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Antioxidant Phytochemicals as Novel Therapeutic Strategies against Drug-Resistant Bacteria

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Abstract:

The antibiotic resistance in pathogenic bacteria is a major concern and the emergence of novel multidrug-resistant (MDR) strains are a growing threat worldwide. Bacterial resistance to antibiotics has become a serious problem of public health that concerns almost all antibacterial agents and that manifests in all fields of their application. Therefore, novel antimicrobial compounds against new bacterial targets and drug resistance mechanisms are urgently needed. Plants are well-known sources of structurally diverse phytochemicals such as alkaloids, flavonoids, phenolics, and terpenes, which plays important roles in human health. Plant-derived antimicrobial agents are an attractive and ongoing source of new therapeutics. Natural compounds that prevent and treat infections through dual action mechanisms such as oxidative stress against pathogens and antioxidant action in the host cell hold promising potential for developing novel therapeutics. Identification of detailed mechanisms of action of such Phyto molecules with both antioxidant and antimicrobial activities may help to develop novel antimicrobial therapeutics and benefit overall human health. The purpose of this chapter is to summarize important antioxidant phytochemicals and focusing on their potential role in the management of drug-resistant bacterial infections.

Keywords**: **Antioxidant, Drug Resistance, Oxidative Stress, Phytochemicals, Drug-Resistant Bacteria.

Introduction:

Antimicrobial resistance has now become a serious public health issue worldwide. Resistance to antimicrobials is a growing challenge that limits treatment options against serious pathogens and therefore new effective treatment strategies are needed [1]. Infections caused by *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Enterococcus faecalis*, and Gram-negative bacteria such as *Escherichia coli, Klebsiella pneumonia, Salmonella typhi, Pseudomonas aeruginosa*, are among the most common bacteria that have developed drug-resistant to many antibiotics. According to the Centres for Disease Control and Prevention (CDC) 2019 AR threats report [2] penicillin-resistant *Pneumococcus*, drug-resistant *Campylobacter* sp., methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* (VRE), multidrug-resistant of *Pseudomonas aeruginosa*, *Salmonella typhi*, *Shigella sp.*, and *Mycobacterium tuberculosis* (MDR-TB) are serious threat and major causes of

worldwide outbreaks of both the community infections and hospitals . While carbapenem-resistant *Enterobacterales,* drug-resistant *Gonorrhea* and *Clostridioides difficile* are grouped among urgent treats. The spread of multidrug-resistant (MDR) strains of pathogenic bacteria necessitates the discovery and deployment of new classes of antibacterial and compounds that can combat resistant strains and the spread of drug resistance. During infections in humans, immune cells produce reactive oxygen and nitrogen species (RONS) which is used as part of warfare activity against pathogens. Oxidative stress induced by intracellular bacterial infection or other metabolic processes can cause inflammation and cellular damage however RONS production helps to kill bacterial pathogens. Unfortunately, pathogens have evolved a number of adaptive mechanisms against host-mediated defence systems and RONS, Microorganisms' survival strategies against RONS include the expression of various enzymes catabolizing RONS such as catalase, peroxidases, and biofilm formation also helps pathogens overcome the immune defines system. Therefore, targeting bacterial redox systems could present an important tool to combat such infections. Indeed, significant progress has been made in identifying several natural sources of antioxidants that may also cause oxidative stress as a part of the antibacterial mechanism of action. This emerging field needs further focus on the redox biology of antioxidants with antimicrobial activity by oxidative stress to cure intracellular bacterial pathogens. Plants have an exceptional ability to produce cytotoxic agents to protect themselves from pathogenic microbes in their environment. Plant-derived secondary metabolites with antibacterial properties can be a source for designing novel therapeutics. Historically, traditional medicines based on plants have made a considerable number of contributions to human health. Plants are rich in a wide variety of secondary metabolites such as terpenoids, alkaloids, polyphenols, and tannins with a diverse set of biological activities. During the last decades, there is increasing interest to explore ancient remedies. A significant number of works, e.g., biological screening, isolation as well as clinical trials have been done for a variety of plants to unlock the secrets of herbal remedies. Antimicrobials with reuse potential, which can be used in combination with drug treatments against drug-resistant pathogens, are identified using this approach. For example, plants derived alkaloids such as tomatidine and berberine are reported to be highly effective against drug-resistant microbes and also show synergy with antibiotics against *S. aureus,* and *E. coli*. Therefore, screening and identification of compounds responsible for antimicrobial activity can be the foundation of a novel class of drugs. In this chapter, we have summarized the importance of medicinal

