Phytochemicals as Potential Alternatives to Counteract Bacterial Antibiotic Resistance: A Mini-Review

*[1]Bello F, [2]Babandi A, [2]Murtala Y, [3]Abdulazeez MA, [2]Kurfi BG

[1]Department of Biochemistry, Kebbi State University of Science and Technology, Aliero, P.M.B. 1144, Birnin-Kebbi, Kebbi, Nigeria
[2]Department of Biochemistry, Bayero University, Kano, P.M.B. 3011, Kano Nigeria
[3]Centre for Biotechnology Research, Bayero University, Kano Nigeria
*Corresponding Author's Bello F, Department of Biochemistry, Kebbi State University of Science and Technology, Aliero, Birnin-Kebbi, Kebbi, Nigeria
Email: fbello677@gmail.com

Abstract

Antibiotic resistance is becoming a serious challenge to the public health, particularly in the treatment of infectious diseases. Bacterial resistance against antibiotics of natural, semi-synthetic origin or purely synthetic compounds such as the fluoroquinolones or those which do not even enter the cells such as vancomycin has been reported. This mini review explored documented literature trend on mechanism of bacterial antibiotic resistance and the efficacy of phytochemicals as antibacterial compounds. According to the documented literature, the mechanisms of bacterial resistance to antibiotics includes antibiotic inactivation using bacterial enzymes such as β-lactamases, aminoglycoside modifying enzymes and acyltransferases, changes in the target sites of the antibiotics as exhibited by *S. pneumonia, E. faecium* and *E. faecalis* and decreased in membrane permeability/increased effluxion as demonstrated in the membrane trafficking of antibiotics such as β-lactam, tetracycline, chloramphenicol and aminoglycosides. The documented literature on polyphenolic compounds derived from *Cassia italica, Hypericum perforatum* and many plants, alkaloids such as berberine and harmane were effective bacteriostatic as well as bacteriocidal substances. Terpernoid essential oil derivatives were reported to actively inhibit bacterial growth. The available literature showcased low toxicity, accessibility, cost effectiveness and remarkable potentiality of phytochemicals as effective antibacterial substances that could complement modern antibiotics and subsequently reduce the bacterial resistance to antibiotics.

Introduction

The emergence and progression of antibiotic resistance in pathogenic bacteria has led to renewed wave of interest in exploring the potential of plant-derived antimicrobials (PDAs) as an alternative therapeutic strategy to combat microbial infections.[1] Antibiotics constitute a collection of chemotherapeutic agents, either bactericidal or bacteriostatic, which are required for the management and deterrence of microbial infections, for example, β-Lactam antibiotics, Tetracyclines, Macrolide antibiotics, Aminoglycosides, Oxazolidinoes, Quinolones, Lincosamides, cyclic peptides and sulfa drugs.[2] However, prolonged use of antibiotics led to bacterial adaptation, resulting in the development of multi-drug resistance in bacteria.[3,4,5,6,7,8] This has significantly limited the efficacy of antibiotics, warranting alternative strategies to combat microbial infections.[1] Antibiotic-resistant infections are already widespread across the globe.[13] There are high proportions of antibiotic resistance by bacteria in all regions of the world. A high percentage of infections acquired in the hospitals are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant (MDR) Gram-negative bacteria.[9,10] Vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens are developing resistance to many common antibiotics.[11]

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The problem of resistance has been exacerbated by the use of antibiotics in prophylaxis intended to prevent infection before it occurs. Indiscriminate and inappropriate use of antibiotics for the treatment of common cold and other viral infections, against which these antibiotics have no effect, removes the antibiotic sensitive-bacteria and allows the development of antibiotic resistant bacteria. Also, the use of antibiotics poultry feed and livestock has promoted the spread of antibiotic resistance and has led to the prevalent contamination of meat and poultry by antibiotic-resistant bacteria.[12]

The Center for Disease Control and Prevention (CDC) declared in 2013 that the human race is now in the "post-antibiotic era" and the World Health Organization (WHO) in 2015 warned that the antibiotic resistance crisis is becoming serious.[13] Earlier on, the pharmaceutical industry introduced many new antibiotics to solve the resistance problem, but after that the antibiotic pipeline began to dry up, less new drugs were introduced as a result, in 2015, many years after the first patients were cured with antibiotics; bacterial infections have again become a danger. [14]

The worldwide spread of drug resistance gram-negative pathogens are particularly worrying because they are becoming resistant to nearly all the antibiotic choices available, creating situations similar to the pre-antibiotic period.[11,9,10] The most serious gram-negative infections occur in health care settings and are most commonly caused by *Enterobacteriaceae* (mostly *Klebsiella pneumoniae*), *Pseudomonas aeruginosa*, and *Acinetobacter.* [9,10] MDR gram-negative pathogens are also becoming increasingly prevalent in the community settings.[10] These include extended spectrum beta-lactamase-producing *Escherichia coli* and *Neisseria gonorrhoeae*. Management failures due to resistance to antibiotics of last option for gonorrhoea (third-generation cephalosporins) have also been reported. In 2013, there were many new cases of multidrug-resistant tuberculosis (MDR-TB), and Extensively drug-resistant tuberculosis (XDR-TB) which has also been identified in many countries.[11,10]

