ORIGINAL ARTICLE

Adjuvant Herbal Therapy Combined with Antibiotics as Methicillin-Resistant *Staphylococcus aureus* (MRSA) Treatment: A Review

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ABSTRACT

Background. Antibiotics used to kill Methicillin-Resistant *Staphylococcus aureus* (MRSA) are often not effective, even stimulate resistance. To overcome this problem, herbal medicines may help improve antibiotics efficacy. Several herbal medicines have been reported for their unique potential in killing MRSA, either with similar or different mode of actions of the conventional antibiotics. In this case, an adjuvant therapy with herbal medicine is a promising option for the MRSA infections.

Objectives. This review aims to identify and elaborate the inhibitory mechanisms of anti-MRSA antibiotics and anti-MRSA herbal medicines, as well as to evaluate the potential of herbal adjuvant therapies when co-administered with anti-MRSA antibiotics.

Methods. A literature search was conducted using Google Scholar, PubMed, and Science Direct for publications from 2010 to 2024, with keywords 'Mode of Anti-MRSA,' 'Anti-MRSA,' 'herbal medicine,' 'MRSA,' and 'adjuvant therapy.' Eligibility criteria included full open-access Indonesian or English articles with detailed information on anti-MRSA mechanisms, herbal medicine against MRSA, and adjuvant therapy. Articles with only accessible abstracts were excluded. Selection involved title and abstract screening, followed by full-text review based on PICO framework. Data extraction captured essential details on study design, interventions, outcomes, and findings related to MRSA and adjuvant therapies.

Results. Using the keyword 'Mode of Anti-MRSA,' 160 articles were retrieved, with 11 included in the final analysis. Most anti-MRSA antibiotics target the cell wall, inhibit efflux pumps, or act on ribosomes. With the keywords 'Anti-MRSA' and 'herbal medicine,' 170 articles were retrieved, and nine were included. Anti-MRSA herbal materials show strong potential, acting not only on cell wall disruption, efflux pumps, and Penicillin-binding protein 2a (PBP2a) but also inhibiting phosphate kinase (PK), quorum sensing, and biofilm formation. For 'MRSA' and 'adjuvant therapy,' 210 articles were retrieved, with 20 included. Certain herbal materials in adjuvant therapy have shown promise in enhancing the efficacy of anti-MRSA antibiotics.

Conclusions. When combined with anti-MRSA antibiotic, adjuvant therapy with herbal materials is a promising alternative for treating MRSA infections.

Keywords: adjuvant therapy, herbal medicine, MRSA, penicillin-binding protein 2a, phosphate kinase, sortase, quorum sensing

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INTRODUCTION

Medication of methicillin-resistant *Staphylococcus aureus* (MRSA) in human infections is challenging. MRSA infections are common. Patients in long-term healthcare facilities or ICU are often colonized with MRSA. Most of nosocomial bacteremia and hospital-acquired pneumonia are also frequently caused by MRSA. In addition, MRSA itself is a problem because of its resistance to all kinds of antibiotics.[1,2] It is more difficult to eradicate antibiotic-resistant pathogenic bacteria, such as MRSA. Therefore, new effective antibiotic against MRSA or new treatment therapeutic approach are searched.[3]

The potential for MRSA to develop resistance makes the use of MRSA antibiotics less effective.[4] The antibiotic resistance limits therapeutic options for MRSA infection. In this case, as an alternative, anti-MRSA herbal materials may be an emerging new drug in the future. Hence, a search for alternative therapy for these infections is inevitable.[3,5,6] Previous studies report many herbal materials show potential for anti-MRSA treatment.[3] It has long been proven that herbal materials are a large and diverse source of antibacterial compounds including anti-MRSA.

This review aimed to compile information on the modes of action of antibiotics used for the treatment of MRSA infections; the modes of action of anti-MRSA herbal materials; and to give considerations on possible adjuvant herbal therapy combined with MRSA-antibiotics. Now is an opportune time to consider the future potential of herbal materials in adjuvant therapies to address the ongoing and evolving challenges of MRSA infections.

METHODS

Ethical Review

This study was approval by The Medical and Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Kristen Krida Wacana, with Ethics Approval Number: 1408a/SKLE/IM/UKKW/FKIK/KEPK/XII/2022.

Study Design

This literature review was conducted to compile information on the modes of action of antibiotics used to treat MRSA infections, the modes of action of anti-MRSA herbal materials, and considerations for potential adjuvant herbal therapies in combination with MRSA antibiotics. This review was conducted over a 20-year period, from January 1, 2004, to June 30, 2024. The definitions of the terms used in the study are as follows:

- **Methicillin resistant *Staphylococcus aureus* (MRSA):** It refers to a strain of *Staphylococcus aureus* bacteria that has developed resistance to methicillin and other beta-lactam antibiotics.
- **Herbal therapy/material:** It refers to natural products obtained from medicinal plants, used either in their raw or processed forms (extracts, powders, or essential oils) for therapeutic applications.
- **Adjuvant therapy:** It refers to a treatment given in addition to a primary therapy to enhance its effectiveness. In the context of infectious diseases, adjuvant therapies may include substances or treatments, such as herbal materials, that support and improve the efficacy of conventional antibiotics.
- **Antibiotics:** It refers to chemical substances that inhibit the growth of or kill bacteria. They are used to treat bacterial infections by targeting specific bacterial structures or functions, such as cell wall synthesis, protein synthesis, or DNA replication.
- **Anti-MRSA:** It refers to substances or treatments specifically designed to combat infections caused by MRSA. This can include antibiotics effective against resistant strains or alternative approaches, such as herbal therapies, to address the challenges posed by MRSA resistance.

Data Collection

Literature searches were conducted using various scientific databases, including Google Scholar, PubMed, and Science Direct, to ensure a comprehensive collection of relevant research articles. These platforms provided access to a wide range of studies on MRSA infections and adjuvant therapies. We used string “MRSA” OR "Methicillin-resistant Staphylococcus aureus" AND "herbal materials" OR "plant extracts" AND "adjuvant therapy" OR "alternative therapy" OR “complementary." To guide the literature review process, the PICO framework (Population, Intervention, Comparison, Outcome) was employed to define the key components of the research question and streamline the selection of relevant studies.

- **P (Population):** Studies that focused on adult or pediatric patients with **MRSA infections**, such as skin and soft tissue infections, pneumonia, or osteomyelitis were selected.
- **I (Intervention):** The literature search emphasized studies investigating **adjuvant therapies** in the treatment of MRSA, including combination antibiotic therapies, surgical interventions (e.g., abscess drainage), immunomodulatory treavtments, and decontamination strategies.
- **C (Comparison):** Articles comparing adjuvant therapies to **standard monotherapy** (e.g., vancomycin, clindamycin) or no adjuvant therapy were prioritized.
- **O (Outcome):** The focus was on studies evaluating **clinical outcomes**, such as infection resolution, mortality rates, prevention of reinfection, and antibiotic stewardship.

