

DOI: [doi.org/10.55627/ppc.003.002.0397](https://doi.org/10.55627/ppc.003.002.0397)**Review Article****Medicinal Remedies for the Treatment of Methicillin-Resistant Staphylococcus Aureus**Nida Saleem<sup>1\*</sup>, Yu-Cheng Chen<sup>2</sup><sup>1</sup>Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan<sup>2</sup>Institute of Health & Society, University of Oslo, Norway.\*Correspondence: [nida.scps@stmu.edu.pk](mailto:nida.scps@stmu.edu.pk)

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**Abstract**

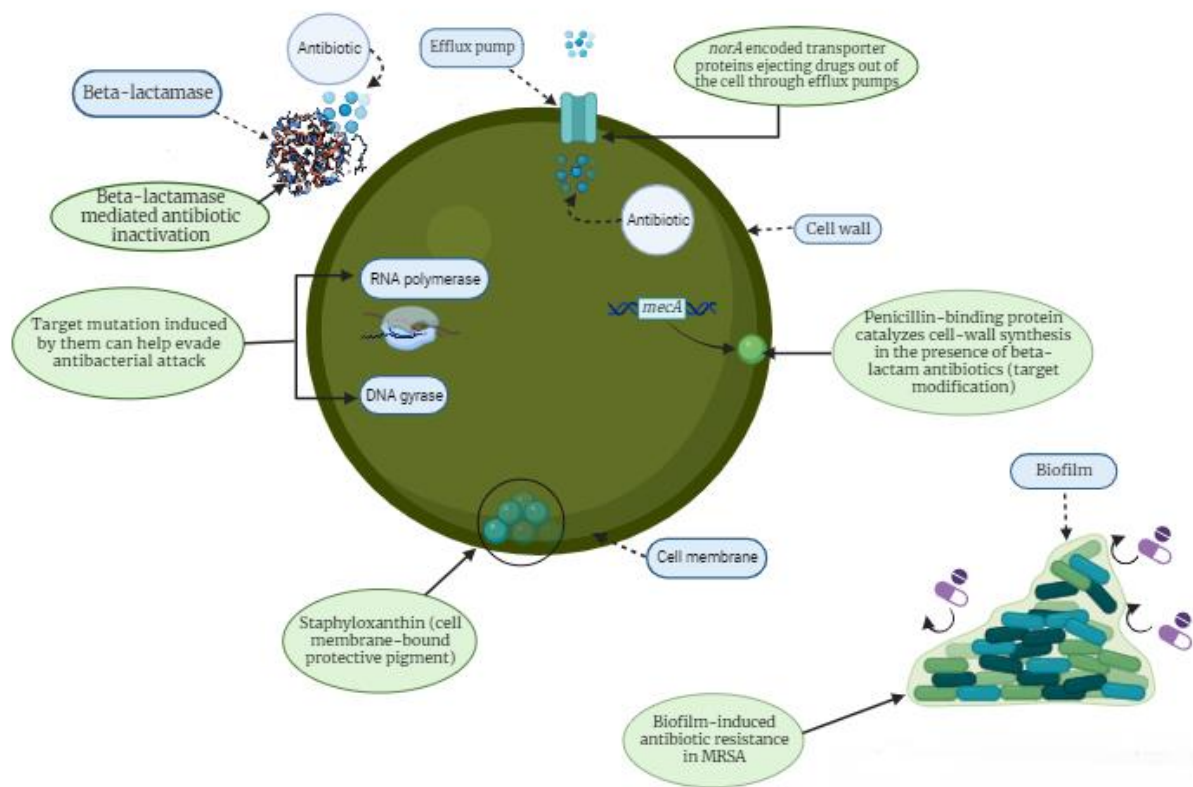
Antimicrobial resistance has led to the rise of formidable microbes like methicillin-resistant Staphylococcus aureus (MRSA). This infection can be acquired at the hospital and in a community, making the search for efficient treatment critical, given the rise in inefficacy of conventional treatments such as vancomycin. Phytocompounds can offer protection against these threats. They not only have the ability to kill MRSA but also enhance its susceptibility to previously ineffective antimicrobial agents. Plant-derived anti-MRSA agents can produce therapeutic effects comparable to some conventional treatments, and in some cases, they may even outperform an antibiotic. This article provided many examples of botanical compounds that have proven potent agents against MRSA in both in vitro and in vivo studies. These compounds achieve these effects by inhibiting the resistance mechanisms in MRSA, breaking down its defenses, making it vulnerable, and eventually killing it. Many of these compounds are inherently bactericidal; however, they may produce a synergistic response when combined with allopathic antibiotics. For example, plumbagin, from *Plumbago zeylanica*, not only disrupts MRSA cell wall morphology, eliciting cytoplasmic changes but also produces a synergistic effect with ciprofloxacin and piperacillin. Moreover, honokiol and magnolol glycosides, from *Magnolia officinalis*, reversed the quintessential resistance of MRSA by repressing genes, responsible for resistance development. The possibilities are indeed endless, but further research and financial investments are required for proper drug development.