As a potential source of solution to the resistance to antimicrobial agents, plant-derived antimicrobial agents showed full potentiality in combating bacterial agents with minimal or no resistance to these phytochemicals as documented, probably due to their multiple mechanisms of action which potentially prevent the selection of resistant strains of bacteria.[15,16] The marked antimicrobial effect, nontoxic nature, and affordability of these compounds have formed the basis for their wide use as effective antimicrobials and disinfectants in many industrial and clinical applications, particularly as a source for development of novel antibiotics in pharmaceutics.[1,17] Natural products, particularly plants extract, either as pure compounds or as standardized extracts, provide unlimited opportunities for new drug discoveries because of the unmatched availability of chemical diversity.

Methods

PubMed, Science Direct, NCBI, Elsevier, MEDLINE databases were searched and used for this mini-review to identify studies/findings available and relevant to the potentials of plants' phytochemicals in combating antibacterial resistance. The key words employed in this study search are "Antimicrobial," "Antibiotic resistance,""Medicinal plants","Phytochemicals,""MICs"and "Plant-derived Antimicrobials." We evaluated data from Europe, America, Asia and Africa. English language was used for the selection and reporting of the articles. The selection and data extraction were performed by 6 independent reviewers, and disagreements, if any, were resolved by consensus. Raw data from the articles were used for this mini-review.

Biochemistry and Mechanisms of Antibiotic Action

Microbial cells grow and divide, replicating repeatedly to reach the large numbers present during an infection or on the surfaces of the body. Antimicrobial agents interfere with specific processes that are essential for growth and/or division. Generally antimicrobials and antibiotics can be classified as either bacteriostatic or bactericidal. For an antibiotic to be effective against bacteria, it has to fulfil the following: i) a susceptible antibiotic target must exist in the cell, ii) the

antibiotic must reach the target in sufficient quantity, and iii) the antibiotic must not be inactivated or modified.[18,19] There are five major modes of antibiotic mechanisms of action:

Bacterial Cell Wall Synthesis Inhibition/Interference

The cell wall is an essential microbial structure responsible for the cell shape. In addition, the cell wall prevents cell lysis due the high cytoplasmic osmotic pressure and allows the anchoring of membrane components and extracellular proteins, such as adhesins.[20] Beta-lactam antibiotics such as penicillins and cephalosporins interfere with enzymes required for the synthesis of the peptidoglycan layer. Glycopeptides (vancomycin, teicoplanin, oritavancin) target the bacterial cell wall by binding to the D-alanyl-D-alanine termini of the peptidoglycan chain, thereby preventing the cross-linking steps.[21] Telavancin, a novel rapidly bactericidal lipoglycopeptide, inhibits peptidoglycan biosynthesis through preferential targeting of transglycosylation.[2223] Extended-spectrum cefalosporins (ceftazidime, cefotaxime, cefepime), carbapenems (imipenem, ertapenem, meropenem) and aztreonam are more potent beta-lactams. The transglycosylase enzyme that transfers the disaccharide of the peptidoglycan precursor to the growing glycan polymer of the cell wall peptidoglycan is inhibited, presumably due to the steric bulkiness of the glycopeptides peptidoglycan precursor. Both the transglycosylase and transpeptidase enzyme reactions that complete the synthesis of the rigid cell wall peptidoglycan are inhibited by the glycopeptides.[20]

