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Beyond Conventional Antibiotics: Emerging Therapeutic Strategies to Combat Antimicrobial Resistance in Multidrug-Resistant Pathogens

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ABSTRACT

Antimicrobial resistance (AMR) has arisen as a significant global health issue, markedly diminishing the efficacy of traditional medicines and exacerbating the prevalence of infectious illnesses globally. The swift advancement of resistance mechanisms, encompassing horizontal gene transfer, biofilm formation, and enzymatic drug inactivation, has significantly undermined the treatment of multidrug-resistant organisms like Klebsiellapneumoniae. This review rigorously evaluates alternative and complementary therapeutic approaches designed to mitigate the increasing constraints of antibiotic-based therapies. Focus is aimed towards herbal and plant-derived chemicals, conventional medical systems, probiotics, bacteriophage therapy, antimicrobial peptides, nanotechnology-based drug delivery methods, host-directed therapies, immunotherapies, and rational combination regimens. These methods provide several modes of action, such as immunological modulation, bacterial pathogenicity disruption, decreased selective pressure on pathogens, and improved treatment efficiency. Notwithstanding significant progress, issues about standardization, safety, and clinical translation persist. A comprehensive, multidisciplinary strategy is crucial for formulating lasting solutions to combat antimicrobial resistance and protect global public health.

Keywords: Antimicrobial resistance; Alternative therapies; Herbal medicine; Probiotics; Klebsiellapneumoniae; Host-directed therapy; Combination therapy

Graphical Abstract:

1. INTRODUCTION AND BACKGROUND

A recent threat warning from the US Centers for Disease Control and Prevention cautions that the habitual use of antibiotics inevitably fosters resistance, converting formerly successful treatments into enduring issues [1]. Antibiotic resistance is widely acknowledged as a pervasive ecological phenomenon of contemporary industrial society, transcending hospitals to infiltrate ordinary settings, including households, food systems, animals, and natural ecosystems [2,3].

Resistant bacteria arise not just in clinical environments but also in soil, aquatic ecosystems, wildlife, and urban areas, illustrating the interrelation of human, environmental, and microbial health.The effective lifespan of an antibiotic is determined by the rate at which resistance develops and disseminates. Resistance genes may arise from spontaneous mutations or natural microbial competition and can spread swiftly through vertical inheritance or horizontal gene transfer facilitated by plasmids and other mobile genetic elements, frequently across bacterial species [4]. Consequently, resistance compromises both established and newly formulated antibiotics.Antibiotic resistance constitutes a substantial worldwide health hazard, markedly increasing morbidity and mortality rates. Methicillin-resistant Staphylococcus aureus (MRSA) alone results in tens of thousands of fatalities each year in the United States and Europe, but multidrug-resistant tuberculosis predominantly impacts poor nations, with hundreds of thousands of cases documented globally. Nosocomial infections exacerbate this issue owing to elevated antibiotic exposure, insufficient infection control measures, and restricted diagnostic capabilities, promoting the establishment and dissemination of resistance strains [7].

Due to the diminishing efficacy of traditional antibiotics and the sluggish rate of novel medication development, alternative and adjunctive strategies are becoming increasingly essential. Non-antibiotic therapies, such as phytochemicals, traditional medicine, probiotics, immunotherapies, and host-directed interventions, present promising strategies by bolstering host defenses, diminishing selective pressure on pathogens, and facilitating sustainable management of resistant infections [8,9]

2. HERBAL, TRADITIONAL, AND MICROBIOME-BASED THERAPIES

Herbal medications originate from plants or plant extracts that contain bioactive medicinal ingredients and are typically classified as complementary and alternative medicine (CAM). Throughout various civilizations and epochs, herbal remedies have been extensively employed for the treatment of infectious diseases in both people and animals, as well as for addressing age-related ailments such as immunological disorders, cognitive decline, and osteoporosis [11,12]. Comprehensive studies globally have assessed the antibacterial

properties of medicinal herbs, confirming their efficacy against many diseases [13–17].
Species including Achilleamillefolium (yarrow), Caryophyllusaromaticus (clove), Melissa officinalis (lemon balm), Ocimumbasilicum (basil), Punicagranatum (pomegranate), Rosmarinusofficinalis (rosemary), and Salvia officinalis (sage) exhibit significant antibacterial properties. Among herbal medicines, essential oils have notably great efficacy, with cinnamon oil identified as the most effective, succeeded by oregano and thyme oils [18,19].