**Keywords:** Phytocompounds, medicinal plants, resistance, antimicrobial, methicillin-resistant staphylococcus aureus, herbal medicine

**1. Introduction**

The Staphylococcus genus has eighty-one species and numerous subspecies, while Staphylococcus aureus (*S. aureus*) is among its most prodigious and significant species in terms of mammalian pathogenicity (Haag, Fitzgerald, and Penadés 2019). *S. aureus*, which translates to "golden cluster seed," is a coccus-shaped, gram-positive, non-spore-forming, non-motile, opportunistic bacterium. Its biochemical profile includes the production of nucleases, proteases, collagenases, and  $\beta$ -lactamase enzymes (Shoib et al. 2023). One of its most notorious variants methicillin-resistant *S. aureus* (MRSA) first appeared in the United

Kingdom in 1961, It is intrinsically resistant to all beta-lactam antibiotics. The pathogen has evolved and continues to outsmart available antibiotics (Azzam et al. 2023). Notably, traditional antimicrobial treatments have proven less effective, often associated with low efficacy, excessive side effects, and toxicity, particularly nephrotoxicity. Moreover, MRSA is no longer confined to the hospitals, it thrives in the communities as well. Interestingly, community-associated-MRSA (CA-MRSA) is usually associated with high morbidity, mortality, and economic burden worldwide, and any history of exposure to the community or the healthcare



**Figure 1: Antibiotic resistance mechanisms employed by MRSA.**

environment has now poor predictive value for distinguishing CA-MRSA and hospital-acquired-MRSA (HA-MRSA). Old anti-MRSA molecules often have unpredictable activity over CA-MRSA strains. Furthermore, some of these agents lack concrete evidence of safety and efficacy, and combination therapy is not advised for routine use (Vena et al. 2023); it is high time that the researchers looked for alternative and safer compounds from natural sources. This is a public health emergency and should be dealt with accordingly.

### 1. Epidemiology of MRSA

A systematic review and meta-analysis study found that the pooled global prevalence of MRSA was 14.69% (95% CI 12.39-17.15%; 16,793/164,717) (Hasanpour et al. 2023). Moreover, the prevalence in Pakistan, Nepal, India, Sri Lanka, and Bangladesh was 17.20% (95%CI; 10.70%, 24.85%),

8.83% (95%CI; 6.77%, 11.11%), 5.65% (95%CI; 3.65%, 8.03%), 22.56% (95%CI; 4.93%, 47.83%), and 4.93% (95%CI; 1.88%, 9.20%), respectively (Giri et al. 2023). This study also concluded that the prevalence of MRSA carriage is slightly higher in South Asia than in the European and American nations, which could lead to an outbreak if the propagation of MRSA were to continue at this rate (Giri et al. 2023).

In 2013, annual health costs due to CA-MRSA infections averaged 3 billion dollars (Lee et al. 2013). Infections from CA-MRSA are associated with high morbidity, mortality, and economic burden worldwide (Vena et al. 2023). The latest study, conducted in the USA, found that the cost of postoperative MRSA joint infection treatment was US\$40,919.13 per patient and that MRSA screening had only a minor impact on infection prevention (Suratwala et al. 2023). Similarly, an Australian research paper calculated that

nosocomial MRSA costs their healthcare system an additional AUD\$24 million (Wozniak et al. 2022). However, an alarming situation has arisen since CA-MRSA has disseminated into hospitals and HA-MRSA has managed to cross the hospital boundaries into communities (Lynch and Zhanel 2023).

## 2. MRSA Pathophysiology and Conventional Treatment Options

Following exposure, MRSA deploys an array of potential virulence factors, which includes surface proteins called “microbial surface components recognizing adhesive matrix molecules” (MSCRAMMs). These factors assist the pathogen in binding to fibrinogen, fibronectin, and collagen fibers in host cells, and subsequently attacking host tissues. This can lead to infections of prosthetics, bones, joints, and endovascular system (Menzies 2003).

MRSA exhibits resistance to penicillin-like antibiotics such as penicillin, amoxicillin, oxacillin, and methicillin in *S. aureus*. Treatment options for MRSA include glycopeptide antibiotics, cyclic lipopeptide antibiotics, cephalosporins, and oxazolidinone antibiotics. The most representative examples of these antibiotics are vancomycin, daptomycin, ceftaroline, and linezolid (Liu et al. 2021).

However, the frequent use of first-line drugs like vancomycin for MRSA has multiplied the number of resistant strains, namely vancomycin intermediate-resistant *S. aureus* and vancomycin-resistant *S. aureus* (Liu et al. 2021).

## 3. The Scourge of Resistance and its Development Mechanisms

In addition to man-made circumstances for antibiotic resistance such as methicillin misuse and abuse, which led to its creation, MRSA has further evolved to resist conventional infection treatment plans. For example, *S. aureus* possesses a diverse virulence profile that influences tissue invasion, membrane damage, and intracellular persistence, making it one of the most prolific

human pathogens. Additionally, the presence of particular genotypes has been associated with antimicrobial resistance (Lynch and Zhanel 2023). The mechanisms of resistance development may include:

### 3.1. $\beta$ -lactamase Enzymes

This strategy developed in MRSA to hydrolytically cleave antibiotic molecules, rendering them ineffective against the pathogen (Murphy, Walshe, and Devocelle 2008).

### 3.2. *MecA* Gene and Penicillin-Binding Proteins (PBP2a)

When MRSA comes into contact with lactam-bearing antibiotics, *mecA* gene is activated and translated to penicillin-binding protein 2a (PBP2a)(Chiu et al. 2021). This protein reduced binding affinities for antibiotics (Murphy, Walshe, and Devocelle 2008).