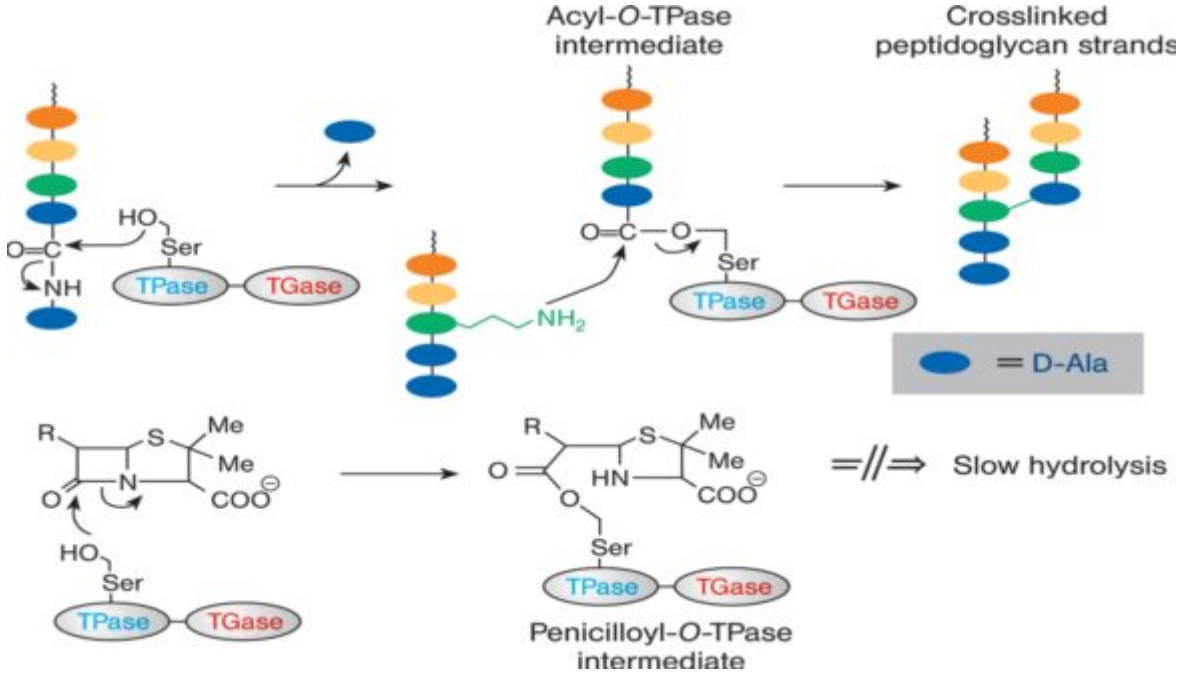

Figure 1. Inhibition of Transpeptidase Activity by Penicillins. Adopted from Waish.[25]

Inhibition of Bacterial Protein Synthesis

Microbial ribosomes contain 70S particles comprising two subunits, of 50S and 30S, which join at the initiation step of protein synthesis and separate at the termination step. Macrolides (large lactone ring compounds) bind to the 50S ribosomal subunit and interfere with the elongation of nascent polypeptide chains.[26] The most important macrolide is erythromycin, which inhibits Gram-positive species and a few Gram-negative species such as *haemophilus, mycoplasma, chlamydia,* and *legionella*. New

molecules such as azithromycin and clarithromycin have greater activity than erythromycin against many of these pathogens. Lincinoids, of which the most important is clindamycin, have a similar site of activity. Both macrolides and lincinoids are generally bacteriostatic, inhibiting only the formation of new peptide chains.[23] Aminoglycosides inhibit initiation of protein synthesis and bind to the 30S ribosomal subunit thus, inducing the formation of aberrant, non-functional complexes as well as by causing misreading. Chloramphenicol binds to the 50S ribosomal subunit blocking peptidyltransferase reaction. Tetracyclines inhibit protein synthesis by binding to 30S subunit of ribosome, thereby weakening the ribosome-tRNA interaction.[22,28]

Distruption/Interference with Nucleic Acid Synthesis

DNA synthesis, mRNA transcription and cell division require the modulation of chromosomal super coiling through topoisomerase-catalysed strand breakage and rejoining reactions.[29] Rifampicin interferes with a DNA-directed RNA polymerase thereby interfering with transcription process by binding with high affinity to the *β*-subunit (encoded by *rpoB*) of a DNA-bound and actively transcribing RNA polymerase.[29,30] Quinolones disrupt DNA synthesis by interference with type II topoisomerases DNA gyrase and topoisomerase IV during replication and by causing double strand breaks.[22] Ciprofloxacin also target DNA replication. Gentamicin, Streptomycin, Spectinomycin also targeted DNA Translation.

Inhibition of an Intermediary Metabolic Pathway

The sulfonamides (*e.g.* sulfamethoxazole) and trimethoprim each block the key steps in folate synthesis, which is a cofactor in the biosynthesis of nucleotides, the building blocks of DNA and RNA.[22] Sulfonamides competitively inhibit the conversion of pteridine and *p*-aminobenzoic acid (PABA) to dihydrofolic acid by the enzyme pteridine synthetase. Sulfonamides have a greater affinity than PABA for pteridine synthetase. Trimethoprim has a tremendous affinity for bacterial dihydrofolate reductase and it inhibits the synthesis of tetrahydrofolate.[27]

Distruption/ Disorganising of the Biomembrane

A number of antimicrobial agents can cause disorganization of the membrane. These agents can be divided into cationic, anionic, and neutral agents. The best-known compounds are polymyxin B and colistemethate (polymyxin E).[22] It is postulated that polymyxins exert their inhibitory effects by increasing bacterial membrane permeability, causing leakage of bacterial content. Polymixin B has several cell-damaging properties: (i) it disturbs the surface charge, lipid composition and structure of the membranes; (ii) it dissipates the K^+ gradient on the cytoplasmic membrane; and (iii) it depolarises the cytoplasmic membrane. The permeability of the outer membrane to lipophilic compounds is one of the main factors controlling bacterial sensitivity to polymixin B.[31]