Medical System	**Origin &Philosophy**	**Source of Therapeutics (Plant/Animal/Mineral)**	**KeyExample**	**Mechanism of Action (Scientific Perspective)**	**Relevance to AMR**
Ayurveda	Ancient India; derived from Atharvaveda; holistic balance of *Dosha* (Vata, Pitta, Kapha)	Primarily plants, also animal products and minerals (Bhasma)	Neem (*Azadirachta indica*), Turmeric (*Curcuma longa*), Ashwagandha (*Withania somnifera*)	Phytochemicals (alkaloids, flavonoids, terpenoids) disrupt bacterial membranes, inhibit enzymes, reduce biofilm formation, and modulate host immunity[20-22]	Acts as antimicrobial agents and resistance modulators; reduces reliance on antibiotics
Allopathy (Modern Medicine)	Western medicine; evidence-based, pathogen-targeted	Synthetic chemicals, semi-synthetic, biologics	β-lactams, aminoglycosides, carbapenems	Direct inhibition of bacterial cell wall synthesis, protein synthesis, DNA replication, or metabolic pathways[23][24]	High efficacy but major contributor to resistance due to selective pressure
Homeopathy	Germany (Samuel Hahnemann); “like cures like” principle	Highly diluted plant, animal, and mineral substances	*Belladonna*, *Arsenicum album*	Proposed stimulation of host self-regulatory and immune responses; no direct antimicrobial action[25][26]	Indirect role; limited experimental evidence in AMR context
Naturopathy	Europe & traditional healing systems; body’s self-healing capacity	Plants, dietary elements, water, sunlight	Herbal decoctions, fasting therapy, probiotics	Enhances host immunity, improves gut microbiota balance, reduces inflammation[27][28]	Supportive role in infection prevention and immune strengthening
Vedic Medicine	Ancient Indian scriptures (Rigveda,	Medicinal plants, ritualistic and dietary components	Tulsi (*Ocimum sanctum*), Soma plant	Antioxidant, immunomodulatory, antimicrobial	Foundational knowledge base for

	Atharvaveda)		(historical)	effects through plant bioactives[29-31]	Ayurveda and herbal drug discovery
Traditional Herbal Medicine (Global)	China, Africa, Middle East, Indigenous systems	Mainly plants, some animal derivatives	Garlic (*Allium sativum*), Clove (*Syzygiumaromaticum*), Cinnamon oil	Essential oils and phenolics cause membrane disruption, efflux pump inhibition, quorum sensing interference[10-12]	Strong potential as alternative or adjunct antimicrobial therapies
Unani Medicine	Greco-Arab origin; humoral theory	Plants, minerals, animal products	*Nigella sativa*, *Glycyrrhizaglabra*	Antimicrobial, anti-inflammatory, and immunomodulatory actions	Useful in managing infections with fewer side effects
Siddha Medicine	South India; elemental balance	Plants, metals, minerals	*Acalyphaindica*, mercury-based preparations	Bioactive compounds exhibit antibacterial and detoxifying properties	Potential against MDR pathogens, but safety standardization needed

Table: Comparative Overview of Traditional and Modern Medical Systems and Their Mechanisms Relevant to Antimicrobial Resistance.

Conventional medical systems, like as Ayurveda, Unani, Siddha, Homeopathy, and Naturopathy, are experiencing a resurgence in global acknowledgment for their contributions to healthcare, particularly in resource-constrained environments. Ayurveda, derived from the Atharvaveda, constitutes one of the first structured medical systems. Pharmaceuticals derived from plants in these traditions are being progressively investigated as potential remedies for Multidrug resistance(MDR).