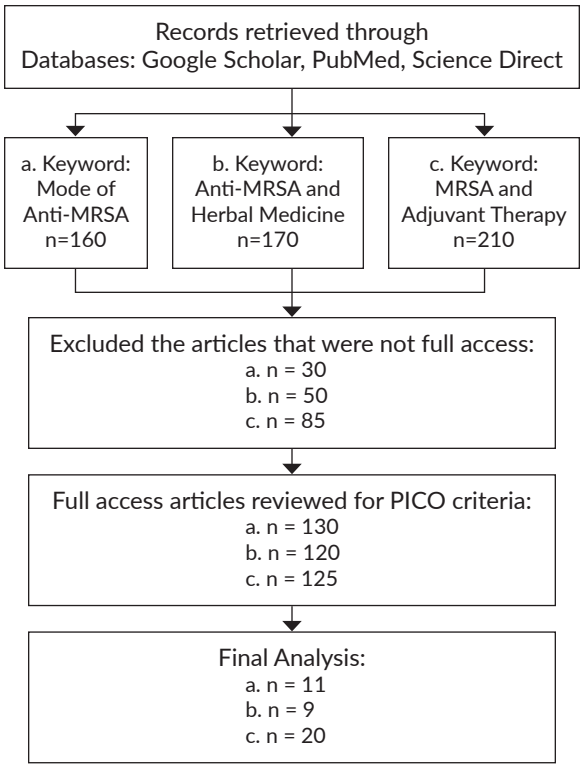

Figure 1. The scheme process to extract the data.

After collecting an initial set of sources, a thorough screening process was performed, where abstracts, keywords, and full texts were reviewed to ensure the studies met the defined PICO criteria. This rigorous selection process helped to identify high-quality, peer-reviewed articles that provided valuable insights into the impact of adjuvant therapies on MRSA infection management and outcomes (Figure 1). We made no assumptions regarding missing data.

Inclusion and Exclusion Criteria

Full open-access articles written in either Indonesian or English that provided detailed information on anti-MRSA mechanisms, herbal medicines targeting MRSA, and the use of herbal adjuvant therapies to enhance anti-MRSA effects, published between January 1, 2004 until June 30, 2024 were included in the study. Articles were excluded if they were only available as abstracts without full text, were not written in Indonesian or English, or did not contain specific details on anti-MRSA mechanisms, herbal medicine, or adjuvant therapy.

Data Review

Two independent reviewers conducted both structured and unstructured searches across relevant databases to identify studies related to MRSA infections and adjuvant herbal therapies. The first reviewer performed level 1 screening by evaluating the titles and abstracts of each publication for relevance to the study objectives. The second reviewer then conducted level 2 screening to determine the eligibility of the shortlisted studies based on pre-defined inclusion and exclusion criteria. Any discrepancies between the reviewers were resolved through discussion, ensuring a consensus was reached before finalizing the included records.

Data Extraction

After completing the manual screening, relevant data from the selected records were transferred to a data extraction grid and verified by both reviewers. The data were then synthesized, and an evidence gap map framework was created to visualize the synthesized findings. The extracted information from each selected study included: 1) the mode of action of anti-MRSA agents; 2) potential herbal materials and their outcomes; 3) mechanisms of action of the herbal materials; and 4) adjuvant therapies involving herbal materials, their respective outcomes, and their role in enhancing antibiotic efficacy.

RESULTS

Modes of Action of Anti-MRSA Antibiotics

Based on the literature, several antibiotics are used to treat Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (Table 1). These antibiotics operate through various mechanisms of action, each targeting different aspects of bacterial survival and replication. The modes of action of these antibiotics are listed in Table 1, highlighting their specific targets and how they disrupt MRSA's ability to thrive.

Herbal Medicine with Anti-MRSA Capacity

The antibacterial properties of herbal medicines are unique and characterized by specific inhibitory mechanisms that differentiate them from conventional antibiotics. Extracts or purified bioactive compounds obtained from various herbal materials have shown significant antibacterial activity against Methicillin-resistant *Staphylococcus aureus* (MRSA). A selection of these herbal materials with confirmed anti-MRSA activity is presented in Table 2. Their potential effectiveness against MRSA is quantified through various metrics, including the Inhibition Zone (IZ >10 mm), Minimum Inhibitory Concentration (MIC <2 mg/mL), and Minimum Bactericidal Concentration (MBC <3 mg/mL).[16-21] These measurements provide crucial insights into the efficacy of herbal medicines as potential alternatives or complements to traditional antibiotic therapies.

Modes of Actions of Anti-MRSA Herbal Materials

The results of the literature review indicate that there are several modes of action for herbal-derived antimicrobial agents used to treat MRSA, including targeting the efflux pump, penicillin-binding protein 2a, sortase, and biofilm formation (Figure 2 and Table 3).

Table 1. Antibiotic Therapy for *Staphylococcus aureus* and MRSA

Antibiotic	Category
Inhibition of bacterial cell wall biosynthesis	
Ampicillin[2]	β-lactam
Ceftaroline[4]	β-lactam
Cefotaxime[7]	β-lactam
Imipenem[8]	β-lactam
Oxacillin[9]	β-lactam
Penicillin[8]	β-lactam
Vancomycin[9]	Glycopeptide
Ribosomally active antibiotic	
Amikacin[7]	Aminoglycoside
Clindamycin[10]	Macrolide
Erythromycin[11]	Macrolide
Linezolid[12]	Axazolidinones
Mupirocin[13]	Carbapenem
Rifampicin[8]	Macrocyclic
Inhibition of DNA replication by inhibiting DNA topoisomerase and DNA-gyrase	
Ciprofloxacin[8]	Fluoroquinolone
Disruption of cell membrane function	
Daptomycin[12]	Cyclic lipopeptide
PVP-peptide[14]	Anti-microbial peptide
Cell-penetrating peptides (CPPs)[15]	Anti-microbial peptide

Figure 2. Targeting strategies of herbal medicine for eradication of MRSA.

