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HERBAL THERAPEUTICS AGAINST ANTIBIOTIC-RESISTANT STRAINS OF *STAPHYLOCOCCUS AUREUS*

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ABSTRACT

The increasing prevalence of antibiotic-resistant *Staphylococcus aureus*, especially methicillin-resistant (*MRSA*) and vancomycin-resistant (*VRSA*) strains, has become a serious global health concern. Standard antimicrobial treatments are losing effectiveness due to resistance strategies such as biofilm development, activation of efflux pumps, and enzymatic modification of antibiotics. As a result, herbal-based therapeutics are being widely investigated as complementary or alternative approaches to combat *S. aureus*. Medicinal plants provide a rich array of bioactive molecules, including flavonoids, alkaloids, terpenoids, tannins, and essential oils, demonstrating strong antibacterial and anti-biofilm properties. Compounds obtained from *Curcuma longa* (curcumin), *Azadirachta indica* (neem), *Allium sativum* (garlic), and *Ocimum sanctum* (tulsi) have shown promising activity against resistant *S. aureus* isolates by disrupting bacterial cell walls, interfering with quorum sensing, and enhancing the efficacy of conventional antibiotics. Importantly, herbal agents are often associated with lower toxicity and a reduced tendency for resistance development compared with synthetic drugs. Nonetheless, limitations such as inconsistency in phytochemical content, insufficient clinical validation, and regulatory challenges hinder their clinical adoption. This review emphasizes the therapeutic promise of herbal remedies against antibiotic-resistant *S. aureus*. It underscores the

importance of comprehensive preclinical and clinical studies to transform experimental findings into practical medical applications.

KEYWORDS: Herbal therapeutics, Antibiotic resistance, *Staphylococcus aureus* (MRSA), Phytochemicals, Synergistic interactions.

INTRODUCTION

Staphylococcus aureus is a Gram-positive bacterium commonly residing on human skin and mucosal surfaces, yet it is also recognized as a significant opportunistic pathogen responsible for numerous clinical conditions. These include skin and soft tissue infections, pneumonia, osteomyelitis, endocarditis, and bloodstream infections.[1] In recent decades, the rise of drug-resistant forms such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA) has become a serious global health issue. These strains are linked to higher morbidity, mortality, and healthcare expenses, largely due to the limited availability of effective treatment options.[2]

The ability of *S. aureus* to resist antibiotic therapy is attributed to multiple mechanisms. These include acquiring resistance genes like mecA, which encodes penicillin-binding protein 2a, forming biofilms that shield bacterial cells from antimicrobial penetration, and activating efflux pumps that expel antibiotics from the bacterial cell.[3] Such mechanisms enable the bacterium to thrive even in the presence of potent drugs, making infections increasingly difficult to control in both hospital and community environments. The declining success of conventional antimicrobials highlights the urgent need for novel therapeutic alternatives.

Herbal remedies have gained growing attention as potential adjuncts or alternatives to conventional antibiotics in addressing resistant infections. Plants produce diverse secondary metabolites such as alkaloids, flavonoids, tannins, terpenoids, and essential oils, many of which possess antimicrobial and anti-biofilm activities. Research has demonstrated that phytochemicals derived from *Curcuma longa* (curcumin), *Allium sativum* (garlic), and *Azadirachta indica* (neem) can effectively inhibit resistant *S. aureus* by mechanisms including disruption of bacterial membranes, inhibition of quorum sensing, and potentiation of existing antibiotics.[4]

Compared with synthetic antimicrobials, herbal agents generally exhibit favorable biocompatibility, lower toxicity, and a reduced risk of resistance development.[5] Nonetheless, significant challenges remain, such as variability in phytochemical content, lack of standardized preparations, and insufficient large-scale clinical validation. Addressing these issues is essential to ensure that plant-based therapies can be translated into reliable and effective clinical applications.

This study investigates the therapeutic potential of herbal compounds against antibiotic-resistant *S. aureus*. By compiling current evidence on plant-derived bioactive agents and their modes of action, the paper emphasizes the relevance of incorporating herbal strategies into modern medical approaches to mitigate the growing problem of antimicrobial resistance.

