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Review

Plant Food-Based Natural Products Are Relevant to the Management of Bacterial Resistance to Antimicrobial Drugs

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Abstract: This paper reviews the antimicrobial and antibiofilm potentials of plant food-based extracts and compounds, highlighting their relevance for the management of bacterial resistance to antimicrobial drugs. Extracts from different dietary sources, such as açaí (*Euterpe oleracea*), cashew (*Anacardium occidentale*), moringa (*Moringa oleifera*), passion fruit (*Passiflora edulis*), and guava (*Psidium guajava*), demonstrated inhibitory effects against both planktonic cells and biofilms, a major resistance mechanism of bacteria. The biological activity of plant food-based extracts and compounds is attributed to the inherent chemical complexity of phytomolecules like flavonoids, alkaloids, and tannins, which enable multi-target actions against microorganisms, with minimal inhibitory concentrations typically ranging from 7–16 µg/mL, and antibiofilm activity observed at minimal biofilm eradication concentrations ranging from 16–500 µg/mL. Combinations of the extracts/compounds with clinically relevant antimicrobial drugs showed promising synergism that could enhance antimicrobial efficacy (such as *Euterpe oleracea*), but some resulted in antagonism (such as *Anacardium occidentale* and *Passiflora edulis*), which can impair treatment. Further standardized in vivo studies and controlled clinical trials are necessary to validate efficacy, safety, and define appropriate clinical applications.

Keywords: antimicrobial; antibiofilm; phytomolecules; bacterial resistance

1. Introduction

Antimicrobial resistance (AMR) is an established cause of substantial morbidity and mortality worldwide, undermining many routine medical interventions and complicating the management of common infections. Several deaths and a burden of disability are associated with bacterial AMR, with the highest impacts concentrated in low-resource settings where diagnostic capacity and access to second-line therapies are limited [1]. Beyond direct clinical harm, resistant infections markedly increase health-care intensity: patients with resistant pathogens experience more frequent treatment failures, longer hospital stays, increased rates of intensive care admission, and higher attributable mortality [1,2]. These clinical consequences cascade into measurable economic harms for health systems and for society, such as higher per-patient treatment costs, greater use of scarce hospital resources (including bed-days and advanced therapeutics), more readmissions, and productivity losses from prolonged illness or even death [2,3]. Economic data indicate wide geographic variation in attributable costs but consistently report substantially higher expenditures for resistant versus susceptible infections, with especially acute effects in tertiary and high-income hospital settings [4]. Several complex biochemical mechanisms of resistance have been described, such as biofilm formation, efflux pumps, modification of molecular targets, and production of drug-inactivating enzymes [1]. Currently, overcoming them with antimicrobial drugs can be a lost battle for several patients.

The clinical and economic burdens of AMR are linked to social determinants and health inequities. Poor sanitary infrastructure, limited access to diagnostics and appropriate antimicrobials, inappropriate use of

antimicrobial drugs in human and veterinary medicine, and constrained public-health capacity amplify both the emergence and the impact of resistance [5]. Consequently, AMR disproportionately affects vulnerable populations, precipitating medical impoverishment in low- and middle-income countries and exacerbating disparities in outcomes within high-income settings. Social consequences also include reduced trust in health systems, increased caregiver burden, and wider/higher costs when common procedures (e.g., childbirth, chemotherapy, complex surgery) become riskier due to the decreased activity of antimicrobial drugs [6,7].

Given the exposure, the need for new antimicrobials becomes clear. Herbal-based natural products remain an exceptionally important source of novel chemical scaffolds for drug discovery [1]. A large fraction of approved antimicrobials and other therapeutic classes derive from natural sources or natural-product-inspired scaffolds. Natural products offer structural diversity and unique mechanisms of action that are often complementary to existing antimicrobial drugs, making them valuable not only as potential drugs but also as adjuvants that can restore or potentiate existing therapies [8,9]. Because the clinical, economic and social issues triggered by AMR are global and growing, diversifying the antimicrobial discovery pipeline with natural-product leads is not only scientifically relevant, but strategically essential [8–10].