and aromatic plants in the management of drug-resistant bacterial pathogens.

Materials and Methods:

Role of Oxidative Stress and Antioxidants Mechanisms in Health and Infectious Diseases:

The paradox of oxidative stress is that it plays a dual role in the disease and health of humans. The importance of oxidative stress mechanisms in living cells is based on a balance between oxidants and antioxidants. During metabolic reactions and infection, various types of RONS are produced in human by enzymes like myeloperoxidase, oxidases, and nitric oxide synthase, however, excess of these RONS can also damage host tissues and thus are reduced by the human cellular antioxidative defense system that includes enzymes like peroxidases, superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and others which eliminates the excess of reactive oxygen species (ROS) such as hydroxyl radicals ($OH^{\cdot}$), superoxide anions ($O2^{\cdot-}$), alkoxyl radicals ($RO^{\cdot}$), and peroxy radicals ($ROO^{\cdot}$). As a result, we require antioxidant supplements like vitamin C, vitamin E, carotenoids, and polyphenols to avoid oxidative stress [18, 19]. Supplementing a low amount of oxidative stress may also help to signal processes to express enzymes that detoxify the RONS. This means low level of physiological oxidative stress can be beneficial to counteract excess oxidants produced during stress and infections that may result in cellular damage. During phagocytosis, NADH-dependent oxidase (NOX) mediated burst of superoxide anion ($O2^{-}$) causes bactericidal oxidative stress. This free radical is converted to hydrogen peroxide (H_2O_2) by superoxide dismutases. Infection control requires the presence of the NOX protein and abnormalities in the genes that produce the NOX protein makes it more vulnerable to bacterial and fungal infections. H_2O_2 produced during phagocytosis passes through bacterial membranes barrier and interacts with ferrous iron (Fe^{2+}) and thiol groups (-SH) of the cysteine in proteins which can eventually inactivate the function of enzymes [5]. During the Fenton reaction, H_2O_2 oxidizes Fe^{2+} to Fe^{3+} and produces hydroxyl radicals (OH^{-}), which further damage bacterial DNA, proteins, and lipids [5]. Myeloperoxidases expressed in macrophages and neutrophils produce hypochlorous acid (HClO) from the reaction between H_2O_2 and chloride ion (Cl^{-}). HClO has a stronger antibacterial effect than H_2O_2. Later phases of phagocytosis activate inducible nitric oxide synthases (iNOS). Nitric oxide ($NO^{\bullet}$) is produced by these enzymes from L-arginine. Peroxynitrite is formed when nitric oxide reacts with the superoxide ion produced by NOX proteins. Peroxynitrite can directly oxidize the thiol groups of sulfur-containing amino acids, or it can break down into nitrogen dioxide and hydroxyl radicals, which can damage the sulfur-containing proteins in bacteria.

Discussion:

Bacterial Antioxidant and Redox Pathway Mechanisms:

As described above, during phagocytosis bacteria are exposed to several RONS but they can still be growing in the intracellular environment under these oxidative conditions. It is important to note that microorganism also possesses several enzymes like catalase, peroxidases, and superoxide dismutase. These protect against oxidative stress with a complex set of enzymatic activities that can be divided into two categories: (i) preventive mechanisms, which are based on protein scavengers to inactivate RONS, and (ii) the repair mechanism.