Epidemiology of Antibiotic-Resistant *Staphylococcus aureus*

Staphylococcus aureus is a highly adaptable bacterium capable of causing diseases ranging from superficial skin infections to severe systemic illnesses. Over the past few decades, the development of antibiotic-resistant variants, particularly methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA), has dramatically reshaped the global epidemiological landscape. These resistant strains have become a critical cause of morbidity and mortality in both healthcare institutions and community populations.

Global Distribution and Burden

The prevalence of MRSA displays significant regional variability, which reflects differences in healthcare infrastructure, antibiotic usage policies, and infection control measures. In the United States, hospitalization rates linked to MRSA have gradually declined since 2010, though community-associated MRSA (CA-MRSA) remains an important public health concern.[6] European countries such as Sweden and the Netherlands maintain prevalence rates below 5% due to robust surveillance and strict control programs, while southern and eastern European nations continue to experience much higher rates (ECDC, 2022). In contrast, many Asian countries, particularly India and China, report prevalence exceeding 40–50%, largely fueled by extensive antibiotic misuse and a weak monitoring framework.[7] Although VISA and VRSA are comparatively rare, their detection in countries like the United States, Japan, and India illustrates the growing danger of multidrug resistance.

Healthcare-Associated MRSA (HA-MRSA)

Initially, MRSA was largely confined to hospital environments. Healthcare-associated MRSA (HA-MRSA) typically affects patients undergoing invasive procedures or those with surgical wounds, implanted devices, or compromised immune systems. Elderly individuals and those in intensive care units are at particularly high risk. Transmission within hospitals occurs primarily through direct contact with colonized healthcare personnel, contaminated equipment, or environmental surfaces.[8] Although stricter infection control has reduced HA-MRSA in some high-income countries, it continues to present a substantial burden in low- and middle-income regions.

Community-Associated MRSA (CA-MRSA)

By the 1990s, MRSA began spreading in individuals without previous healthcare exposure, leading to the emergence of CA-MRSA. This form commonly affects otherwise healthy individuals, particularly children, athletes, military recruits, and prisoners. Unlike HA-MRSA, CA-MRSA frequently harbors genes encoding Panton–Valentine leukocidin (PVL), a potent toxin associated with skin and soft tissue infections and necrotizing pneumonia.[9] The transition of MRSA from hospitals into communities reflects its evolutionary adaptability and its capacity to establish endemicity in diverse environments.

Livestock-Associated MRSA (LA-MRSA)

In recent years, livestock-associated MRSA (LA-MRSA) has been recognized as a new zoonotic variant, particularly in Europe and North America. Its rise is strongly linked to antibiotic overuse in agriculture, where resistant strains emerge in animals and are subsequently transmitted to humans through direct handling or via the food chain.[10] Farmers, veterinarians, and slaughterhouse workers represent the groups most at risk. The growing incidence of LA-MRSA highlights the need for integrated surveillance systems under the “One Health” framework, acknowledging the interconnectedness of human, animal, and environmental health.

Risk Factors and Transmission

The spread of resistant *S. aureus* is shaped by a combination of healthcare- and community-associated factors. In hospitals, long-term admissions, surgery, indwelling devices, and immunosuppression are major drivers.[11] In communities, overcrowding, frequent skin contact, and poor hygiene significantly increase risk. Additionally, international travel and global trade accelerate the dissemination of resistant strains across borders. The bacterium’s

ability to persist on surfaces and colonize the nasal cavity facilitates both symptomatic infection and asymptomatic carriage, perpetuating its transmission cycle.

Public Health Impact

Antibiotic-resistant *S. aureus* remains a serious global health challenge. MRSA alone causes hundreds of thousands of invasive infections each year, with nearly 100,000 deaths reported globally in 2019.[12] These infections are associated with prolonged hospital stays, elevated medical costs, and considerable productivity loss. The epidemiological data highlight the pathogen's resilience and underscore the inadequacy of current containment measures in fully addressing its global spread.