In this work, the antimicrobial potential of natural products is reviewed, focusing on the exploration of plant food-based extracts and isolated phytomolecules. Plant foods and their derivative products belong to a translational and regulatory niche positioned between the nutrition and pharmacology fields, which is unique. These products are consumed daily as part of the regular diet of children and adults, without following strict controls of quantities or medical supervision, and they are not subject to the same stringent regulatory requirements as medicinal products [10]. This widespread, unsupervised use increases the potential for concurrent consumption with medication, especially antimicrobials, establishing a poorly explored and clinically significant scenario of drug-nutrient interactions [9,10]. Thus, focusing on natural products derived from dietary plants offers a complementary perspective to existing reviews on medicinal botanicals or isolated phytochemicals. The essential phytochemistry concerning this topic is also briefly discussed.

2. Natural Products as Antimicrobials: A Phytochemistry Overview

Herbal secondary metabolites occupy a particular place in antimicrobial discovery because they combine chemical complexity with evolved biological function. From a medicinal-chemistry perspective, these molecules are rich in stereochemical complexity, fused and bridged ring systems, heteroatom-containing heterocycles, polyphenolic arrays, and glycosidic ligands [8–11]. These are features that both increase binding surface area and create multi-point molecular recognition that is difficult for a single-point genetic mutation in a microbe to defeat [11]. Two chemical principles make phytochemicals particularly of interest from an AMR perspective. First, many secondary metabolites are not single-site ligands but interact with multiple targets (membrane integrity, enzyme active sites, redox systems, signaling pathways) [9–11]. Second, structural complexity and stereochemistry create conformationally constrained ligands that recognize extended and often non-conserved protein surfaces, reducing the probability that minor changes in the targets may impair proper binding [12,13]. In addition, polar groups (glycosides, polyphenolic arrays) might mediate selective transport into bacterial cells or biofilms, which add features for pharmacokinetic optimization during organic synthesis [10–13].

Flavonoids exemplify how specific functional-group patterns modulate antimicrobial activity. Key structural determinants include the pattern and degree of hydroxylation, C-glycosylation vs. O-glycosylation, conjugation at the C2-C3 bond, and the presence of α,β-unsaturated carbonyl systems, as in chalcones [14]. These chemical motifs enable flavonoids to (i) intercalate or stack with nucleic acid bases, (ii) chelate transition metals that are essential for metalloenzymes, (iii) perturb membrane lipid packing through amphipathic interactions, and (iv) inhibit energy metabolism and efflux pumps [15,16]. The combination of planar aromatic surfaces and variable polar substituents permits both membrane and intracellular targets to be engaged, which contributes to broad-spectrum and resistance-attenuating activity [14–16].

Alkaloids afford a set of antimicrobial mechanisms. The basic (protonatable) nitrogen often mediates electrostatic and hydrogen-bond interactions with anionic biomolecules (nucleic acids, acidic phospholipids), while extended π-systems enable DNA intercalation or topoisomerase inhibition [17]. Many alkaloids are rigid, polycyclic frameworks (e.g., berberine, quinolizidines) that present defined three-dimensional pharmacophores; these rigid geometries can simultaneously disrupt multiple protein-protein or protein-DNA interfaces, reducing the likelihood that a single resistance mutation will abrogate binding [18,19]. Moreover, substituents that modulate pKa and lipophilicity might increase cell penetration and bacterial selectivity [17].

Terpenes and terpenoids (monoterpenes, sesquiterpenes, diterpenes, triterpenes, and their oxidized terpenoid congeners) are chemically diverse and often volatile constituents of essential oils; structurally, they range from

simple acyclic isoprenoids to polycyclic, highly oxidized frameworks [20,21]. Terpenes are characterized by isoprene-derived skeletons with varying degrees of cyclization, alkyl branching, and oxygenation (alcohols, epoxides, carbonyls) [20,22]. These structural features confer membrane-active properties (disruption of lipid bilayers, altered permeability) and, in oxidized terpenoids, the potential for covalent modification of nucleophiles (e.g., thiols in cysteine residues) via electrophilic centers (α,β-unsaturated carbonyls, epoxides) [20–23]. Sesquiterpene lactones and other terpenoids may thus combine reversible physical perturbation with irreversible chemical modification of critical proteins [23].