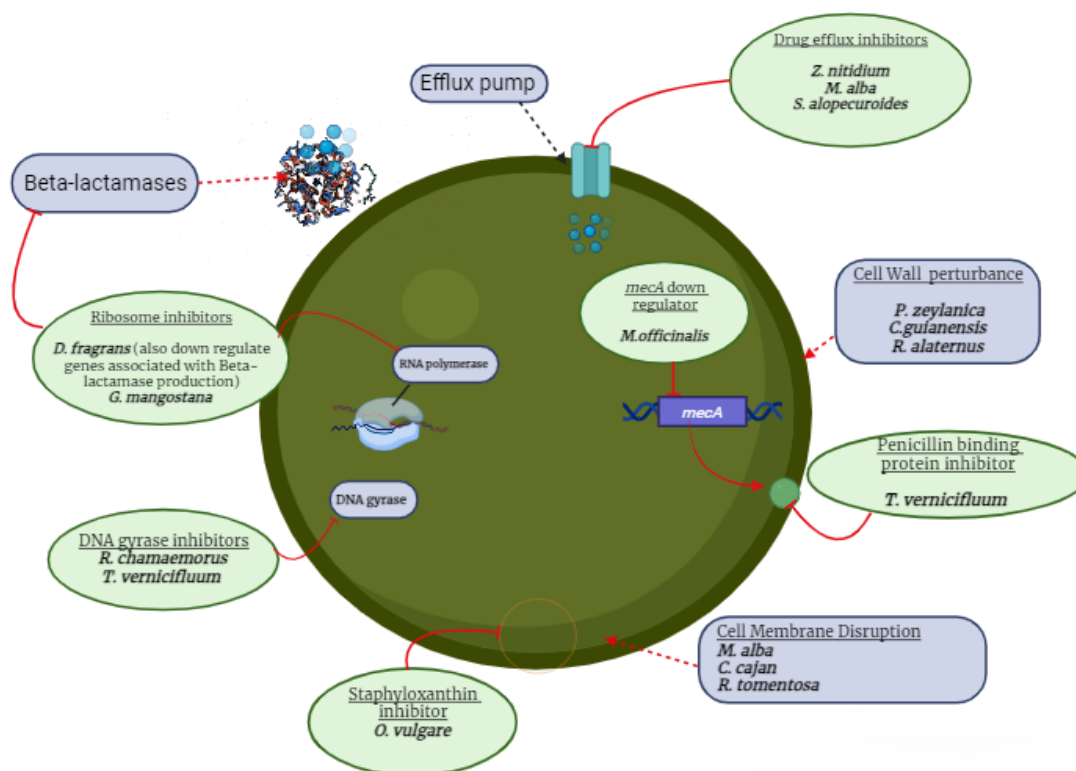
*mecA* expression is regulated by upstream *mecR*. Furthermore, *mecR* includes two genes, *mecI* (encoding a transcriptional regulator to suppress *mecA*) and *mecR1* (encoding a membrane-bound signal transduction protein to activate *mecA*) (Chiu et al. 2021).

### 3.3. Biofilm Formation Mediated Resistance and Associated Genes

Studies report a positive correlation between biofilm formation and resistance development in MRSA. In a systematic review, the highest frequency of biofilm-related genes was observed for the *icaD* gene (67.7%) followed by *clfA* (64.7%) (Hosseini et al. 2020).

### 3.4. Staphyloxanthin and Associated Genes

Staphyloxanthin, a golden-yellow pigment produced by *S. aureus*, is a defense mechanism against reactive oxygen species and neutrophil-based host defenses. Additionally, this pigment contributes to membrane stability, assisting and ensuring MRSA survival in stressful conditions. It is produced by the function of various enzymes encoded by the crtOPQMN operon. Particularly, crtM encodes dehydrosqualene synthase, which catalyzes the first step of the staphyloxanthin biosynthesis and crtN encodes dehydrosqualene desaturase. Targeting the crtM gene resulted in



**Figure 2: Mechanisms of action of anti-MRSA phytocompounds.**

white colonies (denoting a disruption of the gene's activity) (Valliammai et al. 2021, Pelz et al. 2005).

### 3.5. Factors essential for methicillin resistance (*fem*)

Proteins encoded by the *fem* genes (*femA*, *femB*, and *femX* proteins) form a specific structure of peptidoglycan precursors to help microbes resist methicillin; it is hypothesized that it does not affect PBP2a production. The suppression of *fem* gene expression can potentially reduce the resistance to  $\beta$ -lactam antibiotics (Sharif et al. 2009).

### 3.6. Efflux pumps encoding genes

Multidrug-transporter proteins are encoded by *sarA*, *qacA*, *qacB*, *smr*, *norA* and *mdeA*. These genes have been identified to be culpable for resistance to antimicrobial agents in *S. aureus* (Kawai et al. 2009)

### 3.7. Horizontal gene transfer

Resistance can be induced by horizontal gene transfer, mediated by plasmids or other mobile

genetic elements, or mutations in chromosomal genes (Liu et al. 2021).

## 4. Anti-MRSA Compounds from Natural Sources

Throughout history, mankind has relied on plant-based treatment remedies (Hussain et al. 2010, Imran et al. 2012, Al Mughairbi et al. 2021). A similar approach can be adopted to tackle modern threats like antimicrobial resistance. This review article explores various anti-MRSA phytocompounds that have been empirically studied. These plant-based chemicals target resistance mechanisms and structures that make MRSA invincible to various antimicrobial agents. Moreover, they have the full potential to become the future of anti-MRSA therapy.