Mechanisms of Resistance in *Staphylococcus aureus*

The persistence of *Staphylococcus aureus* in both healthcare and community settings is largely due to its ability to employ diverse resistance mechanisms against antimicrobials. One of the most critical determinants of resistance is the mecA gene, housed within the staphylococcal cassette chromosome mec (SCCmec). This gene encodes penicillin-binding protein 2a (PBP2a), an enzyme with extremely low affinity for β-lactam drugs. The presence of PBP2a allows the bacterium to continue peptidoglycan synthesis even when methicillin or other β-lactams are present, forming the molecular basis of methicillin-resistant *S. aureus* (MRSA).[13]

Resistance is also evident against glycopeptide antibiotics such as vancomycin. Vancomycin-intermediate *S. aureus* (VISA) develops a thickened cell wall with excess peptidoglycan layers that sequester vancomycin molecules before they reach their binding sites. In contrast, vancomycin-resistant *S. aureus* (VRSA) typically emerges through acquisition of the vanA operon from enterococci. This gene cluster alters the peptidoglycan terminus from D-Ala-D-Ala to D-Ala-D-Lac, leading to a sharp decline in vancomycin affinity and clinical treatment failure.[14]

Beyond β-lactams and glycopeptides, *S. aureus* employs several additional strategies. Many strains secrete β-lactamase enzymes that hydrolyze the β-lactam ring of penicillins, inactivating them. Another important mechanism is the activity of multidrug efflux pumps, such as NorA, which expel structurally diverse antibiotics—fluoroquinolones, tetracyclines, and macrolides—out of the cell, thereby reducing intracellular drug concentrations.[15] Mutations in the genes encoding DNA gyrase and topoisomerase IV further enhance

resistance to fluoroquinolones by preventing drug binding to their targets, protecting DNA replication.[16] Likewise, erm genes encode rRNA methyltransferases that modify the 23S rRNA, which blocks binding of macrolides, lincosamides, and streptogramins to the ribosome.[17]

Together, these molecular adaptations reveal the extraordinary versatility of *S. aureus*. The organism can acquire resistance genes through horizontal transfer, alter target molecules, degrade drugs enzymatically, or pump antimicrobials out of the cell. Such multifaceted resistance mechanisms explain why *S. aureus* is resistant to nearly every major antibiotic class. This evolutionary capacity underscores the urgent necessity of novel antimicrobial discovery, integration of herbal or natural therapeutics, and robust infection-prevention strategies to contain multidrug-resistant *S. aureus*.

Limitations of Conventional Therapy

Antibiotics have traditionally been the mainstay for treating *Staphylococcus aureus* infections; however, their effectiveness has progressively declined with the rise of antimicrobial resistance. A major drawback is the widespread occurrence of methicillin-resistant *S. aureus* (MRSA), which renders most β-lactam antibiotics ineffective. Likewise, the appearance of strains with reduced susceptibility or full resistance to vancomycin has significantly limited the reliability of glycopeptides, once regarded as critical last-line treatments.

Another obstacle is the scarcity of new antibiotic classes in recent decades. Because very few innovative agents have reached clinical practice, physicians often depend on older drugs, which accelerates resistance selection and narrows treatment choices [18]. Additionally, the long-term or repeated use of conventional agents can result in serious toxicities, such as kidney damage from vancomycin or liver injury caused by rifampicin, posing further challenges in clinical management.[19]

Standard therapies also perform poorly against biofilm-associated infections, where bacteria form protective communities that hinder antibiotic diffusion and enhance tolerance. Such resilience is especially concerning in infections linked to indwelling medical devices, including catheters and prosthetic implants.[20]

Together, these issues underscore the pressing need for novel treatment strategies, such as plant-derived therapeutics and natural bioactive compounds, to counter the persistent threat posed by drug-resistant *S. aureus*.