Tannins and other polyphenolics exert antimicrobial effects through polyvalent, multidentate interactions: their multiple phenolic hydroxyls enable strong hydrogen bonding and hydrophobic stacking with proteins and polysaccharides, causing protein precipitation, enzyme inhibition (including extracellular bacterial enzymes), metal chelation, and interference with cell-surface adhesins important for biofilm formation [24,25]. Condensed tannins (proanthocyanidins) and hydrolyzable tannins (gallotannins, ellagitannins) differ in reactivity and size, which affects their ability to cross membranes or act at extracellular targets; this diversity of molecular weight and conformational flexibility contributes to a multimodal antimicrobial profile that is intrinsically harder for microbes to overcome by single-point resistance mechanisms [24–27].

Coumarins remain among the most abundant secondary-metabolite families in plants, encompassing simple coumarins, furanocoumarins, pyranocoumarins, isocoumarins, bis-coumarins, and other derivatives [28,29]. From a mechanistic standpoint, functionalization by hydroxylation, halogenation, and alkylation modulates lipophilicity, binding affinity, membrane permeability, and target selectivity [29]. Structure–activity relationship (SAR) studies suggest that appended electron-donating or withdrawing groups, bulky aromatics, nitro or hydroxyl substituents, and heterocyclic fusions can enhance affinity for microbial targets [28–30].

3. Bioprospection of Antimicrobial Natural Products in Plant Food

The detection of secondary metabolites across the plant food described in this section supports their antimicrobial and antibiofilm potentials (Table 1). As exposed, these molecules are associated with mechanisms including membrane perturbation, DNA damage, enzyme inhibition, metal ion chelation, and interference with cellular homeostasis in bacteria [15,17,20,29]. Such mechanisms help to explain the inhibition of planktonic growth and biofilm formation, even when precise molecular targets are not properly defined due to experimental limitations.

Table 1. Summary of the antimicrobial activity data of plant food explored in this study.

Plant Food Source/Study	Bacterial Species	MIC	MBC	MBEC	Major Phytochemical Groups/Relevant Molecules
Anacardium occidentale—stem bark hydroethanolic extract [31]	*Staphylococcus aureus*/ *S. epidermidis*	ND	15.2 mg/mL	61.0 mg/mL	Tannins, flavonoids, saponins
Anacardium occidentale—fruit pulp hydroethanolic extract [32]	*Staphylococcus aureus*	15.6 µg/mL	125 µg/mL	500 µg/mL	Phenolic compounds, vitamin C, carbohydrates
Vaccinium myrtillus—fruit juice methanolic extract [33]		ranging from 15.6 to 62.5 µg/mL	ranging from 125 to 500 µg/mL	ND	Polyphenols, flavonoids
Euterpe oleracea—fruit pulp methanolic extract [34]		7.8 µg/mL	62.5 µg/mL	250 µg/mL	Non-anthocyanic polyphenols, flavonoids
Camellia sinensis—black tea hydroethanolic leaf extract [35]	*Staphylococcus aureus*	3.9 µg/mL	15.62 µg/mL	62.5 µg/mL	Flavonoids, tannins, phenolic compounds
	Escherichia coli	31.25 µg/mL	62.5 µg/mL	250 µg/mL	
	Pseudomonas aeruginosa	15.62 µg/mL	125 µg/mL	ND	
Camellia sinensis—green tea hydroethanolic leaf extract [36]	*Staphylococcus aureus*	8 µg/mL	64 µg/mL	128 µg/mL	Catechins, flavonoids, polyphenols
	Pseudomonas aeruginosa	8 µg/mL	32 µg/mL	256 µg/mL	
Moringa oleifera—hydroethanolic leaf extract [37]	β-lactamase-producing *Staphylococcus aureus*	8 µg/mL	8 µg/mL	16 µg/mL	Flavonoids, tannins, carbohydrates, vitamin C
Psidium guajava—fruit pulp methanolic extract [38]	*Staphylococcus aureus*	31.25 µg/mL	62.5 µg/mL	250 µg/mL	Flavonoids, polyphenols, L-5-Propylthiomethylhydantoin
Passiflora edulis—fruit pulp methanolic extract [38]		15.62 µg/mL	125 µg/mL	250 µg/mL	Flavonoids, polyphenols, pentanoic acid
Spondias tuberosa—fruit pulp methanolic extract [39]	Uropathogenic *E. coli*	500 µg/mL	>500 µg/mL	ND	Flavonoids, tannins
Spondias purpurea—fruit pulp methanolic extract [39]		500 µg/mL	>500 µg/mL	ND	
Theobroma grandiflorum—fruit pulp methanolic extract [39]		500 µg/mL	>500 µg/mL	ND	