Table 2. List of Potential Herbal Material (polar extracts) with Antimicrobial Effect on MRSA (IZ >10 mm, MIC <2 mg/mL, or MBC <3 mg/mL)

Species	Part	Extract	Outcomes		
			IZ mm	MIC mg/mL	MBC mg/mL
Alnus nepalensis[16]	Leaves	EtOH	ND	0.26-1.02	1.02->2.05
Artocarpus heterophyllus[17]	Leaves		ND	0.32	1.28
Blumea balsamifera (local name: sembung)[16]	Leaves	EtOH	ND	0.064-0.26	0.26-1.02
Brandisia hancei[16]	Leaves	EtOH	ND	0.032-0.064	0.13-0.26
Callisstemon rigidus[16]	Leaves	MeOH	ND	0.00125-0.08	ND
Camellia sinensis (local name: teh)[18]	Leaves	EtOH	11-25	1.8–7.5	ND
Carex prainii[16]	Leaves	EtOH		1.02-2.05	2.05
Celastrus orbiculatus[16]	Vane	EtOH		0.51-1.02	1.02-2.05
Cichorium endivia[19]	Seed Leaves	MeOH, H_2O	21.3	ND	ND
Curculigo orchioides[16]	Leaves	EtOH		0.26-0.51	0.51-2.05
Curcuma xanthorrhiza (local name: temu lawak) [16]	Rhizome	EtOH		0.5	ND
Cyclobalanopsis austrogaluca[16]	Leaves	EtOH		0.016-0.064	0.13-0.26
Dodonaea angustifolia[16]	Leaves	EtOH		0.59	1.17
Delonix regia[18]	Flowers	EtOH	16–23	5.0-7.5	
Eleutherine bulbosa[20]	Rhizome	EtOH		1.0	
Embelia burm[16]	Leaves	EtOH		0.51-1.02	1.02->2.05

Table 2. List of Potential Herbal Material (polar extracts) with Antimicrobial Effect on MRSA (IZ >10 mm, MIC <2 mg/mL, or MBC <3 mg/mL) *(continued)*

Species	Part	Extract	Outcomes		
			IZ mm	MIC mg/mL	MBC mg/mL
***Euonymus fortunei*[16]**	Vane	EtOH		0.51	1.02->2.05
***Evodia daneillii*[16]**	TBL	EtOH		0.032-0.064	0.064-0.26
***Garcinia mangostana* (local name: manggis)[16,21,22]**	Fruit shell	EtOH		0.05-0.40	0.1-0.4
		EtOH		0.05-0.40	0.10-0.40
		EtOH		0.19	0.39
***Garcinia Morella*[16]**	Leaves	EtOH		0.016-0.064	0.064-0.26
***Holarrhena antidysenterica*[18]**	Bark	EtOH	12-17	2.8–5.6	
***Illicium simonsii*[16]**	Leaves	EtOH		0.51-1.02	1.02->2.05
***Lawsonia inermis*[18]**	Leaves	EtOH	11-24	1.3–7.5	
***Machilus salicina*[16]**	Leaves	EtOH		0.51-1.02	1.02-2.05
***Mallotus yunnanensis*[16]**	Leaves	EtOH		0.008-0.032	0.064-0.26
***Mangliettia hongheensis*[16]**	Leaves	EtOH		0.008-0.13	0.032-0.51
***Melianthus comosus*[16]**	Leaves	EtOH	ND	0.39	1.56
***Melianthus major*[16]**	Leaves	EtOH	ND	0.78	3.12
***Meliosma squamulata*[16]**	Leaves	EtOH	ND	0.032-0.064	0.064-0.26
***Momordica charantia*[23]**	Fruit	EtOH	60%:10.8		
***Ocimum sanctum*[18]**		EtOH	13-20		
***Peltophorum ptercarpum*[16]**	Bark	EtOH	ND	0.1-0.8	6.3
***Psidium guajava*[16]**	Leaves	EtOH	ND	0.2-1.6	6.3
***Polygonum molle*[16]**	Leaves	EtOH	ND	0.26-0.51	1.02-2.05
***Punica granatum* (local name: delima)**	Fruit shell[21.24]	EtOH	ND	0.20-0.40	1.60-3.20
	Rind[18]	MeOH	11-27	1.30-8.20	ND
***Quercus infectoria* (local name: Majakani)[16,21]**	Nutgalls	EtOH	ND	0.20-0.40	0.40-1.60
		EtOH, H_2O	11.75-16.82	0.13	0.13-1.00
		EtOH	ND	0.4-3.2	3.2-6.3
***Schima sinensis*[16]**	Leaves	EtOH	ND	0.016-0.064	0.064-0.26
***Schisandra viridis*[16]**	Vane	EtOH	ND	0.064-0.26	0.26-1.02
***Sellaginella tamariscina*[16]**	Leaves	EtOH	ND	0.51-1.02	1.02-2.05
***Skimmia arborescens*[16]**	Leaves	EtOH	ND	0.016-0.0064	0.13-0.26
***Swietenia mahagoni*[16]**	Seed	EtOH		0.2-0.78	0.78-1.56
***Terminalia chebula*[18]**	Fruits	EtOH	17-27	1.8–7.8	
***Terminalia belerica*[18]**	Fruits	EtOH	18-27	1.5–8.2	
***Tinospira crispa*[16]**	Stem	EtOH		0.4-0.78	0.78-1.56
***Thymus vulgaris*[16]**	Leaves	EOs		0.057	ND
***Uncaria gambir*[16]**	Leaves	EtOH		0.4-0.8	3.2
***Withania somnifera*[16]**	Leaves	EtOH		1.56	6.25

TBL – tender branches and leaves, EtOH – ethanol, MeOH – methanol, EOs – essential oils, ND – not determined