Herbal Therapeutics

The global health crisis caused by multidrug-resistant *Staphylococcus aureus* (MDRSA), particularly MRSA strains, has intensified the search for safe, effective, and affordable alternatives to conventional antibiotics. Among these, herbal medicines are gaining recognition because they are abundant sources of bioactive compounds, often acting through diverse antimicrobial pathways. Unlike single-target antibiotics, phytochemicals typically exert multifunctional effects, including damaging bacterial membranes, suppressing quorum sensing, preventing biofilm formation, and interfering with protein or nucleic acid synthesis.[21] Furthermore, due to their chemical diversity and synergistic action, plant-derived agents are less likely to trigger rapid resistance compared to synthetic antibiotics.

Phytochemicals with Anti-*S. aureus* Potential

Alkaloids

Alkaloids are nitrogenous metabolites that display strong antimicrobial potential. Their mechanisms include disruption of peptidoglycan synthesis, inhibition of bacterial enzymes, and direct binding to DNA. One example, berberine, compromises *S. aureus* cell wall integrity and has been reported to enhance the activity of β-lactam antibiotics when used in combination.[22] Such findings highlight their potential role as therapeutic adjuvants.

Flavonoids

Flavonoids, a diverse group of polyphenols, exhibit bacteriostatic and bactericidal activities. They act by altering membrane permeability, binding bacterial proteins, and suppressing nucleic acid synthesis. Quercetin, in particular, has been shown to reduce *S. aureus* biofilm formation and downregulate genes associated with virulence, making it a promising candidate against MRSA infections.[23]

Essential Oils

Essential oils (EOs), composed mainly of terpenes and phenolic compounds, are potent antimicrobials. Their lipophilic nature enables them to penetrate bacterial membranes, causing structural disintegration and cytoplasmic leakage. Compounds such as eugenol, thymol, and carvacrol effectively inhibit MRSA growth and block adhesion processes crucial

for biofilm development.[24] Their volatile nature also makes them suitable for topical and inhalation-based therapies.

Tannins and Terpenoids

Tannins act by precipitating bacterial proteins and chelating metal ions essential for enzymatic reactions, while terpenoids destabilize membrane integrity and interfere with electron transport chains. Both groups of phytochemicals have been shown to suppress MRSA activity, with several reports noting synergistic interactions when combined with existing antibiotics.[25]

Mechanisms of Action of Herbal Compounds

Herbal-derived compounds demonstrate a wide spectrum of antibacterial strategies, making them effective against multidrug-resistant organisms such as *Staphylococcus aureus*. Unlike conventional antibiotics that typically target a single cellular process, phytochemicals influence multiple molecular pathways at once, which lowers the chances of resistance emergence. Essential oils, including thymol and eugenol, compromise lipid bilayer stability, causing leakage of cellular contents that eventually results in bacterial death [26]. Likewise, terpenoids weaken the bacterial cell wall and hinder respiratory enzymes, thereby reducing bacterial survival.[27]

Another major pathway involves the inhibition of nucleic acid and protein synthesis. For instance, alkaloids such as berberine can intercalate with bacterial DNA and block enzymes like DNA topoisomerases, leading to impaired replication and transcription.[28] Flavonoids, including quercetin, interact with bacterial proteins and enzymes, disrupting enzymatic functions and suppressing virulence gene activity.[29] In addition, tannins exert antimicrobial properties by binding essential metal ions, depriving bacteria of cofactors needed for enzyme activity and metabolic pathways.[30]

Herbal metabolites are also effective against biofilm-associated infections, which are particularly resistant to antibiotics. Biofilms protect bacteria within an extracellular matrix, but natural compounds such as curcumin and epigallocatechin gallate (EGCG) interrupt quorum-sensing systems, hindering bacterial communication and biofilm maturation. This property is crucial in infections linked with catheters, prosthetics, and other medical devices.

In addition to direct antibacterial action, many herbal agents downregulate virulence traits rather than causing outright bacterial killing. Neem-derived compounds like nimbidin decrease toxin secretion, while extracts of tulsi inhibit adhesion molecules that mediate bacterial colonization. By attenuating virulence instead of directly targeting bacterial viability, these compounds apply less selective pressure and thereby minimize the likelihood of resistance development.

Overall, herbal compounds' broad and multifaceted antibacterial mechanisms underscore their therapeutic promise. By simultaneously targeting bacterial membranes, nucleic acids, enzymes, biofilms, and virulence factors, herbal metabolites provide a powerful approach to countering the global problem of antimicrobial resistance, either as stand-alone agents or in synergy with antibiotics.