Medicinal plants' secondary metabolites may serve as innovative antibiotics or chemosensitizers, providing biocompatible and resistance-modulating therapeutic alternatives. The ethnobotanical and ethnopharmacological insights from Ayurveda and Traditional Chinese Medicine are essential for identifying potential plants and formulating novel antibacterial agents [33]. Probiotics are a viable non-antibiotic strategy that restores gut microbial equilibrium and offers health advantages, typically with positive safety profiles [34,35]. Their application is particularly advantageous in recurrent infections and in reestablishingmicrobiota damaged by broad-spectrum antibiotics [36]. Probiotics are frequently advertised as ecological treatments with few adverse effects; yet, being live microbes containing several genes, they may interact with host systems and microbial ecosystems in intricate manners that necessitate thorough assessment [37].

Antibiotic resistance in Klebsiellapneumoniae develops by various processes, including biofilm development and the frequent horizontal transfer of resistance genes. The bacteria generates many β-lactamases, including TEM variations and AmpC enzymes, which deactivate a wide spectrum of antibiotics, encompassing β-lactam/β-lactamase inhibitor combos. Further resistance pathways include mutations that impact efflux pumps, porins, and carbapenemase enzymes, hence diminishing antibiotic penetration and effectiveness. Biofilm development increases resistance by safeguarding bacteria within extracellular matrices made of polysaccharides, proteins, and extracellular DNA, so protecting them from antimicrobial agents and host immunity [38].

β-lactam antibiotics, such as penicillins, cephalosporins, and carbapenems, continue to be extensively utilized due to their efficacy; nonetheless, resistance, predominantly caused by β-lactamase synthesis, has escalated swiftly on a global scale [39]. Bacteria utilize molecular mechanisms, including DNA mutations and enzymatic drug modification, to counteract

antibiotics, such as aminoglycosides, wherein acetyltransferase enzymes inhibit ribosome binding [40].Managing carbapenem-resistant K. pneumoniae (CRKP) infections is notably difficult, with polymyxins, tigecycline, fosfomycin, and aminoglycosides acting as the final therapeutic alternatives [41]. The increasing resistance and restricted antibiotic development highlight the pressing necessity for new approaches. Combination medicines, particularly those based on polymyxins, exhibit synergistic benefits, whereas recently licensed antibiotics and their combinations offer enhanced efficacy and safety relative to conventional regimens [42–44].

3. BIOLOGICAL AND ADVANCED THERAPEUTIC APPROACHES

Bacteriophages (phages) are natural bacterial parasites that have historically been regarded as therapeutic agents for bacterial illnesses [45,46]. Phage therapy, which employs phages as antibacterial agents, relies on the ability of phages to identify, attach to, and proliferate within bacterial host cells, swiftly inducing cell lysis. Although first investigations into phage biology and therapy were ambiguous on the essence of bacteriophages—some positing them as elements of the human immune response or bacterial enzymes—phage therapy has been employed for nearly 90 years. Initial experiments yielded inconsistent outcomes, and phage therapy was never universally embraced. Antimicrobial peptides (APs) are characterized as evolutionarily ancient defenses. Present in both the animal and plant worlds, they have a crucial function in the innate non-specific defense system that provides resistance to diseases without prior exposure to foreign pathogens [51][52]. These reactions are genetically encoded and are inherent to all multicellular creatures [53]. Despite variability in their amino acid sequences, their capacity to adopt amphipathic conformations enables antimicrobial peptides (APs) to interact with and destroy bacterial membranes.[54]

The advent of nanotechnology as a viable alternative to traditional antibacterial methods signifies a transformative change in addressing healthcare-associated illnesses and antimicrobial resistance [55]. Modern nanotechnology methods have attracted significant interest due to the nano-form improvement of active chemicals, resulting in greater stability and increased antibacterial effectiveness compared to the same materials in bulk form [56]. Various kinds of nanomaterials, encompassing polymeric systems (both natural and synthetic), inorganic nanoparticles (metals and metal oxides), and nano-enabled antimicrobial peptides, offer adaptable platforms for the formulation of innovative therapeutic strategies [57]. Chitosan, alginate, and cellulose derivatives are extensively utilized among natural polymers because to their biocompatibility and biodegradability, facilitating encapsulation and regulated or stimuli-responsive drug release [58][59].