Table 3. MRSA-Herbal Antibiotics with their Mode of Inhibition

MRSA-Natural antibiotic	Mode of inhibition
Targeting efflux pumps	
Cumin	Inhibit LmrS drug transport that involves multidrug efflux inhibition[25]
Hydantoin compound (PI8a)	inhibit efflux pump[26]
Limonene	Inhibit efflux pump[27]
α-pinene	Inhibit MRSA that carrying the TetK and MrsA proteins[28]
Alkaloids	Inhibit efflux pump, inhibit PK, QS, and intercalate bacterial DNA[29]
Reserpine	Inhibit multidrug resistance (MDR) efflux pump[30]
Cucurbitane-type triterpenoids from the aerial parts of Momordica balsamina	Inhibit efflux pump[31]
Diterpene isopimaric acid from crude hexane extract of the immature cones of Pinus nigra	Inhibit efflux pump[32]
Quinolines, indoles, pyridines, phenols, and sulfur-containing heterocycles	Inhibit efflux pump[33]
Targeting Penicillin-binding protein 2a (PBP2a)	
Flavonolignan Silibinin A	Support inhibitory activity of Ampicillin with inhibition PBP2a[34]
Epicatechin gallate	Reduce secretion of virulence-associated proteins, disturb cell membrane function and cell wall synthesis, disturb position PBP2a in bilayer[35]
Gallic acid and Luteolin containing ethyl acetate fraction from Pithecellobium clypearia	Suppress PBP2a expression, damage cell wall.[36]
Curcumin from Curcuma longa	Increase sensitivity of MRSA to antibiotics. Downregulate protein level of PBP2a[37]
Morin	Inhibit PBPsa and increase the sensitivity of MRSA to Oxacillin[38]
Quercetin 3-O-rutinoside	Inhibit PBP2a[39]
Bioactive fraction, F-10 from the leaves of Duabanga grandiflora	Inhibit PBP2a[40]
2,3,3-trimethyl-Octane and benzoic from the methanol bark extract of Toxicodendron vernicifluum	Inhibit PBP2a[41]
Aromatic sulfonyls substituted icariin derivatives	Inhibit PBP2a[42]
Naringin, hesperidin, neohesperidin, didymin and icariin	Inhibit PBP2a[43]
Targeting pyruvate kinase	
Bis-indole, an alkaloid from the Topsentia pachastrelloides: Hamacanthin Spongotine, Topsentin, Cis-3,4-dihyrohyrohamacanthin B and Bromodeoxytopsentin	Inhibit MRSA-PK[44,45]
Bisindolyl-cycloalkane	Inhibit MRSA-PK[46]
Indole-benzimidazole-amidine derivatives	Inhibit MRSA-PK[47]
Baicalein from Scutellaria baicalensis	Inhibit MRSA-PK[48]
Diosmin and Diosmetin from citrus fruits	Inhibit MRSA-PK[49]
Hamacanthins, a Bisindole alkaloid	Inhibit MRSA-PK[50]
Indole-containing alkaloids	Inhibit MRSA-PK, efflux pumps, biofilm[51]
Alkaloids	Inhibit the MRSA-PK[29]
Bisindole alkaloids (Hyrtinadine A and Alocasin A)	Inhibit MRSA-PK[52]
Targeting sortase	
Isovitexin	Inhibit sortase activity[53]
Chalcone	Inhibit sortase A activity, inhibit formation of biofilm[54]
Tideglusib	Inhibit sortase A activity[55]
Flavonols: morin, myricetin, and quercetin	Inhibit sortase activity [56]
Erianin, a natural bibenzyl compound	Inhibit sortase A activity[57]
Coptisine	Inhibit sortase B activity[58]
Taxifolin	Inhibit sortase activity[59]

Table 3. MRSA-Herbal Antibiotics with their Mode of Inhibition *(continued)*

MRSA-Natural antibiotic	Mode of inhibition
Targeting quorum sensing mechanism	
Extracts from Ballota nigra, Castanea sativa, and Sambucus ebulus.	Inhibit QS activity, inhibit production of δ-hemolysin[60]
Many alkaloids	Inhibit QS activity, PK, efflux pump, inter-calating of bacterial DNA[29]
Flavone rich extract from Schinus terebinthifolia	Inhibit QS activity, downregulate expression of accessory gene regulator[61]
Biaryl hydroxyketone	Inhibit quorum sensing, promote MRSA-wound healing[62]
Targeting biofilm formation	
Essential oils from Pogostemon heyneanus and Cinnamomum tamala	Prevent biofilm formation[63]
Essential oils from Eucalyptus globulus	Prevent biofilm formation, inhibit QS[64]
Essential oils from Thymus vulgaris	Prevent biofilm formation[65]
Aqueous extract of Aloe vera	Prevent biofilm formation[66]
Ethanol and methanol extracts from Vitis vinifera (rich in catechin esters of gallic acid)	Prevent biofilm formation[67]
Ethyl acetate extract from Abrus precatorus	Prevent biofilm formation[68]
Fraction from Duabanga grandiflora	Prevent biofilm formation, downregulate PBP2a[69]
Azadirachtin from Azadirachta indica	Prevent biofilm formation[70]
Nimbolide from Azadirachta indica	Prevent biofilm formation, inhibit efflux pump[71]
Glabridin	Prevent biofilm formation[72]
Betacyanins from Hylocereus polyrhizus and Amaranthus dubius	Prevent biofilm formation[73]
Bisdemethoxycurcumin	Prevent biofilm formation, downregulate virulence-related exoproteins[74]
Galloylated catechin esters of gallic acid from Vitis vinifera	Prevent biofilm formation[67]
Mupirocin-monoterpene combination	Mupirocin cannot destroy biofilm Mupirocin-1,8 Cineole mixture eliminates biofilm Mupirocin-Menthol mixture shows antagonism Mupirocin-Thymol mixture is inconclusive[75]
Immunomodulation	
Extract of Nigella sativa	Increase cytokine TNF-α in overcoming MRSA infections[3]

Efficacy of Adjuvant Therapy with Herbal Material

Combinations between anti-MRSA herbal materials or ingredients and MRSA-antibiotics have been investigated as well (Table 4). Many of them show synergistic effect even in the sub-inhibitory concentration of the antibiotics.

DISCUSSION

Modes of Action of Anti-MRSA Antibiotics

Preferred antibiotics, such as Daptomycin, Rifampicin, Vancomycin (Table 1), are often used to treat MRSA infections. They rely on the main modes of action, particularly

Table 4. Adjuvant Therapy with Herbal Materials for the Efficacy of Antibiotic

Herbal material	Antibiotic	Mechanism	Outcomes
Herbal extracts			
Extract (Camella sinensis)	Ampicillin (ZI = 11 mm)	Synergistic	Showed zone inhibition (ZI) 27 mm after combining with the herbal material against MRSA.[18]
Extract (Cyperus rotundus)	Ampicillin	Synergistic	This combination caused peptidoglycan and cytoplasmic membrane (CM) of Ampicillin - *S. aureus* (ARSA) was damaged and average cell areas significantly smaller than control.[76]
Bioactive fraction (Duabanga grandiflora)	Ampicillin	Synergistic	This combination inhibits the expression of PBP2a in MRSA.[40]
Extract (Pithecellobium clypearia, enriched in gallic acid and luteolin)	Erythromycin (ERY)	Synergistic	This combination can increase the effectiveness of treatment. The MIC_{50} before combination, S20b (200) and ERY (512), meanwhile after combination the MIC_{50} reduce to 64.[36]

Table 4. Adjuvant Therapy with Herbal Materials for the Efficacy of Antibiotic *(continued)*