### 5.1. *Zanthoxylum nitidum*

*Z. nitidum* has a history of use as an analgesic and hemostatic herbal remedy. To evaluate its potential against MRSA, various compounds were

extracted from the dried roots of *Z. nitidum* and tested in vitro and in vivo. In vitro results showed that MRSA was susceptible to benzophenanthridine alkaloids, through minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). The alkaloids achieved a MIC of 32–64 µg/ml, whereas all the strains were resistant to ampicillin (MIC = 256 µg/ml), methicillin (MIC = 128–256 µg/ml), and berberine (MIC = 128 µg/ml). On the other hand, the tested strain of bacteria resisted ampicillin, methicillin, and berberine doses. Furthermore, the above-mentioned alkaloids produced a synergistic effect with ampicillin, leading to cell membrane wrinkling and subsequent rupture (bactericidal effect). It was observed that one of the benzophenanthridine alkaloids increased ampicillin susceptibility in MRSA by inhibiting the microbial efflux pump. In vivo efficacy was demonstrated using a Murine model of skin infection, where the alkaloid-ampicillin combination significantly healed the MRSA-induced skin infection in mice (Zeng et al. 2022).

### 5.2. *Couroupita guianensis*

*Couroupita guianensis*, colloquially known in Brazil as 'Abricó-de-Macaco' has a traditional history of use as an antihypertensive, analgesic, and anti-inflammatory agent. In a study aimed at exploring the antibacterial effects of *C. guianensis*, particularly against MRSA, various flower extracts were prepared. In-vitro testing by using the agar diffusion method showed its alcoholic extract was effective against MRSA. MIC of dichloromethane extraction of *C. guianensis* was observed at the dose of 156 µg/ml, while for its active compound, tryptanthrin (couroupitine), an indolic alkaloid, it was 62.5 µg/ml. Furthermore, the electron microscopy analysis revealed MRSA treated with sub-MIC of tryptanthrin had significant ultra-structural changes in its cells. The morphological alterations include changes in cell shape, increased cell wall thickness, differences in DNA distribution, the presence of membrane invaginations, and the formation of mesosome-

like structures, indicating a potential loss of cell viability compared to untreated MRSA cells. Interestingly, no cell lysis was observed despite these structural changes. However, these morphological changes were consistent with previous findings related to the effects of antimicrobial compounds (Costa et al. 2017).

### 5.3. *Origanum vulgare*

Carvacrol, also known as 5-isopropyl-2-methylphenol, is an essential oil commonly found in the plant *Origanum vulgare* (Lamiaceae). An in-vivo and in-vitro investigation into its antibacterial activity yielded encouraging results. At 75 µg/ml, carvacrol inhibited MRSA biofilm by 93% and reduced the biofilm formation on polystyrene and glass surfaces. Moreover, a reduction in microcolony formation and a collapsed structure of the biofilm were confirmed upon microscopic analyses. In addition, it significantly reduced the biofilm-associated slime and extracellular polysaccharide synthesis and strongly inhibited the antioxidant pigment staphyloxanthin and its intermediates' synthesis in MRSA. The dual inhibition enhanced MRSA susceptibility to oxidants and healthy human blood. A downregulation in *sarA*-mediated biofilm gene expression and staphyloxanthin-associated *crtM* gene expression was also observed. Furthermore, the in-vivo efficacy of carvacrol against MRSA infection was demonstrated using the model organism 'Galleria mellonella'. The results confirmed that carvacrol was nontoxic to the larvae and highlighted its potential in rescuing MRSA-infected organisms (Selvaraj et al. 2020).

### 5.4. *Garcinia mangostana*

To investigate the anti-MRSA effects of *Garcinia mangostana* (Guttiferae), tannins were extracted from its pericarp. The extract underwent both in-vivo and in-vitro analyses. The extract exhibited significantly stronger MRSA inhibition compared to erythromycin. MRSA strain DMST20651, known for its strong resistance to oxacillin, was impressively inhibited by the phytoextract with an MIC of 14 µg/ml, while the MIC for oxacillin was

>400 µg/ml. Moreover, it also decreased the number of MRSA colonies over the period of ten days of observation. Furthermore, MRSA DMST20651 was selected for in-vivo superficial wound infection in mice, and the *G. mangostana* extract completely healed the infection. It also reduced MRSA-infection-associated inflammation at the wound site by decreasing mRNA levels, and restoring gene expression of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and TLR-2 to normal. In contrast, untreated wounds showed higher expression of these genes and inflammation-induction (Tatiya-aphiradee, Chatuphonprasert, and Jarukamjorn 2019). The researchers believed that the tannin constituents of *G. mangostana* pericarp potentially inhibited extracellular microbial enzymes, leading to the deprivation of essential substances required for microbial growth (Scalbert 1991).