Synergistic Interactions with Antibiotics

A key advantage of herbal-based therapy lies in its ability to complement and enhance the action of conventional antibiotics. Combining phytochemicals with standard antimicrobials not only boosts therapeutic outcomes but can also reduce the required drug dosage, thereby lowering toxicity and slowing the pace of resistance development. For example, the alkaloid berberine has been found to potentiate the effectiveness of β-lactam antibiotics against *Staphylococcus aureus* by suppressing efflux pump activity, which is one of the major mechanisms driving multidrug resistance.[31]

Quercetin, in particular, has shown additive effects with fluoroquinolones by inhibiting DNA gyrase activity, which complements the antibiotic’s target site and significantly reduces the minimum inhibitory concentration (MIC).[32] Similarly, essential oils rich in carvacrol and thymol destabilize bacterial membranes, facilitating greater uptake of aminoglycosides such as gentamicin and thereby amplifying their bactericidal capacity.[33]

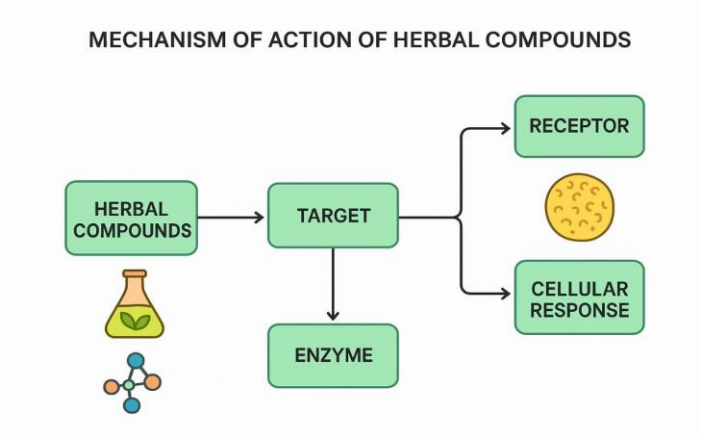

Figure 1: Mechanism of Action of Herbal Compounds.

Flavonoids represent another class of bioactive compounds with synergistic potential.

Curcumin, the principal polyphenol of turmeric (*Curcuma longa*), has demonstrated synergy with oxacillin in combating methicillin-resistant *S. aureus* (MRSA). This effect is attributed to curcumin's ability to downregulate the *mecA* gene, which encodes penicillin-binding protein 2a (PBP2a), the main driver of MRSA resistance.[34] Such findings highlight the potential of herbal compounds to restore the usefulness of antibiotics that have been rendered ineffective by resistance.

In addition, sulfur-rich compounds from garlic, especially allicin, have been reported to enhance the action of vancomycin. This occurs through increased bacterial membrane permeability, which allows higher intracellular accumulation of the antibiotic.[35] Likewise, epigallocatechin gallate (EGCG), a green tea catechin, has been shown to work synergistically with β-lactam antibiotics by inhibiting β-lactamase enzymes, thereby protecting antibiotics from enzymatic degradation and improving their antibacterial performance.

Overall, the integration of herbal compounds with conventional antibiotics provides a dual strategy: while antibiotics directly kill or inhibit bacteria, phytochemicals weaken defense systems such as efflux pumps, biofilm formation, and resistance genes. This combined approach not only revives the efficacy of older antimicrobial drugs but also offers a sustainable therapeutic option at a time when new antibiotic development is limited.