The cyclic lipopeptide daptomycin displays rapid bactericidal activity by binding to the cytoplasmic membrane in a calcium-dependent manner and oligomerizing in the membrane, leading to an efflux of potassium from the bacterial cell and cell death.[5,32]

Biochemistry of Antibacterial Resistance

The main mechanisms for survival of a threatened microbial population are genetic mutation, expression of a latent resistance gene and acquisition of genes with resistance determinants.[33] Bacteria acquire resistance to an antibiotic or multiple antibiotics via one of four ways.[34]

Inactivation

Three enzymes effectively inactivate antibiotics, beta-lactamase, aminoglycoside-modifying enzymes and chloramphenicol actyltransferases.[35] About 300 beta-lactamases have been identified. The most clinically significant of these are associated with gram-negative bacteria and provide resistance to third-generation cephalosporins, most penicillins, aztreonam, cefamandole and cefoperazone in Enterobacteriaceae. This, in turn, has led to increased use of carbapenem anddriven development of carbapenem-resistant Enterobacteriaceae (CRE). First detected in India, CRE are now rated an "urgent concern" in the United States by the Centre for Disease Control and Prevention. Other varieties of beta-lactamases are also found in *Enterobacter*

spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus mirabilis*.[34] The most clinically important resistance are produced by gram-negative organisms[36] and are coded on chromosomes and plasmids. Genes that encode *β*-lactamases are transferred by transposons but also they may be found in the composition of integrons.[37] *β*-Lactamases hydrolyse nearly all *β*-lactams that have ester and amide bond, e.g., penicillins, cephalosporins, monobactams, and carbapenems. Serine *β*-lactamases cephalosporinases, e.g. AmpC enzyme are found in *Enterobacter* spp. and *P. aeruginosa* and penicillases in *S. aureus*. Metallo-lactamases (MBLs) found in *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *Proteus mirabilis* (*P. mirabilis*), *Enterobacter* spp. have the same role as serine *β*-lactamases and are responsible for resistance to imipenem, new generation cephalosporins and penicillins. MBLs are resistant to inhibitors of *β*-lactamases but sensitive to aztreonam. Specific *A. baumannii* carbapenem-hydrolyzing oxacillinase (OXA) enzymes that have low catalytic efficiency together with porin deletion and other antibiotic resistance mechanisms can cause high resistance to carbapenems.[38]

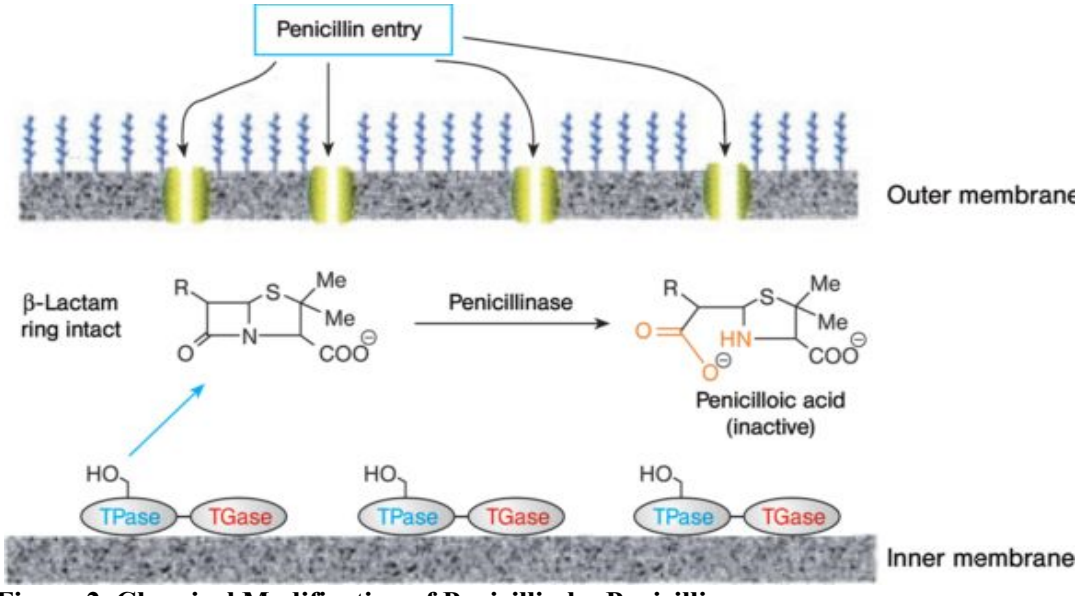

Figure 2. Chemical Modification of Penicillin by Penicillinases.
Adopted from Toleman et al.[39]