Herbal material	Antibiotic	Mechanism	Outcomes
Monoterpenes/essential oils			
1,8-Cineol	Mupirocin	Additive	This combination showed the potentiated biofilm-eliminating effect.[75]
Essential oils (orange and Petitgrain)	MRSA antibiotics (Amikacin and tetracycline)	Synergistic	The combination decreases the growth of MRSA than single therapies.[77]
Alkaloids			
1,4-Naphthoquinones	Imipenem, cefotaxime, cefuroxime	Synergistic	The combination of this alkaloids with antibiotics showed synergistic activity against MRSA clinical isolate but the higher effect was shown by cefotaxime.[78]
Chelerythrine	Oxacillin	Synergistic	The results of the FICI tests showed that the CHE–OXA combination had a synergistic effect (FICI £0.5) against *S. aureus* ATCC43300 (FICI = 0.5). The MIC values of OXA were reduced by 4-fold (from 1 to 0.25 mg/mL) when combined with CHE at a concentration of one-fourth MIC.[79]
Steroidal alkaloids (Holarrhena antidysenteriaca)	Penicillin and vancomycin	Synergistic	N-formylconessimine and conimine showed synergistic effect when combined with penicillin and vancomycin against MRSA.[80]
Phenolic compounds/flavonoids			
Caffeic acid	Erythromycin, clindamycin, vancomycin	Synergistic	The combination decrease the MIC value in several strain of *S. aureus*.[81]
Chalcones	Vancomycin	Synergistic	The association of 4-bromo-3′ -aminochalcone (5f) with vancomycin demonstrated synergistic effect against MSSA and MRSA, with Fractional Inhibitory Concentration Index (FICI) values of 0.4 and 0.3.[82]
Silymarin	Linezolid	Hepatoprotective	The combination showed the minimum elevation of AST, ALT, ALP and LDH levels. The high elevation of that analyte showed liver damage. Therefore silymarin has potential function as hepatoprotective.[83]
Baicaline	Linezolid	Synergistic	The combination were better in reducing the number of colony-forming units (CFU) in the biofilms and lowest in the serum levels of Staphylococcus enterotoxin A (SEA), C-reactive protein (CRP), and procalcitonin (PCT).[84]
Diosmetin (citrus fruit)	Erythromycin	Synergistic	Diosmetin together with erythromycin, could synergistically inhibit the growth of ABC-pump overexpressed MRSA-RN4220/pUL5054, and time kill assay also showed that the antibacterial activities of diosmetin with erythromycin were bactericidal.[49]
Epicatechin gallate	Oxacillin and other β-lactam antibiotics	Synergistic	Epicatechin gallate (ECg) sensitizes methicillin-resistant *Staphylococcus aureus* (MRSA) to oxacillin and other β-lactam agents, reduces virulence protein secretion, prevents biofilm formation, and induces morphological changes in MRSA cells without affecting growth rate.[35]
Curcumin (Curcuma longa)	β-lactam and quinolone antibiotics	Synergistic	Curcumin showed the synergistic effect with β-lactam and quinolone antibiotics by enhancing membrane permeability and ATPase inhibitors.[37]
Cranberry-Derived Proanthocyanidins	β-Lactam antibiotics	Synergistic	cPAC significantly lowers the concentrations of oxacillin and carbenicillin needed to inhibit the growth of PBP2a-producing *Staphylococcus* species, without notably reducing the expression of the PBP2a-encoding mecA gene.[85]
Biaryl hydroxyketone	Cephalothin, nafcillin	Synergistic	The combination showed synergistic activity that enhance the sensitivity of antibiotics against MRSA.[62]
Allicin (garlic)	Vancomycin	Synergistic	PySSRs from Allicin suppress metabolism through interactions with thiophilic metabolites, coenzymes, and/or enzymes, so the growth of *S. aureus* was inhibited and increase the susceptibility of vancomycin.[86]

bacterial cell wall disruption, membrane (efflux pump) function disruption, and protein synthesis inhibition.[87] But, due to the emergence of multiple antibiotic resistance by MRSA, treatments with these antibiotics has become ineffective.[88]

Numerous classes of antibiotic have been used to restrain the emergence of MRSA (Table 1). But, along with the widespread utility of these antibiotics, the emergence of MRSA is increased. This evidence poses a significant therapeutic challenge because MRSA poses a threat to humans. The antibiotic classes used for MRSA are not only β-lactam antibiotics but also glycopeptide, cyclic lipopeptide antibiotic, cephalosporins, and oxazolidinone antibiotic (Table 1). The most representative types of these antibiotics are vancomycin, linezolid, daptomycin, and ceftaroline. The understanding of their modes of action will aid further development for effective MRSA treatment.[6]

Staphylococcus aureus, particularly MRSA, is often involved in dangerous infections. MRSA poses virulence factors that have great effect to patient. MRSA-antibiotics can affect both the expression of virulence factors and the host's immune response. Treatment with ribosomally active antibiotics, such as linezolid and clindamycin, can reduce the expression of virulence factors. In contrast, cell wall-targeting antibiotics, like beta-lactams, may increase the production of MRSA-exotoxins.[89]

Vancomycin is the "gold standard" of treatment for serious MRSA infections. It has become the antibiotic of choice for treatment of MRSA in the critical care setting. Unfortunately, there is a number of vancomycin-resistant MRSA isolates that has higher MIC. There is a significant increase in vancomycin clinical failures.[1] The use of vancomycin is also warned due to its nephrotoxicity and its ability to cause allergy.[87-120]

Linezolid has been shown to be effective in the treatment of infections due to MRSA. It has been recommended for the treatment of skin infections and pneumonia caused by MRSA.[1] But, as in the case of vancomycin, MRSA can also develop high resistance towards linezolid.[93] Even systemic treatment with linezolid achieves a greater beneficial effect than vancomycin in limiting MRSA infections.[94,95]

Daptomycin is usually used in patients with MRSA bacteremia, endocarditis, and in complicated skin infections, but should not be applied to treat MRSA pneumonia.[92] Daptomycin has been proven to be effective for the treatment of MRSA in the bloodstream.[1]

Ceftaroline is recommended also for treating skin infections caused by MRSA. It is an alternative antibiotic often used after the failure of vancomycin. Rifampicin, vancomycin, and linezolid can be used effectively against MRSA from blood stream infections.[96] Rifampicin is often used in combination with linezolid. This combination can reduce linezolid blood concentrations which increases the risk of the emergence of antibiotic-resistant bacteria.[97]

Multiple combinations of MRSA-antibiotics have been tested and have been either synergistic, antagonistic, additive, or indifferent. Several examples of combinatory studies are combinations of synergistic daptomycin and vancomycin, synergistic daptomycin with linezolid and dalbavancin, and dalbavancin with linezolid, linezolid with rifampicin that reduces linezolid blood concentrations, additive and/or synergistic ceftaroline with daptomycin, vancomycin or linezolid, and synergistic linezolid and daptomycin.[12,97–100]

Combining antibiotics for the treatment of MRSA infections is a promising approach, as it can address many of the limitations associated with vancomycin, such as inadequate tissue penetration, slow killing of bacteria, and the development of resistance in certain MRSA.[12] Combination antibiotic therapy offers a significant advantage over monotherapy due to its broader spectrum, synergistic effect, and ability to prevent the development of drug resistance.[98] Despite its theoretical potential, combination therapy for MRSA infections has not been consistently validated and proven in most in vitro and animal studies.