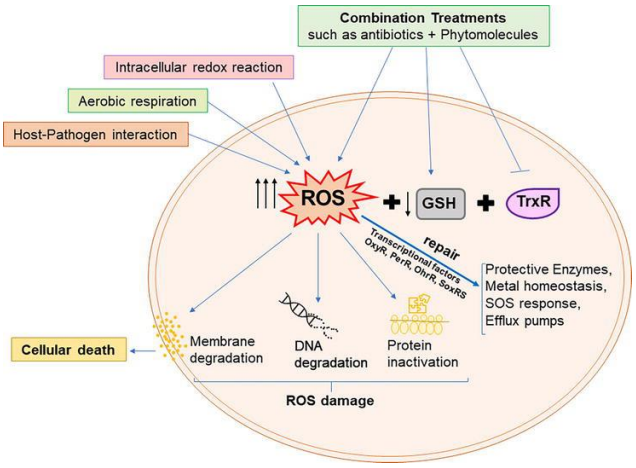

Figure 1: Overview of oxidative stress and response mechanism in bacteria.

Oxidative stress is caused by the accumulation of reactive oxygen species (ROS) caused by both exogenous and endogenous sources. Bacterial cells are damaged by ROS because it causes DNA degradation, protein inactivation, membrane degradation, etc. Bacteria use a variety of mechanisms such as repair mechanisms and protective enzyme synthesis, metal homeostasis, the SOS response, and efflux pumps to counteract oxidative stress. OxyR, PerR, OhrR, and SoxRS are transcriptional factors that control the expression of oxidative stress response in bacteria. The expression of antioxidant enzymes is controlled by transcriptional regulators that can interact with RONS based on thiol switches or metal centers. For example, OxyR is redox regulator that is reported to act as transcriptional activators or repressors in several bacteria [30]. Homologs of the MarR-family, thiol-based transcriptional regulators e.g. the sodium hypochlorite sensor (HypS) are found in the genomes of a variety of pathogens. Oxidation the thiol groups by RONS causes conformational changes in transcriptional regulators and modulates their binding capacity to promoters of genes encoding scavenger enzymes such catalases (Kat), superoxide dismutases, glutathione peroxidases (GPx), and peroxiredoxins (Prx). Many pathogens such as *Mycobacterium tuberculosis* are known to use combination of these

enzymes to overcome RONS challenges. Loss of one or more of these genes directly affects resistance to RONS and survival of bacteria. Extracellular thioredoxins (Etrx) found on the bacterial surface, have been found in human pathogens such as *M. tuberculosis*, *S. pneumoniae*, *N. gonorrhoeae*, as well as in plant-associated bacteria such as *Agrobacterium tumefaciens*, and *Bradyrhizobium japonicum*. Although the targets of Etrx proteins are unknown, deletion of the genes encoding Etrx proteins reduced the pathogenicity of *M. tuberculosis* and *S. pneumoniae*. However, more research is needed to fully understand the role of such surfaceome-associated proteins and their involvement during infection.

Plant as Potential Source of Preventative and Therapeutic Agents of Oxidative Stress and Disease:

Medicinal plants and their extracted phytochemicals are widely used in the treatment of a variety of diseases, including bacterial, fungal, viral and cancer, as well as oxidative stress-related problems. Due to the anti-oxidative, anti-inflammatory, anti-microbial, and wound-healing characteristics natural phytochemicals, these substances have been studied extensively to facilitate their application as phytomedicine in the pharmaceutical field. Several Phyto molecules such as quercetin prevents oxidative damage in human by influencing glutathione levels, enzymes, signal transduction pathways, and ROS production as well as show antibiofilm activity and bacteriostatic properties against several pathogens like *E. coli, S. aureus* and *P. aeruginosa* by means of promoting oxidative cellular stress targeting a wide range of cellular component.