The aminoglycoside-modifying enzymes confer extended-spectrum resistance to aminoglycosides and fluoroquinolones to strains of a number of pathogens, including *S. aureus*, *E. Faecalis* and *S. pneumoniae*. Inactivation is made by binding adenylyl, phosphoryl, or acetyl groups to the periphery of the drug molecule. These modifications are achieved in the process of transport across the cytoplasmic membrane (co-substrate ATP, acetyl-CoA, NAD+, UDP-glucose, or glutathione).[40] These enzymes (AMEs) reduce affinity of a modified molecule, impede binding to the 30S ribosomal subunit and provide extended spectrum resistance to aminoglycosides and fluoroquinolones.[41,42] Some *H. influenzae* strains have the enzyme chloramphenicol transacetylase which increase enzymatic degradation of hydroxyl groups of chloramphenicol, enabling the modified chloramphenicol to bind to a ribosomal 50S subunit properly.[43]

Oxidation and reduction reactions are used by pathogenic organisms as a resistance mechanism against antimicrobials. *Streptomyces virginiae* produces type A antibiotic virginiamycin M1 and protects itself from its own antimicrobial agents by substituting a ketone group to an alcohol residue at position 16.[41]

Changes in Target Site

Modifications in the molecules targeted by the antibiotic can reduce its ability to bind to the pathogen. Common changes include peptidoglycan structure reducing the ability of beta-lactams such as penicillins, cephalosporins, carbapenems and others to inhibit cell wall synthesis. The cause of resistance to the glycopeptide antibacterial agents in *E. faecium* and *E. faecalis* is the acquisition of one of two related gene clusters, known as VanA and VanB. These gene clusters encode enzymes that produce a modified peptidoglycan precursor terminating in D-Alanyl-D-Lactate (D-Ala-D-Lac) instead of D-Ala-D-Ala.[44] The glycopeptides bind with much lower affinity to D-Ala-D-Lac than to D-Ala-D-Ala.[45,46]

Also, microbes have been acquiring some mutational changes in the target that reduce susceptibility to inhibition whilst retaining their cellular function.[31] Resistance to *β*-lactam antimicrobial agents in *S. pneumoniae* is due to the development of penicillin binding proteins (PBPs) with decreased affinity for the drugs.[47,48] Mutations in RNA can create resistance to drugs that target specific ribosomal subunits in gram negative bacteria. These can reduce the effectiveness of macrolides, lincosmaides and streptogramin B. In pathogenic organisms, Erm proteins dimethylate a single adenine in nascent 23S rRNA, which is part of the large (50S) ribosomal subunit.[46] As a consequence of methylation, binding of erythromycin to its target is impaired. The overlapping binding sites of macrolides, lincosamides and streptogramins B in 23S rRNA, account for cross-resistance to the 3 classes of drugs.[49]

Development of Alternative Targets

Some bacteria develop a second enzyme that performs the same function as the one targeted by an antibiotic. While the initial enzyme may be inactivated by the drug, the alternate enables the organism's continued survival. In methicillin-resistant *S. aureus*, a new penicillin-binding protein (PBP2a) ensures cell wall synthesis even in the presence of high beta-lactamase concentrations, providing resistance to all beta-lactam antibiotics as well as streptomycin, tetracycline and, in some instances, erythromycin.[34]

Decreased Membrane Permeability/Increased Effluxion

Microbial cells are capable of reducing antibiotic concentration and effectiveness by decreasing membrane permeability or pushing out more quickly via enhance efflux systems as observed in *P. aeruginosa on* beta-lactam antibiotics, tetracyclines, chloramphenicol and aminoglycosides.[49,50,51] Active efflux of drugs from the cell is one of the common mechanisms of antimicrobials resistance in bacteria. Efflux pumps are energy-dependent transporters that extrude toxic compounds, including antimicrobials, being one of the major mechanisms by which microbial pathogens resist to different classes of antimicrobial agents,[46] with resistance developing when the rate of drug efflux across the membrane exceeds that of drug influx, bacterial genomes encode several membrane-bound multi-drug efflux systems.[52,53]

Antibacterial Phytochemicals

Alkaloids are a group of heterocyclic nitrogenous compounds with broad antimicrobial activity, including morphine and codeine, the oldest known compounds in this group.[54] Some alkaloids found in *Callistemon citrinus* and *Vernonia adoensis* have antibacterial activities against *S. aureus* and *P. aeruginosa.* Diterpenoid alkaloids, commonly isolated from Ranunculaceae or buttercup family of plants, are found to possess antimicrobial properties.[55,56] The mechanism of action of aromatic planar quaternary alkaloids such as berberine and harmane is attributed to their ability to intercalate with DNA thereby resulting in impaired cell division and cell death [57] as depicted in table 1.