MIC: minimal inhibitory concentration. MBC: minimal bactericidal concentration. MBEC: minimal biofilm eradication concentration. ND: not determined in the study.

3.1. Cashew-Based Extracts

The antimicrobial and anti-biofilm activity of a hydroethanolic stem bark extract of *Anacardium occidentale* was investigated against clinical and reference isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* [31]. Using CLSI-based assays, the bactericidal effects were determined on planktonic cells (MBC), inhibition of biofilm formation (MBIC), and eradication of pre-formed biofilms (MBEC), alongside qualitative phytochemical screening. The extract showed bactericidal activity against planktonic staphylococci at 15.2 mg/mL, inhibited biofilm formation at 30.5 mg/mL, and completely eradicated established biofilms at 61.0 mg/mL. Phytochemical analyses revealed the presence of tannins, flavonoids, and saponins, compounds commonly associated with antimicrobial and anti-inflammatory effects [31].

Similarly, the antimicrobial and antibiofilm properties of cashew apple juice pulp (CJP) against clinical isolates of *S. aureus* were described [32]. Frozen commercial cashew pulp samples were first characterized physicochemically, followed by chemical profiling using high-performance liquid chromatography with diode array detection (HPLC-DAD) to detect phenolic compounds and gas chromatography–mass spectrometry (GC-MS) to assess free carbohydrates. The antimicrobial activity was evaluated using standardized CLSI assays to determine minimal inhibitory concentration (MIC), MBC, and MBEC. CJP presented detectable phenolic compounds, high vitamin C levels, and was active against planktonic cells (MIC = 15.6 μg/mL) and biofilms (MBEC = 500 μg/mL). Antioxidant capacity was demonstrated using the β-carotene bleaching method, and interactions between CJP and clinically relevant antimicrobials such as meropenem, ampicillin, and gentamicin were predominantly antagonistic [32].

3.2. Isolated Phytomolecules

Potential drug-nutrient interactions between commonly consumed phytonutrients and clinically relevant antimicrobial agents were investigated, focusing on carotenoids (lycopene and β-carotene) and flavonoids (resveratrol and rutin) [40]. Different antimicrobials were explored against uropathogenic *Escherichia coli* and clinical isolates of *S. aureus*. None of the tested phytonutrients exhibited direct antimicrobial effects; however, most combinations led to statistically significant antagonism. In *E. coli*, cephalexin and amoxicillin showed marked reductions in activity when combined with any of the phytonutrients, while gentamicin and ciprofloxacin were less affected. In *S. aureus*, all tested antibiotics displayed substantial loss of efficacy, with some isolates showing complete absence of inhibition zones, and no synergistic interactions were detected [40].

Likewise, lycopene, β-carotene, curcumin, and diosmin were investigated for their interference with the effectiveness of antimicrobial drugs against *Pseudomonas aeruginosa* [41]. While the nutrients themselves showed no direct antimicrobial activity, they significantly altered the performance of the drugs when combined. Most combinations, particularly of carotenoids or flavonoids with chloramphenicol or aztreonam, produced a synergistic effect. Diosmin was notably the most broadly synergistic, even boosting the effect of meropenem [41].