Herbal Medicine with Anti-MRSA Capacity and their Mode of Action

In vitro studies with IZ, MIC and MBC are not convincing enough to choose candidates of promising herbal materials as therapeutic agents for MRSA infection in the future.[16] Many research activities were stopped after IZ, MIC and MBC studies, and not further followed up. Their potential therapeutic medicine for MRSA infection depend on their richness on flavonoids and phenolic acids.[34] Alkaloid rich extracts also have potential in MRSA inhibition (Table 2). But, many anti-MRSA activities of herbal material are usually weaker than standard antibiotics. Even though, in depth researches have been carried out to understand their modes of inhibitory action against MRSA. Several modes of action have been identified, namely change in efflux pump, down-regulation of and interaction with Penicillin-binding protein 2a (PBP2a), inhibition of pyruvate kinase and sortase, quorum sensing, and biofilm formation (Figure 2 and Table 3).[89] These modes of action are more varied than the standard antibiotics. And, based on their specific mode of action, further application can be made, including adjuvant therapy with herbal materials.

The primary mechanism of antibiotic resistance in MRSA is demonstrated by membrane transport systems that actively expel antibiotic agents from the bacterial cytoplasm, enabling the bacteria to survive and continue growing.[101] Active efflux is a key mechanism of antibiotic resistance, where specific proton-driven multidrug pumps actively export various antimicrobial agents.[25] Antibiotic efflux pumps present an effective target for developing inhibitors that can alter resistance patterns. Blocking these efflux systems can restore the effectiveness of treatments against MRSA infections.[101] Fortunately, several herbal materials have been found to have potential to hinder the bacterial resistance, by

inhibiting the antibiotic efflux system. Herbal-derived efflux pump inhibitors (EPIs) is listed in Table 3.[102]

In addition to the antibiotic efflux pump, PBP2a is a crucial factor in MRSA resistance. PBP2a can perform transpeptidase activity, enabling peptidoglycan synthesis even in the presence of most β-lactam antibiotics. Therefore, the resistance behavior of MSRA depends also on the PBP2a function.[16] Various synthetic and natural PBP2a-inhibitors are discovered. They are targeting PBP2a to address MRSA infections. Targeting PBP2a may open the way to discover novel antibiotics to challenge MRSA infections.[103] In vitro and in silico studies have confirmed that particular herbal materials or notably their flavonoids, are promising source for future adjuvant anti-MRSA. Multiple studies using molecular docking analysis and molecular dynamics simulations have validated the binding interactions of specific flavonoids with PBP2a.[34] (Table 3)

Pyruvate kinase (PK) is an enzyme responsible for catalyzing the final step of glycolysis. It transfers a phosphate group from phosphoenolpyruvate to adenosine diphosphate, producing one molecule each of pyruvate and ATP. PK is regarded as a potential drug target in MRSA treatment. Bacterial PK is unique and different than human PK(s). In silico analysis and enzyme assays confirm that several MRSA-PK inhibitors are more selective for MRSA-PK than for human PK isoforms.[104]

Sortases are enzymes that mediate the covalent attachment of specific proteins to the peptidoglycan layer in the cell wall of Gram-positive bacteria.[105] They are involved in assembling surface protein and pili within the cell wall envelope of these bacteria.[106] These surface proteins facilitate Gram-positive bacteria in adhering to host cells and tissues.[107] Sortase plays a crucial role in the virulence of *S. aureus, making it a significant target for the development of new antibiotics.* Several synthetic organic compounds have been identified as strong inhibitors of sortase A. Although these inhibitors do not inhibit the growth of MRSA, they reduce its virulence, thereby helping to prevent MRSA-related infections.[108] As a result, sortase A inhibitors have emerged as promising alternative anti-virulence agents.[109] Several inhibitors of sortase A are discovered by employing an advanced computer-docking methodology. Several identified sortase A inhibitors are 2-phenyl-2,3-dihydro-1H-perimidine[110] and 3-(4-pyridinyl)-6-(2-sodiumsulfonatephenyl) [1,2,4]triazolo[3,4-b][1,3,4] thiadiazole, and Pyridazinone analogues.[111] Certainly, sortase inhibitors could be advantageous as an anti-infective therapy for eradicating hospital-acquired MRSA infections in high-risk patients, potentially with fewer side effects compared to traditional antibiotics.[112]

Member of microbial population, including MRSA, is communicating with each other chemically. This cell-to-cell communication is named quorum sensing that has the main function to control the cell density. Through quorum sensing (QS) or cell-to-cell signaling, bacteria are able to control their physiological function and gene expressions. QS is also related to biofilm formation, drug efflux pump, and virulence. In high-density population, Adequate small molecule signals are generated to activate various cellular processes, including mechanisms of virulence and drug resistance, antibiotic tolerance, and damage to the host. Therefore, it is necessary to encourage a novel strategy for the treatment of MRSA by using quorum quenching.[113–115] QS is associated with the microbial biofilm formation**.** QS and biofilm formation are prospective novel targets for controlling MRSA infections.[116]

Antibiotic resistance and the ability to form biofilms contribute to MRSA's success as a human pathogen. With its biofilm, MRSA is able to attach to the polymer surface, and colonize at the artificial materials. The adherence of MRSA is facilitated with biofilm.[113,117] MRSA biofilms are highly challenging to treat, as many antibiotics have difficulty penetrating them effectively.[7,118] The burden of MRSA biofilms presents a significant challenge for medical treatment and eradication. However, several herbal materials have shown promise as effective sources for combating biofilm formation (Table 3). Understanding how to inhibit biofilm formation is crucial for developing potential drugs to combat MRSA infections.[119]

Immunomodulation by herbal materials is an important aspect of the human immune response. The modulation of the immune system can enhance the anti-MRSA of herbal materials. The bacterial antigen invasion will stimulate macrophage to do phagocytosis and produce cytokines IL-1, IL-6, and TNF α which can recruit leukocytes to eliminate bacteria.[3]