Polyphenols and Flavonoids

Polyphenolic compounds are a group of aromatic secondary metabolites, diverse in nature and involved in plant defense. More than 10,000 polyphenol compounds have been identified in various plants. They consist of flavonoids, quinones, tannins, and coumarins.[58,57,59]

Quinones are organic compounds consisting of aromatic rings with two ketone substitutions. Quinones are known to complex irreversibly with nucleophilic amino acids in protein, often leading to their inactivation and loss of function.[60] The major targets in the microbial cell include surface-exposed

adhesin proteins, cell wall polypeptides, and membrane-bound enzymes.[61] They are also involved in bioreductive activation affecting metabolic process of microbial cells.[62] Quinones such as anthraquinone from *Cassia italica* possess bacteriostatic effects against pathogenic bacteria such as *Bacillus anthracis*, *Corynebacterium pseudodiphthericum*, and *Pseudomonas aeruginosa* and bactericidal against *Burkholderia pseudomallei*.[63,64] Hypericin, an anthraquinone from *Hypericum perforatum* was reported by Duke in 1985 for its antimicrobial properties.[64]

Flavonoids are pigmented compounds found in fruits and flowers of plants and mainly consist of flavone, flavanones, flavanols, and anthocyanidins.[59,65] Flavones are phenolic structures containing one carbonyl group (as opposed to the two carbonyls in quinones.The addition of a 3-hydroxyl group yields a flavonol.[66] Flavonoids are also hydroxylated phenolic substances but occur as a C_6-C_3 unit linked to an aromatic ring. Since they are known to be synthesized by plants in response to microbial infection [67], they were reported to have *in vitro* antimicrobial activities against a wide array of microorganisms. Their activity is probably due to their ability to complex with extracellular and soluble proteins and to complex with bacterial cell walls as exhibited by quinones. More lipophilic flavonoids may also disrupt microbial membranes, affecting membrane integrity.[68,69] Catechins, the most reduced form of the C_3 unit in flavonoid compounds exhibit inhibitory activity against both Gram-positive and Gram-negative bacteria.[66] These compounds inhibited *in vitro Streptococcus mutans*,[71,72,73,74] *Shigella* and some bacteria.[75,72,76] The catechins inactivated cholera toxin in *Vibrio*[75,77] and inhibited isolated bacterial glucosyltransferases in *S. mutans*,[78] possibly due to complexing activities similar to those observed in quinones. It was later reported that *in vivo* tests of conventional rats fed a diet containing 0.1% tea catechins, fissure caries (caused by *S. mutans*) was reduced by 40%.[79]

There are conflicting reports on the possible mechanisms of action of flavones and flavonoids in relation to their structures and the microbial activities they exhibited. Flavonoids lacking hydroxyl groups on their β-rings are more active against microorganisms than are those with the −OH groups;[80] this finding supports the idea that their microbial target is the membrane. However, some authors observed the opposite effect that, the more hydroxylation, the greater the antimicrobial activity.[81] Thus, there is no clear predictability for the degree of hydroxylation and the antimicrobial activities. Some antimicrobial activities of flavonoids are presented in table 1.

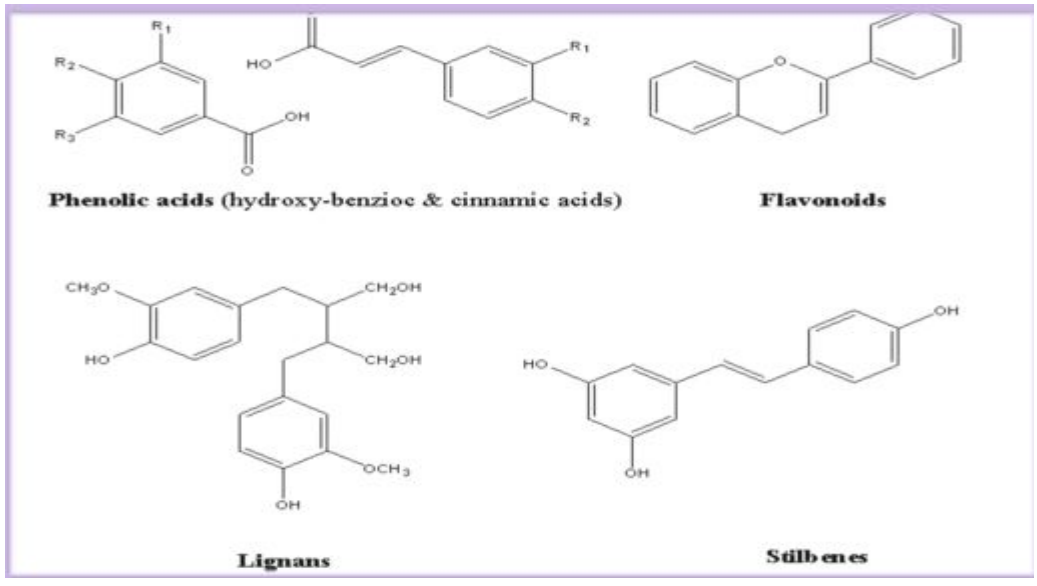

Figure 1: Some Polyphenolic Compounds with Antimicrobial Activity Isolated from Medicinal Plants.
Adopted from An-Na et al.[82]

