

Herbal and spice extracts as antibacterial and anti-inflammatory adjuvants: Opportunities and limitations of artificial intelligence-assisted research

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Abstract

Herbal and spice extracts contain bioactive compounds with antibacterial and anti-inflammatory activities that may support but should not replace conventional antimicrobial and anti-inflammatory therapies. Polyphenols, flavonoids, terpenoids, alkaloids, and organosulfur compounds have been linked to disruption of bacterial membranes, inhibition of enzyme activity, suppression of biofilm formation, interference with quorum sensing, and modulation of inflammatory signaling pathways. This review summarizes selected extracts and phytochemicals, emphasizing their potential role as adjuncts to antibiotics. Researchers often examine interactions between plant-based compounds and antibiotics using checkerboard assays and the fractional inhibitory concentration index (FICI). Synergy interpretation depends on experimental design and should be validated with additional assays. Various compounds, including curcumin, ginger components, garlic-derived sulfur substances, and flavonoids, have been shown to impact processes such as NF- κ B activity, COX-2 and LOX expression, cytokine production, oxidative stress responses, and immune cell functions. However, translating these findings into clinical applications is complicated by variations in extract composition, the low bioavailability of certain compounds, insufficient pharmacokinetic data, potential toxicity at therapeutic levels, and interactions between herbs and medications. Moreover, artificial intelligence-driven analytical methods may help researchers pinpoint phytochemicals and combinations worth further investigation. Nonetheless, researchers must validate these predictions in independent laboratory settings. However, computational predictions and in vitro findings are hypothesis-generating, not clinical evidence. Progress will require authenticated, chemically characterized botanical materials; standardized susceptibility testing; rigorous safety evaluation; animal studies where appropriate; and adequately powered clinical trials.

Keywords: Antimicrobial resistance; medicinal plants; spice extracts; antibiotic adjuvants; inflammation; phytochemicals; artificial intelligence.

Introduction

Antimicrobial resistance (AMR) threatens the continued effectiveness of antibiotics used to treat bacterial infections. The inappropriate use of antibiotics in human health and agriculture contributes to the selection and spread of resistant organisms, increasing the need for strategies that preserve existing antibacterial drugs and identify new therapeutic leads (World Health Organization 2021; Ventola, 2015).

Plants used as foods, spices, and traditional medicines contain diverse secondary metabolites, including phenolics, flavonoids, terpenoids, alkaloids, and organosulfur compounds. Many of these compounds show antibacterial or anti-inflammatory effects in laboratory studies (Cowan, 1999; Alvarez-Martinez *et al.*, 2021). Their potential value lies not only in direct antimicrobial activity but also in the possibility that some constituents could act as antibiotic adjuvants. An adjuvant may enhance antibiotic activity by affecting bacterial permeability, biofilm formation, efflux, virulence-associated signaling, or resistance-associated enzymes (Dhanda *et al.*, 2023; Liang *et al.*, 2022).

Inflammation is also relevant to infectious and chronic diseases. While a regulated inflammatory response is protective, sustained cytokine production, oxidative stress, and activation of inflammatory enzymes may contribute to tissue injury. Curcumin, ginger-derived compounds, garlic constituents, capsaicin, and plant flavonoids have been investigated for effects on inflammatory mediators and signaling pathways, particularly NF- κ B, COX-2, LOX, TNF- α , IL-1 β , and IL-6 (Aggarwal & Harikumar, 2009; Grzanna *et al.*, 2005; Srinivasan, 2020).

Although computational methods may help prioritize compounds for investigation, experimental pharmacognosy, microbiology, and pharmacology remain essential for establishing biological relevance and

therapeutic potential. The data curated appropriately on phytochemical structures, microbial susceptibility, target biology, pharmacokinetics, and toxicity may help prioritize natural-product candidates and antibiotic combinations for laboratory testing. Models used for testing protocols must be properly validated, and the predictions of such studies must be confirmed experimentally before they are interpreted as therapeutic findings (Daina *et al.*, 2017; Xiong *et al.*, 2021; Zhang *et al.*, 2022).

This review explores and outlines the antibacterial and anti-inflammatory activities of selected herbal and spice extracts, considers their potential as antibiotic adjuvants, discusses quantitative endpoints such as MIC, MBC, and FICI, and outlines a cautious role for computational assisted discovery.

Literature search

A literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and reliable phytochemical and pharmacological resources. English-language publications from 2005 to 2024 were prioritized, with older seminal articles included when relevant. Search terms included *herbal medicine, plant extract, natural product, antibacterial, anti-inflammatory, NF- κ B, COX-2, synergy, combination index, machine learning, network pharmacology, molecular docking, and drug discovery*.