Adjuvant Herbal Therapy Combined with MRSA Antibiotics

Although various antibiotics are used to treat MRSA infections, the emergence of MRSA strains with decreased sensitivity to vancomycin has significantly reduced the effectiveness of conventional antibiotics, leaving very few costly options available. There are efforts to produce new MRSA antibiotics. But, an alternative therapy is combinatorial and adjuvant therapies with herbal materials. Combinations of various herbal materials or/with MRSA-antibiotic are possible. There is evidence that encourages these possibilities. MRSA-antibiotic combinatory therapy may have effective synergistic effects. Antibiotic combination therapy can be used to overcome antibiotic resistance and reduce the likelihood of genetic mutations in MRSA.[120] Actually, limited number of MRSA antibiotics are available. Therefore, the intervention of herbal materials to the MRSA antibiotics is a good choice (Table 4).[80]

Combinations between anti-MRSA herbal materials or ingredients and MRSA antibiotics have been investigated as well (Table 4). Many of them show synergistic effect even in the sub inhibitory concentration of the antibiotics. Therefore, anti-MRSA potential of herbal materials or ingredients support their utility to adjunct the conventional MRSA antibiotics.[84]

By applying herbal extracts or ingredients as adjuvant therapy in combination with antibiotics, MRSA eradication is more possible. MRSA can be killed by combined or mixture drugs which have different angles of mode of action. The utility of herbal materials is useful in increasing the efficacy of MRSA antibiotics that have narrower variety of modes of action than herbal materials. Therefore, multiple inhibition approaches against MRSA can be achieved by using herbal materials as adjuvant therapy. This combination approach will increase the efficacy of the antibiotic in killing MRSA.

It is interesting also to note that beside our understanding on modes of action, there is evidence that the use of particular natural compound, such as silymarin, can reduce the toxicity of linezolid. Linezolid is an effective option for eradicating MRSA infections, but its use is restricted due to potential side effects such as hepatotoxicity, myelosuppression, and lactic acidosis. Silymarin has been shown to mitigate the hepatotoxic effects of linezolid therapy in MRSA cases. It exhibits significant hepatoprotective properties by reducing liver marker enzymes, improving serum parameters, and showing favorable cytological changes. Additionally, silymarin helps protect against myelosuppression and lactic acidosis, as evidenced by bone marrow smears and serum lactate levels. Its antioxidant effects are confirmed by reduced lipid peroxidation and the restoration of both enzymatic and non-enzymatic liver antioxidants to near-normal levels. Thus, silymarin emerges as a valuable herbal therapeutic agent for protecting against linezolid-induced hepatotoxicity in MRSA treatment.[83]

Anti-MRSA herbal materials can be classified based on their main bioactive compounds, namely flavonoids, alkaloids, and essential oils. Flavonoids, such as quercetin, naringenin, 7-O-buthylnaringin, and mupirocin, are often have potential inhibitory activity against MRSA.[121] Many essential oils are also good in MRSA inhibition. For adjuvant therapy, appropriate herbal materials can be chosen based on their flavonoid, alkaloids, or essential oils. Unfortunately, our literature review has limitation, we have not discussed the specific constituents of each herbal material because the researcher did not mention it.

For the herbal adjuvant delivery, two administrations are possible, as herbal tea and topical medicine. Herbal tea should be considered due to the fact that there are many polar extracts found to have anti-MRSA activities (Table 2). Topical application is appropriate for MRSA skin infections, such as wound healing or post-operation skin treatment. Further studies are needed to prove the efficacy of the herbal tea in inhibiting MRSA.

CONCLUSIONS AND RECOMMENDATIONS

Conventional MRSA antibiotics act by disrupting efflux pumps, peptidoglycan, and protein biosynthesis, while herbal-derived compounds offer diverse modes of action through bioactive flavonoids, phenolic, and alkaloids. These herbal materials can enhance antibiotic efficacy when used in adjuvant therapy.

Future efforts should focus on standardizing herbal materials, optimizing extraction, and conducting phytochemical studies to identify potential anti-MRSA agents. Understanding their inhibitory mechanisms is essential, as is studying their combinations with MRSA antibiotics to ensure safe and effective use in adjuvant therapies.

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REFERENCES

1. Tverdek FP, Crank CW, Segreti J. Antibiotic therapy of methicillin-resistant Staphylococcus aureus in critical care. Crit Care Clin. 2008 Apr; 24(2): 249-60. doi: 10.1016/j.ccc.2007.12.013. PMID:18361944.
2. Eshetie S,Tarekegn F,Moges F, Amsalu A, Birhan W, Huruy K. Methicillin resistant Staphylococcus aureus in Ethiopia: a meta-analysis. BMC Infect Dis. 2016 Nov; 16(1): 689. doi: 10.1186/s12879-016-2014-0. PMID:27871245.
3. Nitihapsari GY, Sari OP, Ferine M. The Effect of Black Cumin (Nigella sativa) Extract on TNF-α in MRSA-Infected Balb/c Mice. In: Proceeding National Seminar of LPPM Unsoed. 2020.
4. Van Eperen AS, Segreti J. Empirical therapy in methicillin-resistant Staphylococcus aureus infections: an up-to-date approach. J Infec Chemother 2016 Jun; 22(6): 351-9. doi: 10.1016/j.jiac.2016.02.012. PMID:27066882.
5. Nursanty R, Yunita Y. The Potent of Methanol Extracts of Cashew (Anacardium Occidentale L.) Against Methicillin-resistant Staphylococcus Aureus (Mrsa). Jurnal Natural. 2012 Sept; 12(2), https://jurnal.usk.ac.id/natural/article/view/836 (2012, accessed 27 June 2024).
6. Liu W-T, Chen E-Z, Yang L, Peng C, Wang Q, Xu Z, et al. Emerging resistance mechanisms for 4 types of common anti-MRSA antibiotics in Staphylococcus aureus: A comprehensive review. Microb Pathog. 2021 Jul; 156: 104915.
7. Singh R, Ray P, Das A, Sharma M. Penetration of antibiotics through Staphylococcus aureus and Staphylococcus epidermidis biofilms. J Antimicrob Chemother. 2010 Sep; 65(9): 1955-8. doi: 10.1093/jac/dkq257. PMID:20615927.
8. Akanbi OE, Njom HA, Fri J, Otigbu AC, Clarke AM. Antimicrobial susceptibility of Staphylococcus aureus isolated from recreational waters and beach sand in Eastern Cape Province of South Africa. Int J Environ Res Public Health. 2017 Sep; 14(9): 1001. doi: 10.3390/ijerph14091001. PMID:28862669.
9. Bissong MEA, Tahnteng BF, Ateba CN, Akoachere JFTK. Pathogenic Potential and Antimicrobial Resistance Profile of Staphylococcus aureus in Milk and Beef from the Northwest and Southwest Regions of Cameroon. Biomed Res Int. 2020 Oct; 2020: 1-12. doi: 10.1155/2020/6015283. PMID:33195695.
10. Cadena J, Sreeramoju P, Nair S, Henao-Martinez A, Jorgensen J, Patterson JE. Clindamycin-resistant methicillin-resistant Staphylococcus aureus: epidemiologic and molecular characteristics and associated clinical factors. Diagn Microbiol Infect Dis. 2012 Sep;74(1):16-21. doi: 10.1016/j.diagmicrobio.2012.05.010. PMID: 22795962.
11. Ullah K, Khan SA, Mannan A, Khan R, Murtaza G, Yameen MA. Enhancing the antibacterial activity of erythromycin with titanium