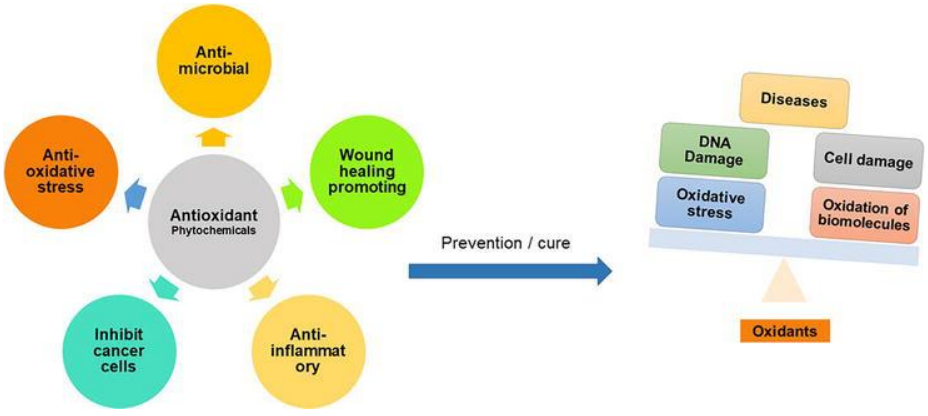

Figure 2: Schematic representation of the potential roles of antioxidant phytochemicals.

Natural products have shown to be a never-ending source of novel medicines. Medicinal plants have been used in drug development since ancient times, and they continue to provide novel and important roles against a variety of medicinal targets, including infections, cancer, HIV/AIDS, Alzheimer's disease, and malaria . Ayurveda and Charaka Samhita have contributed significantly to the discovery of new drugs and chemical entities due to India's abundant biodiversity and traditional medicinal herbs. Ancient Chinese and African traditional medicine have a long history of medicinal plants for several physiological conditions. Early pharmaceuticals such as cocaine, codeine, digitoxin, and quinine, as well as morphine, were discovered from medicinal plants, and are still used today. Natural compounds or chemicals inspired by nature provide more than 80% of all medicines used today. On the other hand, drug discovery from natural plants is a time-consuming and laborious process. To date, several bioactive chemicals have been identified and described from medicinal plants that have been successfully exploited for biomedical purposes. There are more than 100 natural product-derived compounds already in clinical studies. Traditional medicinal systems have a long history, dating back more than 60,000 years Herbal remedies are used in all developed countries, and the WHO estimates that approximately 75% of the world's population uses medicinal items as an alternative to allopathic medicines. It is interesting to note that medicinal plants provide 35% of all drugs recommended and prescribed today. Natural source phytomedicine in pure is either used directly or converted using appropriate chemical or microbiological processes until used as medicine [6]. Alkaloids, phenolics, and terpenes are examples of natural chemicals that have been demonstrated to be effective against many pathogens. Pomolic acid, oleanolic acid [5], gallic acid, chebulagic acid, and other galloyl glucose [4] have also been reported to inhibit HIV integrase. Researchers continue to uncover phytochemicals in many plants that are important for drug development; Their actions may offer new hope in treating various infections or diseases as well as reducing toxicity.

Classification of Phytochemicals:

Natural bioactive compounds or phytochemicals have significant physiological effects on human health. They are a major source of diver's chemicals, making them a potential source of new drugs. Phytochemicals are classified as primary and secondary constituents according to their importance in plant metabolism (Figure 3). Generally, primary metabolite includes carbohydrates, proteins, lipid, and chlorophyll; the secondary metabolite has been classified into six major categories (i.e., phenolic, coumarins, glycoside, chalcones, terpenes, and alkaloid) based on chemical structures and characteristics.