Peer-reviewed original studies, systematic reviews, and related clinical studies with quantitative outcomes were considered. Conference abstracts, duplicate reports, studies lacking interpretable outcomes, and articles focused exclusively on synthetic non-herbal compounds were excluded. This option was considered mainly because the included literature differs substantially in botanical identity, extraction method, chemical composition, microorganism, dose, and assay conditions and should therefore be interpreted cautiously.

Antibacterial activity of herbal and spice extracts

Antibacterial mechanisms

Plant-derived antimicrobials act through multiple mechanisms. Lipophilic constituents of essential oils and some flavonoids tend to disturb bacterial membranes, alter permeability, and promote leakage of intracellular constituents. The outer membrane of Gram-negative bacteria can limit access to many antimicrobial compounds, whereas Gram-positive bacteria lack this barrier; nevertheless, susceptibility depends on the specific organism, compound, concentration, and experimental conditions (Burt, 2004; Nikaido, 2003; Alvarez-Martinez *et al.*, 2021).

Eugenol, a major constituent of clove oil, and thymol, abundant in thyme oil, are frequently cited examples of membrane-active phytochemicals. Membrane perturbation may increase access of co-administered antibiotics to intracellular targets, but this possibility requires direct confirmation for each compound–antibiotic–pathogen combination (Burt, 2004; Gonelimali *et al.*, 2018).

Plant extracts may also influence bacterial enzymes and resistance pathways. Allicin and related garlic-derived sulfur compounds can react with thiol-trapping agents and may impair bacterial metabolic functions. Berberine-containing extracts have been studied in relation to multidrug efflux systems, and accompanying plant constituents may enhance berberine activity by interfering with efflux-mediated resistance (Ankri & Mirelman, 1999; Stermitz *et al.*, 2000).

Biofilms create a protected microbial community in which bacteria can become less susceptible to antimicrobial therapy. Polyphenols and other phytochemicals have been investigated for their ability to reduce biofilm formation or interfere with quorum-

sensing-associated processes. Such effects could be important for the development of adjunctive strategies, but biofilm results should not be extrapolated directly to clinical efficacy without being supported by animal and human studies (Friedman, 2007; Zhao *et al.*, 2021).

Quantitative interpretation: MIC and MBC

The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent that prevents visible growth under defined assay conditions. The minimum bactericidal concentration (MBC) is generally the lowest concentration that produces a specified bactericidal endpoint, often operationalized as a 99.9% reduction in viable bacteria. MIC and MBC values are useful for early screening, but they cannot be compared uncritically across studies using different plant materials, solvent systems, strain collections, inocula (the microbial cultures used for testing), media, and incubation conditions (Eloff, 1998).

Extracts from common spices and herbs like cinnamon, garlic, oregano, thyme, clove, guava, olive, sage, mulberry, and *Ziziphus* have shown antibacterial activity in selected in vitro studies. The magnitude of activity is variable. One such study reported extract- and strain-specific MIC and MBC values for *Psidium guajava*, *Salvia officinalis*, *Ziziphus spina-christi*, *Morus alba*, and *Olea europaea* against several bacterial species. Olive extract showed a reported MIC of 250 µg/mL against *Escherichia coli*, whereas other extract–organism pairs required substantially higher concentrations (Hemeg *et al.*, 2020). These findings demonstrate screening potential but do not establish a therapeutic dose or clinical utility.

Herbal–antibiotic synergy

The fractional inhibitory concentration index (FICI) is commonly used to characterize the interaction between two antimicrobial agents:

$$\text{FICI} = \frac{\text{MIC of A in combination}}{\text{MIC of A alone}} + \frac{\text{MIC of B in combination}}{\text{MIC of B alone}}$$

A FICI of 0.5 is often used as a criterion for synergy, whereas higher values are variously classified as additive, indifferent, or antagonistic depending on the convention used. However, a single FICI result does not fully describe concentration-dependent interactions or bactericidal activity. Checkerboard data should therefore be supported where possible by replicated experiments, testing across relevant clinical isolates, and mechanistic investigations (Fatsis-Kavalopoulos *et al.*, 2024).

Table 1 presents examples of combinations reported as synergistic or potentially synergistic in laboratory studies. These findings should be regarded as starting points for validation rather than clinical recommendations.

Anti-inflammatory properties of selected phytochemicals

Inflammation is mediated by coordinated signaling among immune cells, cytokines, chemokines, transcription factors, reactive oxygen species, and lipid mediators. Persistent activation of these pathways can contribute to chronic inflammatory disease. Researchers have studied plant-derived compounds as modulators of these processes, particularly

through effects on NF- κ B signaling, COX and LOX activity, cytokine production, and oxidative stress (Kunnumakkara *et al.*, 2018; Srinivasan, 2020).