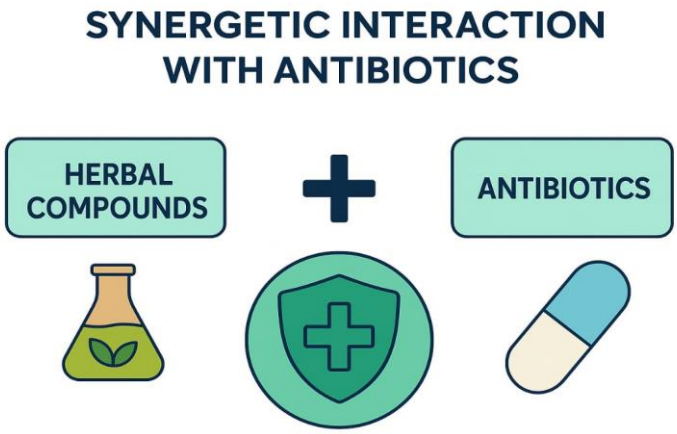

Figure 2: Synergetic Interaction with Antibiotics.

Challenges in Herbal Drug Development

Although plant-derived compounds hold considerable therapeutic potential, several obstacles limit their advancement into clinically validated drugs. A primary difficulty is the variability in phytochemical composition. The levels of active molecules within plants can fluctuate based on cultivation conditions, soil type, seasonal changes, and harvesting methods, which often results in inconsistent pharmacological outcomes.[36] Ensuring standardization of herbal extracts remains a critical but unresolved challenge in developing reliable formulations.

Another major barrier involves poor pharmacokinetics. Many phytochemicals, including well-studied agents like curcumin and quercetin, exhibit low aqueous solubility and undergo rapid metabolism, leading to inadequate concentrations in systemic circulation.[37] While strategies such as nanoencapsulation, liposomal delivery, or chemical derivatization have shown promise in enhancing bioavailability, these technologies substantially increase production costs and regulatory hurdles.

Safety concerns must also be addressed. The perception that "natural" equates to safe is misleading, as numerous phytochemicals can exert hepatotoxic, nephrotoxic, or hematological side effects. Moreover, some plant-based compounds can interact with prescribed medications, complicating therapeutic management.[38] Comprehensive preclinical testing and rigorously designed clinical trials are, therefore, essential to establish acceptable safety profiles.

Intellectual property rights and regulatory frameworks pose additional complications. Unlike synthetic drugs, which usually involve well-defined active ingredients, herbal medicines typically consist of complex mixtures, making it difficult to isolate single bioactive components for patenting or regulatory approval. This complexity discourages major pharmaceutical industries from investing in herbal drug development.[39]

Finally, the lack of robust clinical evidence significantly hampers progress. Much of the available research remains confined to in vitro assays or animal studies, with only limited data from human trials. Without large-scale randomized controlled trials, regulatory authorities remain hesitant to authorize herbal therapeutics as primary interventions, particularly for infections caused by resistant *Staphylococcus aureus*.

To overcome these barriers, integrated research strategies are needed. Advanced analytical platforms can ensure chemical standardization, while innovative delivery systems may improve therapeutic performance. Establishing international guidelines for quality control and regulatory approval, alongside collaborations between traditional medicine practitioners and modern pharmacologists, could help translate herbal therapeutics into clinically viable options.

Future Perspectives in Herbal Therapeutics

The accelerating threat of antimicrobial resistance demands novel therapeutic strategies, and plant-based medicines are increasingly viewed as a vital part of future interventions. A major research direction will involve optimizing delivery platforms for herbal compounds. Modern systems such as nanoparticles, liposomes, and biodegradable polymers are being explored to improve the solubility, stability, and targeted distribution of poorly absorbed phytochemicals, including curcumin and epigallocatechin gallate (EGCG). Such innovations could overcome one of the greatest pharmacokinetic limitations of herbal agents and enhance their clinical performance.[40]

Advances in systems biology are also expected to transform the study of herbal therapeutics. High-throughput technologies—particularly metabolomics, proteomics, and transcriptomics—offer opportunities to map the multiple pathways affected by phytochemicals within both pathogens and host cells. These approaches can clarify the broad-spectrum mechanisms of action that define many herbal compounds and provide a foundation for designing evidence-based combinations.[41] In addition, artificial intelligence and

computational modeling are likely to accelerate the screening of extensive phytochemical libraries, allowing rapid identification of candidates with strong therapeutic potential.