Other polyphenols, stilbenes pinosylvin, pinosylvin monomethyl ether and piceatannol were demonstrated to have antimicrobial activities by disrupting the integrity of outer membrane of Gram-negative microorganisms.[83] It was reported that polyphenol extracts from industrial sour cherry pomaces contained a considerable proportion of polyphenols; anthocyanins, hydroxycinnamic acids and flavonoids that exhibited antimicrobial activities against *Salmonella*, *Escherichia coli* 0157:H7 and *Listeria* spp. The sour cherry extracts reduced the growth of *Salmonella* and *Escherichia coli* O157:H7 at concentrations higher than 2500 µg/mL, and inhibited *Listeria* spp. growth.[84] Some studies demonstrated that tea polyphenols have antibacterial effects towards heat resistant *Bacillus stearothemophilus* and *Clostridium thermoaceticum* spores. Epigallocatechin-3-gallate, the major catechin found in green tea, was reported to have antimicrobial effects against a number of bacterial pathogens. The antimicrobial activity against *Stenotrophomonas maltophilia* was proved *in vitro.* [85,86]

Tannin is a name applicable to a group of water-soluble oligomeric and polymeric phenolic compounds capable of tanning leather or precipitating gelatin from solution, a property referred to as astringency. They have molecular weights ranging from 500 to 3,000 Kd,[87,88] and available in almost every plant part: bark, wood, leaves, fruits, and roots.[89] Their mode of antimicrobial action is related to their ability to inactivate microbial adhesins, enzymes, cell envelope transport proteins and ability to complex with polysaccharide.[90]

In 1991, Scalbert reviewed the antimicrobial properties of tannins and reported a list of 33 studies which had documented the inhibitory activities of tannins. According to these studies, tannins can be toxic to filamentous fungi, yeasts, and bacteria.[91]

Coumarins substances made of fused benzene and α-pyrone rings.[79]

They are responsible for the characteristic odour of hay. Approximately, 1300 coumarins have been identified since 1996.[91] Some coumarins such as scopoletin and chalcones have been isolated as antitubercular constituents of the plant *Fatoua pilosa*.[92] In addition, phytoalexins, which are hydroxylated derivatives of coumarins, are produced in plants in response to microbial infections. General antimicrobial activity was documented in woodruff (*Galium odoratum*) extracts.[76]

Terpenes are large group of secondary metabolites consisting of five carbon isoprenoid units.[60] They are diverse with over 55,000 members isolated so far.[93] The major groups consist of diterpenes, triterpenes, tetraterpenes as well as hemiterpenes and sesquiterpenes.[91] Terpenenes or terpenoids are active against bacteria, [94,95,96,97,98,99,100,101,102,103] and it was reported that 30% of terpenoid essential oil derivatives were active inhibitors of bacterial growth.[104] Other common terpenoids are methanol, camphor (monoterpenes), farnesol and artemisin (sesquiterpenoids). Sesquiterpenoids are reported to exhibit bactericidal activity against Gram-positive bacteria, including *M. Tuberculosis*.[59,92] The mechanism of antimicrobial action of terpenoids is not clearly defined, but it is attributed to membrane disruption in microorganisms.[105]

Table 1: Phytochemical Constituents for the Treatment of Antibiotics Resistant Bacterial Infections

Name of the Herbal Plant	Phytoconstituents	Class of Phytochemical	Targeted mode of action with respect to its utility	Category on the basis of mode of action	References
Berberis Aristocrat	Berberine	Alkaloid	Produce MDR inhibitors 5methoxyhydranocarpin D and pheophorbide A	Antibiotic Resistance Modifier	[106]
Punica Granatum	Ellagitannin	Tannin	Synergistic interaction with Chloramphenicol Gentamicin, ampicillin, Tetracycline and Oxacillin	Antibiotic action Potentiator	[107]
Rosmarinus Officinalis	Carnosic acid, Carnosol		Act synergistically with Erythromycin	Antibiotic action Potentiator	[108]
Jatropha Elliptica	2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylic acid diethylester	Alkaloid	Act synergistically with Ciprofloxacin, Norfloxacin, Pefloxacin, Acriflavine and Ethidium bromide	Antibiotic action Potentiator	[109]
Camellia Sinensis	Epicatechingallate Epigallocatechi Ngallate	Flavonoids	Synergistic interaction with Norfloxacin, Imipenem, Panipenem, β-Lactams and reverses the methicillin resistance to some extent	Antibiotic action potentiator and antibiotic resistance modifier	[110]
Acorus Calamus	Acoradin, Asarone		Synergistic interaction with Tetracycline and ciprofloxacin	Antibiotic action Potentiator	[111]
Hemidesmus indicus	p-methoxy salicylic aldehyde, pregnane glycoside	Glycoside	Synergistic interaction with Tetracycline and ciprofloxacin	Antibiotic action Potentiator	[111]
Holarrhena antidysenterica	Kurchicine, conessidine, holarrhine	Alkaloid	Synergistic interaction with Tetracycline and ciprofloxacin	Antibiotic action potentiator	[111]