### 5.5. *Morus alba*

To observe the anti-MRSA activity of *Morus alba* (Moraceae) in in-vivo and in-vitro setups, various compounds from the root bark of *M. alba* were separated through column chromatography and identified using spectroscopic methods. With MIC values ranging from 2 to 16µg/ml, the analysis indicated that geranyl and prenyl units of extracted compounds displayed strong anti-MRSA activity. Notably, these compounds exhibited a persistent antimicrobial effect, displaying concentration-dependent and time-dependent killing properties. For in-vivo analysis, the active fraction MA-6 reduced bacteria in the liver, spleen, and kidney, in addition to lowering mortality of acutely infectious mice, which was more promising than that of the positive drug berberine chloride. In the mechanism of action evaluation, it was identified that kuwanon O (flavonoid) damaged bacterial cell membranes, facilitating the accumulation of antibiotics within the bacterial cells. Additionally, *M. alba* compounds, MA-6, and kuwanon O, inhibited the efflux of drugs, such as methicillin, reducing its MIC by 3-fold, making MRSA susceptible to methicillin (Zhu et al. 2021).

### 5.6. *Cajanus cajan*

To understand the antimicrobial effect of longistylin A, a stilbene isolated from the leaves of *Cajanus cajan* (Fabaceae), an investigation was conducted using both in-vivo and in-vitro methods. Longistylin A exhibited impressive anti-MRSA activity with a MIC of 1.56µg/ml and demonstrated rapid bactericidal activity, outperforming vancomycin with a 3-log decrease in MRSA survival within 8 hours. In the in-vivo study, topical treatment of a skin injury with longistylin A improved wound healing and closure in an MRSA-infected wound-healing mouse model. After 3 days of treatment, MRSA bacterial count declined in the wounded region, decreased the immune cell accumulation at the injury site, and alleviated the induction of the inflammatory cytokines TNF- $\alpha$  and IL-6 in the serum. The antimicrobial activity was attributed to the ability of longistylin A to perturb the bacterial cell membrane, change the membrane potential, and subsequently increase membrane permeability. Importantly, this caused harm to the bacteria while causing relatively less damage to immune cells, such as murine macrophages (Wu et al. 2020).

### 5.7. *Plumbago zeylanica*

To assess the pharmacological effects of plumbagin, a bicyclic naphthoquinone, an in-vitro analysis was conducted on extracts from its source plant, *Plumbago zeylanica* (Plumbaginaceae). Notably, against 100 MRSA isolates, including some multi-drug-resistant (MDR) phenotypes, the active compound consistently exhibited activity with a narrow MIC range of 4–8 µg/ml. Moreover, the time-kill study showed 99% kill, 8 hours after exposure to plumbagin, of a reference MRSA strain. In the combination MIC study, plumbagin exhibited synergistic effects with ciprofloxacin and piperacillin. The transmission electron micrograph, of the plumbagin-treated reference MRSA strain, confirmed cell wall and cytoplasmic alterations. Interestingly, the anti-MRSA activity of plumbagin was not impacted by MDR. This study represents the first investigation into the antimicrobial action of plumbagin and highlights

**Table 1: Plants and phytochemicals showing activity against MRSA.**

Plant	Family	Part Used	Compound	Class	Activity	Reference
<i>Zanthoxylum nitidum</i>	Rutaceae	Dried roots	Benzophenanthridine	alkaloids	Efflux pump inhibition	(Zeng et al. 2022)
<i>Couroupita guianensis</i>	Lecythidaceae	Flowers	Tryptanthrin (aka Couroupitine)	Indolic alkaloid	Alterations in bacterial cellular structure	(Costa et al. 2017)
<i>Origanum vulgare</i>	Lamiaceae	Leaves	Carvacrol	Essential oil	Inhibits staphyloxanthin synthesis	(Selvaraj et al. 2020)
<i>Garcinia mangostana</i>	Guttiferae	Pericarp	Tannins	Tannins	Microbial enzyme inhibition, deprivation of essential substances	(Tatiya-aphiradee, Chatuphonprasert, and Jarukamjorn 2019)
<i>Morus alba</i>	Moraceae	Root bark	kuwanon O	Flavonoid	Enhanced permeation, drug efflux inhibition.	(Zhu et al. 2021)
<i>Cajanus cajan</i>	Fabaceae	Leaves	Longistylin A	Stilbene	Increased membrane permeability.	(Wu et al. 2020)
<i>Plumbago zeylanica</i>	Plumbaginaceae	Roots	Plumbagin	Bicyclic naphthoquinone	Cell wall and cytoplasmic changes.	(Periasamy et al. 2019)
<i>Rubus chamaemorus</i>	Rosaceae	seeds	sanguin H-6	oligomeric ellagitannin	MRSA DNA-gyrase inactivation	(Aguilera-Correa et al. 2021)
<i>Rhamnus alaternus</i>	Rhamnaceae	Whole plant	emodin	anthraquinone	Morphological alterations of the cell wall	(Zeouk et al. 2021)
<i>Carex baccans</i>	Cyperaceae	Fruit	Curcusinol	stilbenoid	Impaired biosynthesis	(Liu et al. 2024)
<i>Sophora alopecuroides</i>	Fabaceae	Roots	sophoraflavanone G	tetrahydroxyflavanone	inhibits norA efflux pump	(Sun et al. 2020)
<i>Rhodomyrtus tomentosa</i>	Myrtaceae	Leaves	Rhodomyrtosone B	acylphloroglucinol	Perturbation of bacterial membrane	(Zhao et al. 2019)
<i>Dryopteris fragrans</i>	Dryopteridaceae	Whole plant	aspidinol	phloroglucinol derivative	Inhibition of the formation of ribosomes.	(Hua et al. 2018)
<i>Toxicodendron vernicifluum</i>	Anacardiaceae	bark and stem	2,3,3-trimethyl-Octane and Benzoic	Organic compounds	Affects NBTI and PBP2a	(Saravanakumar et al. 2019)
<i>Magnolia officinalis</i>	Magnoliaceae	Bark	Honokiol and magnolol	glycosides	Reduced resistance	(Chiu et al. 2021)

the need for further research (Periasamy et al. 2019).