3.3. Anthocyanidins and Anthocyanins-Colored Fruit

The antimicrobial activity and drug-interaction profile of a methanolic extract prepared from commercially available *Vaccinium myrtillus* (blueberry) juice was investigated against clinical isolates of *S. aureus* [33]. The juice was lyophilized and extracted with 80% methanol, and antimicrobial activity was evaluated using CLSI-based broth microdilution assays to determine MIC and MBC. The extract demonstrated antimicrobial activity with MIC values ranging from 15.6 to 62.5 μg/mL and MBC values from 125 to 500 μg/mL. Interference assays were performed by combining the extract at its MBC with antimicrobial drugs (levofloxacin, amoxicillin, and gentamicin). Statistical analysis revealed no significant synergistic or antagonistic interactions, despite minor, non-significant variations in inhibition zones [33].

The antimicrobial and antibiofilm properties of a methanolic extract of artisanal *Euterpe oleracea* (açaí) pulp were investigated against clinical isolates of *S. aureus* [34]. Chemical and physicochemical characterization of the pulp was performed, including protein and carbohydrate quantification, antioxidant activity assays, and qualitative and chromatographic analyses (UPLC-DAD and GC-MS), which confirmed the presence of non-anthocyanic polyphenols and volatile bioactive compounds. Antimicrobial activity was assessed using CLSI-adapted microdilution assays to determine MIC, MBC, and MBEC. The extract was active against planktonic cells (MIC = 7.8 μg/mL) and biofilms (MBEC = 250 μg/mL). Importantly, the extract showed statistically significant synergism when combined with antimicrobial drugs (ciprofloxacin, gentamicin, and chloramphenicol), except for erythromycin. Cytotoxicity assays demonstrated selective antiproliferative activity against HepG2 hepatocellular carcinoma cells, while showing no toxicity toward normal fibroblast-like BGM cells [34].

3.4. Leaf-Based Extracts

The antimicrobial potential of *Camellia sinensis* was investigated in different stages of oxidation of the leaves. As black tea (full oxidation), the antimicrobial activity of the plant extract was investigated against clinical isolates of *S. aureus*, *E. coli*, and *P. aeruginosa* [35]. Phytochemical screening confirmed the presence of flavonoids, tannins, and phenolic compounds, while antioxidant capacity was demonstrated using the β-carotene bleaching assay. Antimicrobial efficacy was evaluated through broth microdilution assays to determine MIC, MBC, and MBEC. The extract exhibited antimicrobial activity and effectively eradicated biofilms of *S. aureus* and *E. coli*, although *P. aeruginosa* biofilms remained resistant at the tested concentrations. Cytotoxicity assays using BGM cells showed no significant toxicity, supporting the biological safety of the extract. Interference assays combining the extract with multiple antimicrobials resulted in predominantly antagonistic trends, although selective synergistic interactions were eventually detected [35].

As green tea, *C. sinensis* extract was tested against *S. aureus* and *P. aeruginosa* [36]. Phytochemical characterization by UPLC and GC–MS indicated the presence of flavonoids and other polyphenolic compounds, including catechin derivatives. The extract exhibited MIC values of 8 µg/mL for both *S. aureus* and *P. aeruginosa*, with MBC values of 64 µg/mL and 32 µg/mL, respectively, and MBEC values of 128 µg/mL for *S. aureus* and 256 µg/mL for *P. aeruginosa*. Cytotoxicity assays using BGM cells demonstrated no significant toxicity, while antioxidant activity reached approximately 76% protection in the β-carotene bleaching assay. Drug interaction assays revealed frequent antagonistic effects when the extract was combined with antimicrobials against *S. aureus*, but synergistic or additive interactions against *P. aeruginosa* [36].

A study investigated the antimicrobial, antibiofilm, anti-inflammatory, and cytotoxic properties of the hydroethanolic extract prepared from spray-dried *Moringa oleifera* leaves, targeting β-lactamase–producing clinical isolates of *S. aureus* [37]. The extract was chemically characterized using biochemical assays and UPLC, confirming the presence of flavonoids, tannins, carbohydrates, proteins, and vitamin C. The extract presented MIC values of 8 µg/mL against planktonic *S. aureus* cells and MBEC values of 16 µg/mL against established biofilms, representing the lowest concentrations reported to date for *M. oleifera* leaf extracts. Anti-inflammatory activity was confirmed via inhibition of bovine serum albumin denaturation at MIC and MBEC concentrations, outperforming tenoxicam at higher doses, while cytotoxicity assays using BGM cells showed no toxic effects even at elevated concentrations. Notably, the extract did not significantly interfere with the activity of clinically relevant antimicrobial drugs [37].