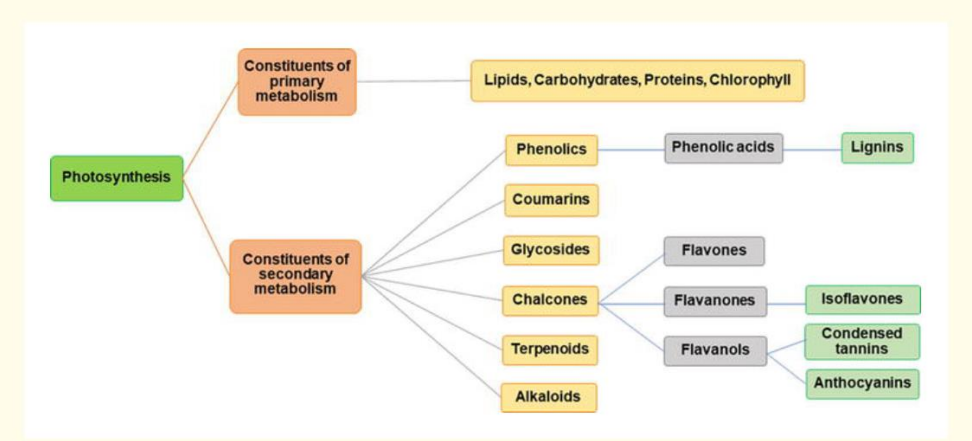

Figure 3: Phytochemical classification demonstrating the link between primary and secondary metabolism in plants.

Alkaloids:

Alkaloids are produced by plants as protective agents against attack by predators. Alkaloids are basic compounds that contain heterocyclic nitrogen atoms that react with acids to produce salts. Most of all alkaloids are sour in taste. Morphine, the first alkaloid discovered in *Papaver somniferum*, has antibacterial properties [51]. Antimicrobial activities were discovered in diterpene alkaloids from Ranunculaceae plants [52]. Berberine is an is quinoline alkaloid isolated from berberine species that has antibacterial and antiviral properties Quinine, an alkaloid, was the first successful antimalarial drug extracted from the Cinchona tree. Atropine, codeine, coniine, caffeine, hyoscyamine, scopolamine, sanguinarine, etc., are the other examples of alkaloid found in nature. Alkaloids have diverse physiological effects and have been reported to possess antibacterial, anaesthetic, anti-inflammatory, antimitotic, analgesic, hypnotic, psychotropic, and antitumor activity, and many others.

Flavonoids:

Flavonoids are polyphenolic chemicals found in vascular plants that come in the form of aglycones, glucosides, and methylated derivatives. Tomatoes, grapes, berries, apples, onions, kale, and lettuce are rich sources of flavonoids. Flavonoids are divided into two groups: flavone and isoflavone depending on the position of the benzenoid substituent. The majority of flavonoids are found in the conjugated form in nature and can be classified as Mon glycosidic, diglycosidic, or polyglycolide within each class. The carbohydrate unit might be L-rhamnose, D-glucose, galactose, or arabinose, and the glycosidic linkage is usually found at position. Plants, animals, human, and microorganisms all use flavonoids for a range of biological functions. Flavonoids have been linked to improved human health, and they are currently being studied for antibacterial activity and chemoprevention. Apigenin, quercetin,

kaempferol, fisetin, glaring, and myricetin are most studied flavonoids. Flavonoids act as antioxidants and also insilico modeling and docking studies suggest potential as an antibiotic activity. Apigenin, and quercetin are known to show antibacterial activity [5]. Quercetin and its analog penta-O-ethylquercetin were found to be potential inhibitors of New Delhi metallo-β-lactamase-1 (NDM-1). Several research have reported synergy between flavonoids and antibiotics against resistant strains of bacteria.

Phenolics and Polyphenols:

Phenolic acids contain carboxylic acid functional group. The hydroxycinnamic and hydroxybenzoic structures are found in naturally occurring phenolic acids Phenolic compounds possess strong anti-inflammatory, antioxidant, and antimicrobial activities. Plant phenolic compounds and phenolic compound-rich herbal extracts control cell proliferation, survival, and apoptosis via modulating the amounts of reactive oxygen species (ROS) in cells. Recent research has also shown that phenolic compounds undergo change in the gut microbiota, gaining new characteristics that enhance their biological activity. Tennins are polyphenolic chemicals that can form complexes with nucleic acids, proteins, and polysaccharides among other elements [2]. Phenolic compounds such as catechins, epigallocatechin gallate, galangin are reviewed for their antibacterial activity. Ferulic acid, coumaric acid, chlorogenic acid, and caffeic acid have shown efficacy against *S. aureus*.