### 5.8. *Rubus chamaemorus*

To establish the anti-MRSA efficacy of *Rubus chamaemorus*, of family Rosaceae, sanguin H-6 (ellagitannin) was separated from its seeds and subjected to in-vivo and in-vitro experiments. For the in vitro assessment, the effect of the extract on the biofilm development of MRSA was observed. Sanguin H-6 significantly decreased the biofilm growth between 85.1%- 91.1% at 0.25 mg/ml and 90.7%-92.4% at 0.5 mg/ml in all three MRSA strains compared to the control. It also inhibited the 24-hour mature MRSA film development between 31.6%- 52.8% at 0.25 mg/ml, and 44.2%-71.1% at 0.5 mg/ml compared to the control, showing a concentration-dependent effect. The anti-MRSA effects were further evaluated successfully through biofilm development in a wound-like medium, with reductions of 77.2% and 85.3% at 0.5 mg/ml compared to the control. Sanguin H-6 showed promising results in countering MRSA infection development in an in-vivo wound model. Twenty-four hours after MRSA exposure, the wound area increased significantly (11%) in the control group ( $p$ -value = 0.0206) but decreased significantly (10.5%) in the sanguin H-6 treated group ( $p$ -value = 0.0206). The study concluded that sanguin H-6 could potentially be used as a prophylactic agent in surgical sites to avoid postoperative MRSA infections (Aguilera-Correa et al. 2021).

### 5.9. *Rhamnus alaternus*

*Rhamnus alaternus* (Rhamnaceae) has been traditionally used by Moroccan traditional medicine practitioners for treating skin infections. To empirically understand its efficacy, a bio-guided fractionation of *R. alaternus* was done by using successive chromatographic separations. This was followed by nuclear magnetic resonance and mass spectrometry analysis which yielded emodin, an anthraquinone. Emodin was subjected to in-vitro evaluation against MRSA. The extract of *R. alaternus* demonstrated the most potent inhibitory effect with a MIC of 0.5 mg/ml against

MRSA, and emodin exhibited the most active MICs, ranging between 15.62 and 1.95  $\mu$ g/ml, while the other extracts showed MICs between 4 and 16 mg/ml. Moreover, emodin did not display toxicity toward murine macrophage cells. However, its low solubility, poor bioavailability, and limited oral absorption may hinder its development into a pharmaceutical product; this barrier can be overcome by further research and using modern drug-engineering methods (Zeouk et al. 2021).

### 5.10. *Carex baccans*

*Carex baccans* (Cyperaceae) is a significant herb from an ethnopharmacological perspective in Chinese traditional medicine. To understand this, an investigation into the substance responsible for the antimicrobial activity against MRSA, in both in-vivo and in-vitro settings, was conducted. A bioactivity-guided isolation method was used to extract and identify the active compound, curcusinol, from *C. baccans* fruit. In-vitro the active compound exhibited significant bactericidal and anti-biofilm activities against MRSA. *C. baccans* fruit 95% ethanol crude extract exhibited antibacterial activity against gram-positive bacteria at a dose of 50 $\mu$ g/ml. Furthermore, it acted as an antibiotic adjuvant, enhancing the activity of various commonly used antibiotics against both gram-positive and gram-negative MDR bacteria without cytotoxicity to mammalian cells at 64  $\mu$ M. Regarding the mode of action, curcusinol significantly affected the biosynthesis of arginine, cysteine, and methionine, in addition to alanine, aspartate, and glutamate metabolism, in MRSA cells under stress. Additionally, in-vivo, curcusinol effectively treated MRSA-infected mice skin wounds, leading to accelerated wound healing (Liu et al. 2024).

### 5.11. *Sophora alopecuroides*

Sun et al. 2020 conducted a study to discover anti-MRSA natural compounds with synergistic antibacterial properties from traditional Chinese herbs that were not substrates for the efflux mechanisms of MRSA and could potentially overcome bacterial MDR by novel mechanisms.

For this purpose, sophoraflavanone G (a tetrahydroxyflavanone) was isolated and studied from the roots of *S. alopecuroides* (Fabaceae). In-vivo, MICs of sophoraflavanone G and norfloxacin were determined to be 4 mg/L and 32 mg/L, respectively, against MDR *S. aureus*. While it did not show any inhibitory effect alone, sophoraflavanone G demonstrated a significant synergistic antimicrobial effect with norfloxacin, resulting in a 16-fold reduction in the MIC of norfloxacin (from 32 mg/L to 2 mg/L). This synergism was elicited by the inhibition of norA efflux pumps in the norfloxacin-resistant strain under study. This synergy can be harnessed to reduce the dose of norfloxacin required for antibacterial efficacy, potentially decreasing the incidence of norfloxacin-induced serious side effects and toxicity during its clinical use (Sun et al. 2020).