Curcumin, the principal curcuminoid in turmeric, has been extensively evaluated in cell, animal, and human studies. Reported mechanisms include modulation of NF- κ B-associated signaling, COX-2, 5-LOX, cytokines, and oxidative stress pathways (Aggarwal & Harikumar, 2009; Gupta *et al.*, 2012). Its interpretation as a therapeutic agent remains constrained by formulation-dependent bioavailability, heterogeneity among clinical trials, and differences between mechanistic and clinical endpoints.

Ginger contains gingerols, shogaols, paradols, zingiberene, and related constituents. Experimental and clinical literature has associated ginger preparations with modulation of prostaglandin and leukotriene pathways and with improvements in some inflammatory or pain-related treatments. Differences in product composition, dose, treatment duration, and population make broad clinical conclusions difficult and more complicated (Grzanna *et al.*, 2005; Bartels *et al.*, 2015).

Table 1. Selected plant-derived compounds or extracts reported in antibiotic-combination studies

Plant-derived agent	Antibiotic	Test organism(s)	Reported outcome	Reference
Curcumin (<i>Curcuma longa</i>)	Ciprofloxacin	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Enhanced antibacterial activity reported in vitro	Mun <i>et al.</i> (2013)
Garlic-derived compounds (<i>Allium sativum</i>)	Gentamicin	<i>Pseudomonas aeruginosa</i>	Combination activity reported; requires standardized extract confirmation	Ankri & Mirelman (1999)
Green-tea polyphenols (<i>Camellia sinensis</i>)	Ampicillin	<i>E. coli</i>	Potential interaction reported in experimental studies	Friedman (2007)
Thyme oil (<i>Thymus vulgaris</i>)	Erythromycin	<i>E. coli</i>	Enhanced activity reported in laboratory testing	Khan <i>et al.</i> (2009)
Berberine-containing plant material	Conventional antibiotics	<i>S. aureus</i> and other bacteria	Efflux-related potentiation reported for plant-derived combinations	Stermitz <i>et al.</i> (2000)

Garlic contains allicin and additional sulfur-containing compounds, including diallyl sulfides (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and S-allyl cysteine. These compounds have been associated with antioxidant effects and modulation of inflammatory mediators. However, garlic preparations differ in active-compound content, and high-dose supplementation may interact with medications or increase bleeding risk in susceptible individuals (Ankri & Mirelman, 1999; Posadzki *et al.*, 2013).

Flavonoids may influence inflammatory enzymes, nitric oxide synthase, cytokine production, and transcriptional regulation. Their activities *in vivo* are often observed at concentrations that may not be readily achieved systemically after oral administration. Thus, pharmacokinetic exposure should be considered alongside *in vitro* mechanisms (Kim *et al.* 2004; Yuan *et al.* 2021).

A randomized crossover-controlled feeding trial in adults at risk of cardiometabolic disease reported that four-week consumption of a spice blend influenced selected inflammatory cytokines and monocyte-related outcomes. The study is informative because it evaluated a suboptimal American style dietary mixture rather than an isolated compound, but its short duration and limited sample size restrict application to disease treatment (Ester *et al.* 2021).

Safety, standardization, and translational limitations

The assumption that “natural” equates to “safe” is not scientifically justified. Extract composition varies with bioactive botanical compounds, plant part, geographic origin, growing conditions, harvesting time, extraction method, storage, and formulation. This variability limits reproducibility and complicates dose selection and regulatory assessment (Bae *et al.* 2021).

Assessment of toxicity is based on concentrations relevant to the intended route

of administration. Essential oils and other lipophilic constituents may have *in vitro* antimicrobial activity at concentrations that are inappropriate for systemic use. Similarly, a compound that produces favorable laboratory interaction with an antibiotic may also alter host metabolism, transporter activity, or toxicity.

Herbal interactions with drugs are a particular concern. Phytochemicals may influence cytochrome P450 enzymes or transporters such as P-glycoprotein, potentially modifying drug exposure. Garlic supplementation has altered saquinavir pharmacokinetics in humans, illustrating that botanical products can have clinically meaningful interactions (Piscitelli *et al.*, 2002). Curcumin and berberine have also been investigated for effects on drug-metabolizing enzymes, although the clinical relevance depends on dose, formulation, route, and co-administered medication (Volak *et al.*, 2008; Feng *et al.*, 2020).

Most antibacterial and anti-inflammatory findings for herbal extracts remain preclinical. *In vitro* assays cannot reproduce the absorption, distribution, metabolism, elimination, protein binding, immune effects, tissue penetration, and microbial ecology as presented in *in vivo* studies. The next steps for promising candidates should include chemically characterized preparations, reproducible microbiological and pharmacokinetic studies, safety assessments, validated animal models where justified, and adequately designed clinical trials.