4. IMMUNOTHERAPY AND COMBINATION TREATMENT STRATEGIES

A complementary technique is host-directed treatment (HDT) utilizing biologics or small compounds. HDT can disrupt host mechanisms essential for a pathogen's effective replication or persistence; augment the immune response by activating host defense mechanisms against the pathogen; target pathways disrupted by a pathogen that contribute to hyper-inflammation; and modulate host factors that result in imbalanced responses at the site of pathology. Consequently, HDT for infectious disorders exhibits parallels with traditional treatment of non-communicable diseases.[60]

Current cancer immunotherapy strategies involve targeting co-inhibitory T-cell checkpoint receptors, such as ipilimumab (CTLA-4) and pembrolizumab (PD-1), to mitigate immune depletion and enhance tumor responses. The regulation mechanisms of metabolism and co-receptor immune checkpoints are frequently interconnected. PD-1 activation modifies T-cell metabolic reprogramming by suppressing glycolysis and enhancing lipolysis and fatty acid oxidation [61] Unlike antibiotics, which typically impede critical bacterial functions, monoclonal antibodies (mAbs) can attach to both essential and non-essential antigens, such as virulence factors. This may correlate with a diminished likelihood of selecting for resistant mutants, as mutations in these targets could lead to decreased virulence and improved elimination by the immune system. The likelihood of acquiring resistance mechanisms to vaccines is exceedingly low [62], and even in the infrequent cases where vaccine resistance has been shown [63]

a decrease in disease burden has been accomplished nonetheless. Unlike medications that target specific germs, vaccines elicit immune responses against many targets (known as antigens) and/or several epitopes of the same antigen (polyclonal antibodies). As a result, the likelihood of vaccination escape mutants emerging is much reduced, as many mutations would be necessary for various epitopes [64].

One strategy for addressing MDR infections is the combination of two or more antimicrobial agents in a therapy regimen. The potential for drug-drug interactions poses a significant risk to this technique and must be considered during the drug development process. Combination therapy are crucial for treating bacterial infections, particularly for Mycobacterium TB,

where combinations of up to four medications are standard.[65]

CONCLUSION

Antimicrobial resistance has developed into a complex, multifaceted global health concern that surpasses clinical limits and illustrates wider ecological, cultural, and biological linkages. This review's research unequivocally indicates that sole dependence on traditional antibiotics is inadequate for managing multidrug-resistant infections, especially those induced by high-risk platforms, host-directed therapies, immunotherapies, and rational combination regimens. These strategies provide varied modes of action, diminished selective pressure on infections, and potential to bolster host immune responses. Nonetheless, obstacles pertaining to standardization, mechanistic validation, safety evaluation, and clinical translation persist as significant impediments. Effectively addressing antibiotic resistance necessitates a comprehensive, interdisciplinary approach that merges scientific innovation with bacteria like Klebsiellapneumoniae.The swift development of resistance mechanisms, such as biofilm formation, horizontal gene transfer, and enzymatic drug inactivation, has dramatically undermined therapeutic efficacy and patient outcomes.

This review emphasizes the expanding potential of alternative and complementary therapeutic approaches, encompassing herbal and plant-derived compounds, traditional medical systems, probiotics, bacteriophages, antimicrobial peptides, nanotechnology-based traditional knowledge, rigorous clinical assessment, and global stewardship initiatives. A comprehensive plan is crucial to guarantee sustainable infection control and maintain the efficacy of future antimicrobial measures.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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