#### 5.12. *Rhodomyrtus tomentosa*

In Chinese traditional medicine, *Rhodomyrtus tomentosa* (Myrtaceae) leaves have been traditionally used for their antibacterial properties. Rhodomyrtosone B, a natural acylphloroglucinol, is thought to be the principal ingredient responsible for the antimicrobial qualities. To understand its mechanism of action and anti-MRSA activity in-vivo and in vitro, a study was conducted. The results showed that rhodomyrtosone B exhibited distinct antibacterial activities against MRSA with an MIC of 0.62–1.25 µg/ml. Moreover, it displayed much more rapid bactericidal activity against MRSA than that of vancomycin. Notably, rhodomyrtosone B had a weak cytotoxicity to mammalian cells (IC<sub>50</sub> >14 µg/ml and exhibited advantageous specificity against selected gram-positive bacterial membranes rather than RBCs. Furthermore, in-vivo, MRSA-induced skin ulcer formation in a murine model of MRSA infection was significantly attenuated with a single dose of 40 µg of rhodomyrtosone B per mouse. Membrane-targeting experiments exhibited significant bactericidal activity by perturbing bacterial

membrane potential and subsequently increasing membrane permeability (Zhao et al. 2019).

#### 5.13. *Dryopteris fragrans*

A study with the aim of investigating the anti-MRSA qualities of aspidinol a phloroglucinol derivative extracted from *Dryopteris fragrans* (Dryopteridaceae), was conducted. The study involved treating MRSA isolates with aspidinol and determining the differential expression of genes and associated pathways. The key in-vivo and in-vitro findings suggested that aspidinol displayed significant anti-MRSA activity with MIC of 2 µg/ml, achieving an antibacterial effect comparable to that of vancomycin. In the lethal septicemic mouse study, a dose of 50 mg/kg of either aspidinol or vancomycin provided significant protection from mortality equally. Whereas, in the non-lethal septicemic mouse study, both aspidinol and vancomycin significantly reduced the mean bacterial load in murine organs, including the spleen, liver, and lungs. Interestingly, aspidinol permeated cellular membranes and killed MRSA located inside eukaryotic cells at the dose of 20 µg/ml, reducing the intracellular bacterial load by 100-fold. In contrast, linezolid (20 µg/ml) and vancomycin (10 µg/ml) were successful at reducing the bacterial burden inside the infected macrophages by 5- to 10-fold only. This ability of MRSA to internalize into mammalian cells might result in long-term host colonization and lead to clinical failures. Post-treatment RNA-seq and RT-PCR experiments revealed that the inhibition of ribosome formation was predominantly the mechanism by which *S. aureus* cells were killed by aspidinol. Additionally, there was down-regulation of most genes associated with β-lactam antibiotic resistance, as well as genes involved in pathways related to amino acid synthesis, ribosome structure, iron transport, virulence factors, and more (Hua et al. 2018).

#### 5.14. *Toxicodendron vernicifluum*

*Toxicodendron vernicifluum* (Anacardiaceae) exhibits antibacterial qualities in addition to its anticancerous activities. In a study by

Saravanakumar et al. in 2019, the anti-MRSA effects of *T. vernicifluum* were investigated through in-vivo and in-vitro methods. The methanolic bark extract of *T. vernicifluum* showed significant antibacterial activity with an impressive MIC of 7.12µg/ml, as compared to the seed extract of *T. vernicifluum* (MIC=9.25µg/ml). The bark extract was further analyzed in vivo through *C. elegans* animal experiment. The treatment with MRSA induced cell disruption, damage, and increased mortality of *C. elegans* as compared to the untreated and MBE-treated *C. elegans*. Moreover, *C. elegans* treated with the bark extract after MRSA exposure showed an increase in survival rate. Upon evaluation of the molecular mechanism of the MRSA cell death, induced by the extract, it was revealed that the compounds, such as 2, 3, 3-trimethyl-Octane and benzoic from the MBE, metabolized the novel bacterial topoisomerases inhibitor and PBP2a (Saravanakumar et al. 2019).

#### 5.15. *Magnolia officinalis*

*Magnolia officinalis*, a member of Magnoliaceae family, is not only used in Chinese traditional medicine but is also a part of Japanese ethnopharmacology. Honokiol and magnolol, two isomers isolated from *M. officinalis*, are used in food and cosmetics. To investigate its antibacterial qualities, an in-vivo and in-vitro examination was carried out by a group of researchers. Interestingly, despite the isomeric aspect of honokiol and magnolol, they had significantly different antimicrobial effects on the tested microbes, as the former showed better inhibition of MRSA growth on agar plates than the latter. The MIC dose of both the compounds against MRSA was 10µg/ml. However, the MBC of honokiol was 20µg/ml, while magnolol exhibited MBC against MRSA at 30µg/ml. Moreover, biofilm assay revealed that at 10 µg/ml honokiol and magnolol significantly inhibited the formation of microbial biofilms. In a biofilm removal assay, both honokiol and magnolol at a concentration of 5µg/ml were effective in removing preformed biofilms of MRSA. The results also indicated that at the dose

of 5µg/ml, both compounds had a significant impact on antibiotic-resistance gene expression. Honokiol significantly repressed the expression of *mecA*, *mecR1*, *femA*, *femB*, and induced the expression of *mecI*. Magnolol significantly repressed the expression of *mecA* and *mecI*, and upregulated *mecR1* expression. Due to the alteration in gene expression, when tested in combination with ampicillin, honokiol, and magnolol at low doses (1µg/ml) significantly reduced the drug-resistance property of MRSA. At concentrations below 2.5µg/ml, they were found to inhibit biofilm-related MRSA genes, like *icaA*. Furthermore, both 0.5µg/ml and 2.5µg/ml honokiol and magnolol treatments reduced *sarA* expression in MRSA (Chiu et al. 2021).