Computational approaches in phytochemical research

Computational approaches can improve the efficiency of natural-product research when applied to reliable, traceable input data. A practical workflow begins with authenticating botanical materials and chemically characterizing extracts or purified constituents. Researchers can then combine structural and biological data with microbial

Table 2. Representative phytochemicals and reported anti-inflammatory mechanisms

Compound or class	Principal source	Reported molecular targets or pathways	Key limitation
Curcumin	<i>Curcuma longa</i>	NF- κ B, STAT3, COX-2, 5-LOX, TNF- α , IL-1 β , IL-6	Limited and formulation-dependent oral bioavailability
Gingerols and shogaols	<i>Zingiber officinale</i>	Prostaglandin and leukotriene-related pathways; cytokine modulation	Variable composition across preparations
Garlic sulfur compounds	<i>Allium sativum</i>	NF- κ B-associated pathways, oxidative-stress responses	Potential drug interactions and bleeding-related concerns
Flavonoids	Multiple plants	COX, LOX, iNOS, cytokines, gene-expression pathways	Exposure <i>in vivo</i> may differ from <i>in vitro</i> test concentrations
Capsaicin	<i>Capsicum</i> spp.	NF- κ B and cytokine-related pathways	Dose-dependent tolerability and formulation issues

Sources: Aggarwal & Harikumar (2009); Grzanna *et al.* (2005); Kim *et al.* (2004); Srinivasan (2020); Yuan *et al.* (2021).

susceptibility data, known or predicted targets, and pharmacokinetic and toxicological information. Machine-learning (ML) models, quantitative versus qualitative relationship, network-pharmacology, and graph-based approaches can rank candidate compounds or combinations for further testing before declaring them as effective treatments (Wishart *et al.*, 2018; Zhang *et al.*, 2022).

Deep Synergy prediction is challenging because interactions depend on drug concentrations, bacterial genotype, growth medium, assay endpoint, and the chemical identity of the herbal preparation. Data-driven models can be trained using combination-screening data, but their usefulness depends on transparent model development, independent test sets, calibration, and experimental validation. Predicted combinations should undergo checkerboard testing using Fractional Inhibitory Concentration Index (FICI), time–kill analysis, resistance-selection studies, host-cell cytotoxicity assessment, and, where applicable, mechanistic analysis using genomic, transcriptomic, proteomic, or metabolomic methods (Preuer *et al.*, 2018; Fatsis-Kavalopoulos *et al.*, 2024).

ADMET prediction platforms can help prioritize compounds with more favorable predicted absorption, distribution, metabolism, excretion, and toxicity properties early in the drug discovery process. Such tools are useful for early prioritization, but predicted safety or bioavailability is not a substitute for measured pharmacokinetic data, toxicology studies, or clinical pharmacology. SwissADME and ADMETlab 2.0, ADMETlab 3.0, ADMET-AI, and admetSAR 3.0 are examples of resources that may inform early-stage candidate selection (Daina *et al.*, 2017; Xiong *et al.*, 2021).

Natural-language processing (NLP) and knowledge-graphs (KGs) approaches may also assist researchers in organizing evidence about plants, constituents, targets, biological pathways, antibiotic combinations, and adverse events. These systems are vulnerable to errors in the underlying literature, incomplete reporting, and terminology ambiguity. Therefore, outputs must be reviewed by domain experts and traced back to the primary evidence (Lee *et al.* 2020; Zeng *et al.* 2022).

Future directions

Future investigations should prioritize authenticated botanical materials, standardized

extraction procedures, reproducible antimicrobial testing protocols, and careful evaluation of pharmacokinetic compatibility and safety. Studies involving multiple clinical isolates, rigorous toxicity assessments, and well-designed clinical trials will be necessary before plant-derived adjuvants can be considered for broader therapeutic use.

Bioinformatics approaches may be particularly useful when incorporated into this evidence-generation pipeline: it can assist candidate prioritization, identify gaps in experimental data, help design combination-testing matrices, and support pharmacokinetic modeling. Its appropriate role is to narrow a large search space and improve validation efficiency, not to replace experimental reproducibility or clinical judgment.

Conclusion

Herbal and spice extracts contain numerous bioactive compounds with demonstrated antibacterial and anti-inflammatory activities in experimental systems. Although selected phytochemicals have shown promise as adjuncts to conventional therapies, significant challenges remain regarding standardization, pharmacokinetics, safety, and clinical efficacy. Future progress will depend on rigorous experimental validation, careful clinical investigation, and transparent reporting of both positive and negative findings. Data-driven analytical tools may support candidate prioritization, but experimental evidence must remain the basis for therapeutic development.

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