoprotein (P-gp/MDR1/ABCB1), belonging to ABC transporter proteins leading to MDR has also been extensively studied. To this, combating strategies involve the co-administration of synthetic or natural protein modulators, but studies to confirm the non-toxicity of these modulators are still in process (46). A phytochemical study of *Euphorbia boetica* showed the presence of P-gp modulators. This plant species contains- unique macrocyclic diterpenes having lathyrane and jatrophane skeletons known as MDR modulators (47). This study involved chromatographic separation and further analysis of fractions using H-NMR to find the compounds having macrocyclic diterpenes. Using transport assays, and chemosensitivity assays, in mouse model and Colo320 cell models MDR reversal activity was examined. As per the study, macrocyclic diterpenes have MDR reversal activity; additionally, it was noted that combining such compounds with antineoplastic drugs synergistically enhances their effect (48). Another phytochemical compound, cinnamophilin (Fig. 3.) isolated from *Cinnamomum philippinense*, also reported P-gp inhibition thus cancer MDR reversal and drug resensitization. This compound is a dual allosteric inhibitor of the protein through an ATPase binding pocket and drug binding pocket (49).

Other processes such as Epithelial-mesenchymal transition (EMT) pathways are also involved in drug resistance (50). Epithelial cells change to mesenchymal cells and gain fibroblast-like characteristics, through the EMT process. Natural products have been reported to reverse EMT and prevent drug resistance (51). One of the studies on Farrerol also suggested EMT ablation in lung squamous cell carcinoma cells (52). These studies, showed successful coping of drug resistance in cancer using phytochemicals.

Phytochemical-based nanoparticles application in drug resistance modulation-

Nanotechnology has gained increased applications in combating drug resistance. Studies suggest the positive effect of nanoparticles, thus establishing nanoparticles (NPs) as a –'nanobiotic'(53). Nanoparticles made using biological synthesis reduce the release of toxic by-products after production. One such method for the synthesis and stabilization of nanoparticles is the usage of phytochemicals as capping agents (54). US FDA (Food and

Drug Administration) lists zinc oxide nanoparticles under GRAS (Generally recognized as safe) metal oxide(55). These nanoparticles have drug delivery ability and show antifungal, antibacterial, antidiabetic, anticancer, and antioxidant properties. The study under consideration focused on the application of these NPs along with *Bryophyllum pinnatum* leaf extract as a capping agent, to treat drug-resistant strains of uropathogens. After characterizing synthesized nanoparticles, the antibacterial potential was analyzed using the agar disc diffusion method against clinical Gram-negative uropathogens. The assay confirmed the antibacterial activity of NPs against MDR strains, thus opening a new dimension in nanoantibiotics (56). Another green synthesized metal nanoparticle was studied against antibiotic-resistant *Pseudomonas aeruginosa*. *Cinnamomum tamala* (Tejpata) leaf extract-derived silver nanoparticles (AgNPs) were subjected to molecular characterization using spectroscopic and microscopic techniques followed by antibacterial activity testing using the agar disc diffusion method. Zones of inhibition on agar plates confirmed the required effect of synthesized AgNPs. The inhibitory effect of leaf extract was found to be enhanced by the addition of AgNPs (57).

Another instance showed combinatorial therapy success towards antibacterial resistance combat. Conventional antibiotic combined with embelin-loaded, chitosan-gold NPs were checked for antibacterial activity against MDR-resistant strains of *Pseudomonas aeruginosa* and *Escherichia coli*. The synergistic activity of NPs with conventional antibiotics displayed an inhibitory effect against the pathogens. Molecular docking revealed the efflux pump inhibition mechanism, wherein Emb and efflux pump-related proteins were noted. Therefore, the bacteria retained the antibiotic, causing the organism's death. Such formulations of phytochemical and metallic nanoparticles along with antibiotics, can also be applied to other MDR-resistant strains (58). Not only antibacterial resistance but many studies suggest the effectiveness of phytochemicals and nanoparticles in anticancer resistance medication. One of the studies suggested the cytotoxic effect of lactoferrin-associated Betulinic acid nanoparticles in laryngeal and triple-negative breast cancer types. Betulinic acid, a triterpenoid is extensively found in *Betula alba*'s bark. Two cell lines used for the study were HEp-2 and MDA-MB-231. Synthesized nanoparticles achieved faster cellular uptake and induction of cellular death at much lower concentrations than previous reports. The study confirmed the ability of phytochemical-based nanoparticles in drug-resistant cancers (59).

Summarizing some of the phytochemical-based studies and their mechanism of action in microbial diseases and cancer in Table 1.