Terpenes:

Terpenes are natural occurring chemicals found in plants and are known for the aromas and Flavors. Terpene contains isoprene units made up of five carbons atoms. Terpene chemical formula is $(C_5H_8)_n$ and their hydrocarbons are characterized by number of isoprene units. Terpenes are important for plant growth and development, physiological processes, and response to the environment. Cannabis is important terpenes known for several uses such as aroma and taste. Terpenoids are essential oils and volatile chemicals found in higher medicinal plants. Terpenoids also show antimicrobial activity . Monoterpenes such as menthol, sabinene, limonene, and carvone have shown strong antibacterial activity against *S. aureus* ,Sesquiterpene (Patchouli alcohol), Diterpene (Artemisinin and Andrographolide), and Triterpene (Oleanolic acid) also show antibacterial activity in bacterial strains.

Antioxidant Phytochemicals: Mechanism of Action:

Antioxidants are a type of defense mechanism that protects the human body from oxidative damage caused by free radicals. There are many different types of naturally occurring antioxidants with different physical and chemical properties, processes, and mechanisms of action. Antioxidant activity has been reported in medicinal plants rich in vitamins, carotenoids, flavonoids,

polyphenols, and anthocyanins. The antioxidant mechanism of phytochemicals has been reviewed in detail [6]. Briefly, phytochemicals exert antioxidant activity by the following means: 1. Free radical scavenging activity; antioxidants are known to chelate free radicals, transition metals, and remove electrons or hydrogen from substance. 2. Inhibition of the expressions of free radical creating enzymes or induce the expressions of other antioxidant enzymes, e.g., modulation of host nuclear factor erythroid 2 (Nrf2), a master regulator of antioxidant defense system, that controls over a dozen of enzymes such as glutathione S-transferases (GSTs) and NAD(P)H: quinone oxidoreductase 1 (NQO1) [6]. Resveratrol, anthocyanins, and curcumin are phytochemicals that modulate prostaglandin formation and Nrf2 activity, inhibit enzymes, and increase cytokine production, all of which may help reduce inflammation [5]. 3. Prevents lipid peroxidation, DNA damage, and protein modification caused by ROS.

Anti-microbial Phytochemicals: Mechanism of Action:

The use of medicinal plants and their extracts for the treatment of all infectious ailments was widespread. In recent years, many research works have been conducted on the efficacy of plant phytochemicals as antibacterial agents *in vitro* and *in vivo* [3]. The intervention of redox homeostasis is becoming a potential target for combating drug resistance in bacteria. RONS-generating plant-derived antimicrobials have received a lot of attention in recent years. Because of their ability to generate dose-dependent oxidative shifts in the bacteria, some plant-derived chemicals have been shown to have antibacterial activity. Several pathways have been discovered using system biology approaches to disrupt the antioxidant systems of bacterial pathogens [4]. Ebselen (also known as PZ 51, DR3305, and SPI-1005) is reported for antioxidant activity in humans, however, in bacteria such as *M. tuberculosis* or *S. aureus,* it can inhibit growth by causing oxidative stress [3]. Allicin, a defensive molecule, produced by garlic (*Allium sativum*) is the most investigated. Allicin can oxidize proteins' thiol groups in a dose-dependent manner. In *S. aureus* and *Bacillus subtilis*, allicin's antibacterial efficacy and oxidative role have both been proven. Allicin causes high disulfide stress in these bacteria, lowering their viability considerably. Curcumin, a strong antioxidant substance found in turmeric is reported as an antibacterial compound which disrupts bacterial quorum sensing system, cell wall and cell membrane, biofilm and virulence gene expression, and also shows synergy with antibiotics [2]. Recent published work on glabridin also showed dose-dependent activity as antioxidant, antibacterial as well as anti-biofilm against multidrug-resistant *S. aureus*.

Table: List of antioxidant phytochemicals summarized for their antimicrobial properties, chemical class, source, and major mode of action against pathogenic bacterial strains.