3.5. Tropical Fruits-Based Extracts

A study assessed the antimicrobial and antibiofilm activities of methanolic extracts obtained from the pulps of *Psidium guajava* (guava) and *Passiflora edulis* (passion fruit), against clinical isolates of *S. aureus* [38]. Phytochemical profiling using GC-MS and UPLC indicated the presence of flavonoids and other bioactive compounds that are likely responsible for antimicrobial effects. Antimicrobial testing indicated MIC of 31.25 µg/mL, MBC of 62.5 µg/mL, and MBEC of 250 µg/mL for *P. guajava,* whereas for *P. edulis* the results indicated MIC of 15.62 µg/mL, MBC of 125 µg/mL, and MBEC of 250 µg/mL. Cytotoxicity assays performed on BGM cells demonstrated that neither pulp extract exhibited toxic effects at active concentrations. Interaction assays showed predominantly antagonistic effects when the extracts were combined with conventional antimicrobial drugs [38].

The extracts of fruit pulps of *Spondias tuberosa* (umbu), *Spondias purpurea* (seriguela), and *Theobroma grandiflorum* (cupuaçu) were investigated for their antimicrobial activity against uropathogenic *E. coli* isolates [39]. The 80% methanolic extracts presented MIC of 500 µg/mL, but the MBCwas superior to the highest tested concentration, supporting a predominantly bacteriostatic profile. Cytotoxicity assays using BGM cells demonstrated no detectable toxicity at concentrations up to the MIC, highlighting a favorable preliminary safety profile. Phytochemical screening and HPLC-DAD analysis confirmed the presence of flavonoids and tannins in all pulps, and the antioxidant assays indicated moderate to high protection against β-carotene oxidation, particularly for *S. tuberosa* and *S. purpurea* [39].

The in vitro antimicrobial and antibiofilm evidence reported for plant food-derived extracts are not without limitations. The chemical composition of food-based extracts is inherently variable, being influenced by factors such as geographic origin, agricultural practices, soil nutrition, frequency of rain, processing and storage conditions, and extraction methodology [1,16,19,34]. Standardizing these parameters is a rather complex endeavor, and such variability makes reproducibility technically difficult; they are relevant requirements for considering clinical applications. In addition, the concentrations required to achieve antimicrobial or antibiofilm effects in vivo, especially through oral intake, are expected to be substantially higher than those used in vitro, due to limitations related to absorption, metabolism, distribution, and elimination of phytomolecules [1,9,10].

Bioavailability is further hampered by extensive first-pass metabolism and interactions with the food matrix itself, which may reduce systemic exposure to active compounds [10]. As reviewed here, plant food-derived extracts and isolated phytomolecules may interfere with the activity of antimicrobial drugs and compromise therapeutic efficacy. Therefore, assumptions of safety should not be made based solely on food status. Controlled clinical investigations, pharmacokinetic studies, and toxicological assessments are necessary to ensure effective and safe use in clinical settings.

4. Conclusions

Plant food-derived natural products represent a strategically relevant and still underexplored resource of bioactive molecules to combat antimicrobial resistance. Their biological effects are intrinsically linked to the chemical diversity and structural complexity of the secondary metabolites, which enable simultaneous targeting of multiple microbial pathways and virulence mechanisms, thereby increasing the barrier to the development of resistance. Nevertheless, while certain extracts potentiate the activity of conventional antimicrobials through synergistic interactions, others display antagonistic effects that can compromise therapeutic efficacy. This complexity highlights that the translational value of plant-based antimicrobials extends beyond their use as standalone agents, encompassing their potential roles as adjuvants, resistance-modulating compounds, or scaffolds for the development of novel antimicrobial drugs. Well-designed in vivo studies, pharmacokinetic evaluations, and controlled clinical trials are necessary to elucidate issues related to bioavailability, metabolism, safety, and drug–drug interactions, ensuring their safety and effectiveness in clinical routines.

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Conflicts of Interest

The author declares no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were used for this paper.

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