### 5. Discussion

An antibiotic compound from a botanical source is not a novel idea, but rather a revival of traditional medical practices that many consider outdated. With the rise in antimicrobial resistance due to affordability, leading to ease of access and over-prescribing of antibiotics (Laxminarayan and Chaudhury 2016), and bacterial evolution, looking for newer and robust antimicrobials is a need of the hour. The sum of the plethora of resistance mechanisms, the antibiotic resistome, is a serious threat to antibiotic discovery, development, and use. In addition to comprehending the resistance development mechanisms the modification of naturally occurring antibiotic scaffolds, or developing adjuvant therapies that overcome resistance mechanisms can aid in fighting the invisible enemy (Hobson, Chan, and Wright 2021). Out-of-the-box thinking is required, like combining plant-based antimicrobial compounds with mainstream antibiotics can reduce the dose required to achieve the antibacterial effect (Zeng et al. 2022). Furthermore, plants like *Magnolia officinalis*, *Plumbago zeylanica*, and *Sophora alopecuroides* yield compounds that have been empirically proven to have synergistic effects with modern antibiotics. In many instances, plant-derived anti-MRSA compounds were able to have

a therapeutic response superior to that of commonly used antibiotics. For example, rhodomirtosone B, derived from *R. tomentosa*, proved to be a more potent bactericidal agent than vancomycin (Zhao et al. 2019). Additionally, a study revealed that tannins possessed both bacteriostatic and bactericidal activity with MIC and MBC of 0.78 and 1.56 mg/ml, respectively, against all tested MRSA. Scanning and transmission electron microscopy of MRSA treated with tannins showed a decrease in cellular volume, indicating disruption of protein synthesis (Adnan, Ibrahim, and Yaacob 2017). This lends further credibility to the studies done by using tannins against MRSA, e.g. anti-MRSA tannins from *Garcinia mangostana* (Tatiya-aphiradee, Chatuphonprasert, and Jarukamjorn 2019). Interestingly, many phytochemicals, especially those mentioned in the article, are able to tackle specific resistance mechanisms, which makes them more attractive candidates for further research and development. This can bring forth better, cost-effective, and relatively safer antibacterial agents for dealing with dangerous threats like MRSA.

However, there are certain challenges that impede the implementation of these plant-based substances in the treatment of infections like MRSA. One of the major challenges is the development of effective extraction and purification systems for novel and safer plant-based antimicrobials (AlSheikh et al. 2020). Moreover, not all phytochemicals are suitable candidates for becoming a pharmaceutical product like *Rhamnus alaternus* (Zeouk et al. 2021), this weakness of plant-sourced anti-MRSA substances can be overcome by rationalizing their chemical synthesis, structural modifications, and optimizing drug-delivery methods for elevating their efficacy status. Furthermore, while there is a need to make nutrition, health, and disease research, and host genetics needs a part of the treatment equation, hypothesis-driven field trials, with proper controls, should also be mandatory to validate the safety, efficacy, and return of

investment of antibiotic alternatives (AlSheikh et al. 2020, Callaway et al. 2021).

## 6. Conclusions

The rise of resistance to antibiotics is a serious threat to public health, especially the rise of nosocomial infections, which turn hospitals into breeding grounds for lethal infections that can impact wider populations. The fear of superbugs is not unfounded, as the current status of antibiotic use is concerning and MRSA offers a glimpse into the grim future of how efficiently a bacterial cell can evolve. In many studies, mentioned in this review article, various phytochemicals performed well against MRSA. Kuwanon O flavonoid (*M. alba*) is among the most notable examples, as it produced a bactericidal response by hitting multiple targets. It not only damaged the cell wall and cell membrane of MRSA but also inhibited efflux pumps which led to intrabacterial drug accumulation. Furthermore, carvacol, an essential oil from plant *O. vulgare*, targeted MRSA by inhibiting staphyloxanthin pigment (a cell-membrane-bound protective pigment) making it vulnerable to hostile elements like antibiotics and reactive oxygen species. Rhodomirtosone B, extracted from the leaves of *R. tomentosa*, was found to produce a potent bactericidal response in MRSA, superior to that of vancomycin, by destabilizing the cell membrane potential and increasing its permeability. In addition, aspidinol (*D. fragrans*) permeated cellular membranes and killed MRSA located inside eukaryotic cells, reducing the intracellular bacterial load by 100-fold, whereas linezolid and vancomycin, at almost equal doses, reduced the bacterial burden inside the infected macrophages by 5- to 10-fold only, highlighting the impressive potency and efficacy of aspidinol. Moreover, these compounds have proven to be safe in both in-vivo and in-vitro studies. All stakeholders, including investors, researchers, and pharmaceutical companies should invest in these potent antibacterial phytochemicals for further exploration and proper drug development. Nature offers many

remedies to address the threat of drug-resistant bugs, with plant-based antibiotics being one of them. Increased investment in these avenues can provide physicians with better antimicrobial agents to combat the menace of MDR microbes like MRSA.

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The authors declare that they have no competing interests.

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### Authors Contribution

NS performed literature review, data collection and evaluation, literature search and manuscript preparation. YCC and NS refined manuscript for publication. The authors read and approved the final manuscript for publication.

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All the relevant data of this manuscript is available with the authors.

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