Phytochemical class	Phytochemicals	Source	Mode of action	Reported pathogens
Alkaloid	Lysergol	*Ipomoca muricata*	Efflux pump inhibitor	*E. coli*
	Reserpine	*Rauwolfia serpentina*	Efflux pump inhibitor	*Streptococcus sp., Staphylococcus sp.,*
	Berberine	*Berberis species*	Cell division/Protein/DNA synthesis inhibitor	*E. coli*
	Tomatidine	*Solanaceous plants*	ATP synthase inhibitor	*Staphylococcus spp., Listeria sp., Bacillus sp.*
	Matrine	*Thermopsis lanceolata R. Brown*	Protein synthesis inhibitor	*E. coli, E. aerogenes, P. vulgaris, S. epidermidis, B. subtilis*
	Lycorine	*Pancratium Foetidum Pom*	Protein synthesis inhibitor	*E. coli, S. aureus, P. aerugin, E. cloac*
	Chabamide	*Piper chaba*	Protein synthesis inhibitor	*M. tuberculosis*
	Apigenin	*Petroselinum crispum*	DNA gyrase inhibitor	*P. aeruginosa, L. monocytogenes, Aeromonas hydrophila,*
	Quercetin	*Vaccinium* sect. *Cyanococcus*	DNA gyrase inhibitor	*P. aeruginosa*
	Kaempferol	*Brassica oleracea var.*	DNA gyrase inhibitor	*E. coli*

Some conventional antibiotics such as Norfloxacin, Kanamycin, Rifampicin, and Quinones can also generate RONS as part of their mechanism of action [8, 75]. Combining RONS-generating antimicrobials with antibiotics may have a synergistic effect against specific bacterial infections. Similarly, combining antimicrobials with silver nanoparticles may improve RONS production and, as a result, can improve the treatment's efficacy. These unique therapeutic techniques have the potential to improve the antibacterial activity of some repurposable medicines. Antimicrobials that have been clinically approved to treat common infections could even be employed in combination therapy against novel multidrug-resistant bacteria. Natural compounds can not only provide novel antimicrobial treatment options but can also lower the cost of antibiotics treatments in combination, reduce the dose of antibiotics, and therefore can slow the resistance development. Phytochemicals causing oxidative stress with multitarget mode of action further warrant less chance of developing resistance in pathogens.

Conclusion and Future Perspectives:

Medicinal and aromatic plants are an appealing source for novel therapeutics in the era of antibiotic-resistant "superbugs." Plants frequently produce phytochemicals as pathogen-defeating compounds. Many phytochemicals derived from various plants, showed promising antibacterial, antifungal, and antiviral action against a variety of human diseases to date. Phytochemicals offer a lot of potentials when it comes to managing and treating microbial infections and wounds. Antibacterial mechanism of action of several phytochemicals is well-known, and knowledge of these bioactive substances has exploded in recent years. In general, phytochemicals disrupt the bacterial membrane, reduce certain virulence factors such as enzymes and toxins, and prevent the formation of bacterial biofilms, etc. Antimicrobial, antioxidant, and wound-healing phytochemicals promote blood coagulation, infection prevention, and wound healing. Phytochemicals, with dual potential of antioxidants and antimicrobial activity, in alone or combined with antibiotics can not only boost the human immune response to fight infection but can also present newer treatment strategies to combat drug-resistant microbes. Natural compounds such as curcumin, and carotenoids are antioxidants themselves but are also known to modulate Nrf2. Thus, identification, evaluation, and formulation of such natural antimicrobials with dual oxidative stress and antioxidant actions can play an important role to cure infectious diseases while at the same time can repair ROS-induced stress damage and inflammation in the host. It is critical to research and evaluate all accessible solutions that can combat infections, and antimicrobial resistance, and simultaneously improve human lives. Phytochemicals are not only less expensive and more accessible, but they are also safer, less toxic, and have wider acceptance than allopathic pharmaceuticals. However, before suggesting phytochemicals for medicinal purposes, standardization, safety, and scientific evaluation are required.

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