Herb–drug co-therapy represents another exciting avenue for future clinical application. Numerous preclinical studies already suggest that certain phytochemicals enhance antibiotic activity through synergistic mechanisms. Establishing standardized treatment regimens via well-structured clinical trials may extend the lifespan of existing antibiotics and improve outcomes in resistant infections.[42]

Sustainability and resource management will remain critical in the coming years. Overexploitation of medicinal plants threatens ecological balance and long-term availability. Biotechnological strategies, such as large-scale plant tissue culture, genetic engineering, and metabolic pathway optimization, can provide sustainable and consistent sources of bioactive molecules while protecting biodiversity.

Finally, global acceptance of herbal therapeutics will depend on harmonized regulation. Disparities in standards of quality assurance, safety assessment, and efficacy testing currently limit widespread adoption. Developing international frameworks for evaluation and approval would support the integration of herbal medicines into conventional healthcare and strengthen their credibility within evidence-based practice.

In sum, the future of herbal therapeutics lies in combining modern scientific tools with sustainable practices and global cooperation. These approaches may enable herbal compounds to evolve from complementary remedies into mainstream solutions for tackling pressing health challenges such as drug-resistant infections.

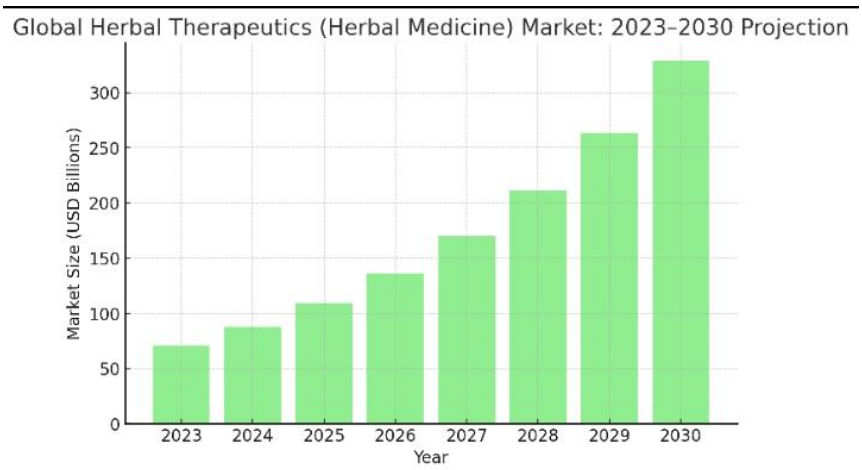

Figure 3: Future Market Size of Herbal Therapeutics (USD Billion).

CONCLUSION

The emergence of antibiotic-resistant *Staphylococcus aureus*, especially methicillin-resistant strains (MRSA), remains a major public health challenge due to diminishing effectiveness of conventional drugs. In this context, herbal therapeutics are gaining increasing recognition as potential alternatives, owing to their wide range of bioactive molecules and multifaceted antimicrobial actions. Natural compounds such as berberine, curcumin, quercetin, allicin, and epigallocatechin gallate (EGCG) have shown significant inhibitory activity against *S. aureus*. These phytochemicals act through diverse mechanisms, including disruption of bacterial membranes, inhibition of efflux pumps, suppression of resistance-associated genes, and restoration of antibiotic effectiveness—providing both direct antibacterial action and synergistic enhancement with existing drugs.

Despite this promise, several barriers restrict their clinical application. Variability in phytochemical concentration, poor solubility, limited absorption, and potential adverse effects hinder reproducibility and therapeutic reliability. Furthermore, difficulties in standardizing herbal formulations, insufficient large-scale clinical evidence, and complex regulatory pathways limit their integration into conventional medicine. Overcoming these obstacles requires robust standardization techniques, advanced formulation strategies, and collaborative research approaches.

Looking ahead, innovations such as nanotechnology-based delivery systems, omics-driven mechanistic insights, and artificial intelligence-guided drug discovery may accelerate the development of effective herbal therapies. Moreover, ensuring sustainable cultivation and conservation of medicinal plants is vital for future availability.

Overall, herbal therapeutics hold strong potential as complementary or adjunct options against resistant *S. aureus*, provided that scientific, technological, and regulatory gaps are systematically addressed.

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