Anti-obesogenic and cardioprotective potentials of phytochemicals-

As the antibacterial and anticancer drugs face the issue of resistance, available anti-obesogenic drugs are of low efficacy, show undesirable side effects, and result in short-term weight loss. Through various studies, phytochemicals have also been identified as preventives and therapeutics for obesity (68). A study suggested that the anti-obesogenic property of curcumin is conferred by its ability to induce apoptosis in preadipocytes and inhibit preadipocyte differentiation, thus blocking adipogenesis (69). Another study on Allium-derived propyl propane thiosulphinate(PTS), confirmed PTS as an anti-obesogenic and protective agent. This chemical prevented weight gain, decreased adipocyte size, and also changed lipid metabolism, and increased thermogenic capacity markers of brown adipose tissue (70). Reduction in the expression of proteins responsible for adipogenesis and raising the expression of fatty acid oxidation proteins results in the anti-obesogenic character of broccoli sprout powder and *Sinapis alba* L. seed powder. Moreover, activation of the AMPK signaling pathway also helps in weight loss (71). Many other mechanisms involving stimulation of thermogenesis, promoting lipolysis, and inhibiting hypothalamic enzymes have been established in

Table 1. Preclinical studies of phytochemicals showing resistance modulation activity in microbial diseases and cancer

Genus/ Species	Phytochemical in study	Therapeutic agent	Disease/ Infections	Strategy adapted/ Mechanism of action	References
Olea europaea L.	Olive	Metformin	All types of breast cancer	Through p53-independent apoptosis, the viability of MCF-7 reduced synergistically.	(60)
Plumbago zeylanica L.	Plumbagin	Cisplatin	Tongue squamous cell carcinoma	Apoptosis through activation of JNK, Suppression of cell viability, and repression of AKT/mTOR signaling pathways synergistically	(61)
Allium sativum L	Allicin	5-Fluorouracil	Colorectal and lung Carcinoma	In comparison with single-agent IC50, enhanced cytotoxic activity in half of their IC50.	(62)
Scrophularianodosa	Diosmin	Dactolisib	Colorectal cancer	For Dactolisib and Diosmin, induction of apoptosis at IC50 of 1μM and 250μM respectively.	(63)
Mulberries, Peanuts, Grapes	Resveratrol	Docetaxel	Prostate cancer	Suppressed cell growth with a rise in the sub-G0/G1 peak, ROS, and mitochondrial dysfunction synergistically.	(64)
Citrus lemon	Limonene	D-Limonene	Abscesses (boils), furuncles, and cellulitis	Disrupts cell membrane integrity.	(65)
Thymus vulgaris L.	Thymol	*p*-cymene	Candidiasis	Disturbance in efflux pump, inhibition of H (+)-ATPase in the cell membrane and cytoplasmic membrane	(66)
Cymbopogon	Citronellol	-	Athlete's foot, Tinea pedis, breast cancer.	Apoptosis in MCF-7 and MDA-MB-231 by mitochondrial -mediated activation in human mammary tumour cell lines.	(67)

phytochemicals, proving their anti-obesogenic properties (72).

Obesity is a multifaceted disorder that can be linked to the emergence of other diseases, such as cardiovascular diseases (73). Phytochemicals have also been instrumental in this perspective to protect the individual from cardiovascular diseases. A recent study on phytochemicals of *Morus nigra* (*M. nigra*) fruit showed that phytochemical extracts of this fruit can increase antioxidant enzymes, reduce transaminases, lactate dehydrogenase, lipids, liver and also blood pressure, contributing to its cardio-protective nature (74). Another study using rat animal models of chicory acid extract from Romanian chicory (*Chicory intybus*) gave promising results in curing myocardial ischemia (75). Icariin and associated metabolites also have a protective nature towards myocardial cells (76).

Conclusion and Future Perspectives

Phytochemicals are an essential part of the biodiversity available on the earth. Phytochemicals show an enormous scope in managing the drug resistance problem in microbial diseases and cancer. These plant-based products show inhibitory effects on resistance-causing genes, efflux pump proteins, quorum sensing, and biofilm formation in microbial drug resistance strains. Concerning cancer-drug resistance coping, many phytochemicals target ABC transporter proteins. Phytochemical-based nanoparticles synergistically improve the therapeutic effect of phytochemicals, thus emerging as a promising solution. Cardioprotective and anti-obesogenic characteristics of these plant-based derivatives have also been recognized. A shift from chemical-based antibiotics to phytochemical-based nano-biotics can successfully tackle the drug resistance. More such studies of effective extraction strategies and characterization of phytochemicals will help mankind to access efficient and cost-effective treatment options. It is also important to note that, most of the studies are yet to reach animal model in-vivo studies, and drug testing has not even started. Clinical trials should be undertaken to confirm the safety, drug efficacy, and metabolomics of phytochemical-based nanoparticle drugs. The gap between knowledge and application is persisting, requiring extensive research in commercializing phytochemical-based drugs.

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Authors' contributions

KJ devised the article, searched the literature, wrote the manuscript and plotted figures. MP, KAP and JKS revised the work. MD, SJR, AC, and KA searched and supplemented the literature. MP conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical approvals: None.

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