Name of the Herbal Plant	Phytoconstituents	Class of Phytochemical	Targeted mode of action with respect to its utility	Category on the basis of mode of action	References
Plumbago Zeylanica	Plumbagin, Lupeol		Synergistic interaction with Tetracycline and ciprofloxacin	Antibiotic action Potentiator	[111]
Caesalpinia Spinosa	Ethyl gallate	Flavonoid	Synergistic interaction with β lactams	Antibiotic action Potentiator	[112]
Abrus Precatorius	Abrin, precatorine, trigonelline		Increases both cellular and humoural immune response. Shows symptomatic Relief against diarrhoea	Immunomodulator and symptomatic relief provider	[113]
Aegle Marmelos	Propelargonidin, aegelenine and marmelosin		Treatment of irritable bowel syndrome and also shows moderate inhibiton of complement pathway.	Immunomodulator and symptomatic relief provider	[113]
Andrographis paniculata	Andrographolide, Neoandrographolide	Anthocyanin	Inhibits the action of enterotoxins and stimulates humoural immune response	Immunomodulator and symptomatic relief provider	[113]
Caesalpinia Bonducella	Caesalpinin		Antidiarrhoeal activity	Immunomodulator and symptomatic relief provider	[113]
Cyperus Rotundus	Triterpenes, cyperene, cineole and limonene	Terpenes	Shows bactericidal effect against various gram negative bacteria	Antibacterial Activity	[113]
Adhatoda vasica	Vasicinolone, quercetin, falavanoids	Polyphenol/ Flavonoid	Shows bronchodilatory effects and antibacterial activity	Antibacterial activity and symptomatic relief provider	[113]
Piper longum	Piperine	Alkaloids	Cholinergic activity, increases absorption from the intestine by enhancing permeability of intestinal cells	Symptomatic relief provider	[113]
Syzygium cuminii	Phellandrene, pinene , quercetin and eugenol	Polyphenol/ Flavonoid	Reduction in excessive gastrointestinal motility	Symptomatic relief provider	[113]

Name of the Herbal Plant	Phytoconstituents	Class of Phytochemical	Targeted mode of action with respect to its utility	Category on the basis of mode of action	References
Plantago Ovate	Polysaccharides and fibers	Glycosides	Increases viscosity of intestinal contents and shows laxative effects	Symptomatic relief provider	[113]
Euphorbia hirta	Quercitin, myristin, euphorbins	Polyphenols	Increased colonic fluid absorption and is an immunostimulant	Immunomodulator and symptomatic relief provider	[113]
Cassia italica	Anthraquinone	Quinone	Bacteriostatic and bactericidal	Bacteriostatic and bactericidal activities	[63]
Fatoua pilosa	scopoletin and chalcones	Coumarins	antitubercular constituents	antitubercular activity	[114]

Adopted and modified from Pallavi et al.[115]

Possible Constraints in the Use of Phytochemicals for Combating Antibiotic-Resistant Pathogens

Although this review explored some finely documented literature on the potentialities and efficacies of phytochemicals in combating bacterial pathogens, it is however pertinent to glance at the possible challenges facing the use these plant chemicals as alternative agents to neutralize/reverse bacterial resistance to modern antibiotics. It is relevant to consider the nature of the bacterial pathogens, their virulence in relation to the host on various intrinsic and extrinsic factors. Indeed, the Physiochemical properties of the plant-derived antibacterial agents such as their solubility in aqueous medium, hydrophobicity, biodegradability, bio-availabilities and stability are major constraints that may halt their clinical applications as natural bio-control agents.[116,117] Furthermore, some abiotic factors including environmental temperature and atmospheric composition also influence their antimicrobial efficacy.[118] Moreover, differences in extraction protocols may generate chemical variability in plant-derived antibacterial agents,[122,123] affecting the antimicrobial efficacy.[124] In food products, major food components such as fat, carbohydrates and proteins affect the efficacy of these plant-derived antibacterial agents.[119,120,121] Hence administering pure compounds may minimize this problem.

Conclusion

In recent times, there has been a flow of supportive literature on the potentiality of phytochemicals as possible alternatives for the development of effective antibacterial substances, either alone or in combination with canonical antibiotics. This development may pave a way for the finding of more promising antibacterial agents, capable of reversing the established bacterial resistance against conventional antibiotics. However, there is a wave of challenges ahead, including finding phytochemicals that have low toxicity, bio-availabilities and with sufficiently lower MICs and required effectiveness.

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