dioxide nanoparticles against MRSA. Curr Pharm Biotechnol. 2020; 21(10): 948-54. doi: 10.2174/1 389201021666200128124142. PMID:31994459.
12. Davis J, Hal S, Tong S. Combination Antibiotic Treatment of Serious Methicillin-Resistant Staphylococcus aureus Infections. Semin Respir Crit Care Med. 2015 Feb; 36(1): 3-16. doi: 10.1055/s-0034-1396906. PMID:25643267.
13. Al-Asousi F, Dadgostar A, Javer A. Sinonasal methicillin-resistant Staphylococcus aureus: updates on treatment. Curr Opin Otolaryngol Head and Neck Surg. 2017 Feb; 25(1): 19-23.
14. Memariani H, Memariani M, Robati RM, Nasiri S, Abdollahimajd F, Baseri Z, et al. Anti-Staphylococcal and cytotoxic activities of the short anti-microbial peptide PVP. World J Microbiol Biotechnol. 2020 Oct; 36: 174. doi: 10.1007/s11274-020- 02948-6.
15. Randhawa HK, Gautam A, Sharma M, Bhatia R, Varshney GC, Raghava GPS, et al. Cell-penetrating peptide and antibiotic combination therapy: a potential alternative to combat drug resistance in methicillin-resistant Staphylococcus aureus. Appl Microbiol Biotechnol. 2016 May; 100: 4073-83. doi: 10.1007/s00253-016-7329-7. PMID:26837216.
16. Okwu MU, Olley M, Akpoka AO, Izeybuwa OE. Methicillin-resistant Staphylococcus aureus (MRSA) and anti-MRSA activities of extracts of some medicinal plants: A brief review. AIMS Microbiol. 2019 Apr; 5(2): 117-37. doi: 10.3934/microbiol.2019.2.117. PMID:31384707.
17. Ningsih I, Rosalinda DA, Kiranasari A, Dewi BE, Sjatha F. In vitro antibacterial activity test of jackfruit (Artocarpus heterophyllus Lam.) leaf extract against methicillin-resistant Staphylococcus aureus (MRSA). In: BROMO Conference, symposium on natural product and biodiversity, pp. 245–249.
18. Aqil F, Khan MSA, Owais M, Ahmad I. Effect of certain bioactive plant extracts on clinical isolates of β-lactamase producing methicillin resistant Staphylococcus aureus. J Basic Microbiol. 2005; 45(2): 106-14. doi: 10.1002/jobm.200410355. PMID:15812867.
19. Amer AM. Antimicrobial Effects of Egyptian Local Chicory, Cichorium endivia subsp. pumilum. Int J Microbiol. 2018 Nov; 2018(1): 1-6. doi: https://doi.org/10.1155/2018/6475072.
20. Paramita S, Yasir Y, Yuniati Y, Sina I. Bioautography Analysis of Thin Layer Chromatography and Antibacterial Activity of Ethanolic Extract of Tiwai Onion (Eleutherine bulbosa (Mill.) Urb.) Against Methicillin-Resistant Staphylococcus aureus (MRSA) Science and Health Journal. 2018; 1(8): 470-8. doi: 10.25026/jsk.v1i9.86.
21. Voravuthikunchai SP, Kitpipit L. Activity of medicinal plant extracts against hospital isolates of methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect. 2005 Jun; 11(6); 510-2. doi: 10.1111/j.1469-0691.2005.01104.x. PMID:15882206.
22. Chomnawang MT, Surassmo S, Wongsariya K, Bunyapraphatsara N. Antibacterial activity of Thai medicinal plants against methicillin-resistant Staphylococcus aureus. Fitoterapia. 2009 Mar; 80(2): 102-4. doi: 10.1016/j.fitote.2008.10.007. PMID:19022354.
23. Ramdaya M. The Inhibitory Effect of Ethanolic Extract of Bitter Melon Fruit on the Growth of Methicillin-Resistant Staphylococcus aureus. Undergraduate, Universitas Muhammadiyah Semarang, http://repository.unimus.ac.id/3147/ (2018, accessed 28 June 2024).
24. Hardana H, Warganegara E. Pomegranate Fruit Extract as an Antibiotic for MRSA Infection Treatment. Majority: Medical Journal of Lampung University 2015; 4: 83–87.
25. Kakarla P, Floyd J, Mukherjee M, Devireddy AR, Inupakutika MA, Ranweera I, et al. Inhibition of the multidrug efflux pump LmrS from Staphylococcus aureus by cumin spice Cuminum cyminum. Arch Microbiol. 2017 Apr; 199(3): 465-74. doi: https://10.1007/s00203-016-1314-5. PMID:27830269.
26. Dymek A, Armada A, Handzlik J, Viveiros M, Spengler G, Molnar J, et al. The activity of 16 new hydantoin compounds on the intrinsic and overexpressed efflux pump system of Staphylococcus aureus. In Vivo. 2012 Mar; 26(2): 223-9. PMID:22351662.
27. de Araújo ACJ, Freitas PR, Dos Santos Barbosa CR, Muniz DF, Ribeiro-Filho J, Tintino SR, et al. Modulation of Drug Resistance by Limonene: Inhibition of Efflux Pumps in Staphylococcus aureus Strains RN-4220 and IS-58. Curr Drug Metab 2021; 22: 110–113.
28. Freitas PR, de Araújo ACJ, Barbosa CR, Muniz DF, Tintino SR, Ribeiro-Filho J, et al. Inhibition of Efflux Pumps by Monoterpene (α-pinene) and Impact on Staphylococcus aureus Resistance to Tetracycline and Erythromycin. Curr Drug Metabolism. 2020 Aug;22(2):123-6. doi: https://10.2174/ 1389200221999200730212721.
29. Pervaiz A, Khan R, Anwar F, Mushtaq G, Kamal MA, Khan H. Alkaloids: An Emerging Antibacterial Modality Against Methicillin Resistant Staphylococcus aureus. Curr Pharm Des. 2016; 22(28): 4420-29. doi: 10.2174/ 1381612822999160629115627. PMID:27356778.
30. Gibbons S, Udo EE. The effect of reserpine, a modulator of multidrug efflux pumps, on the in vitro activity of tetracycline against clinical isolates of methicillin resistant Staphylococcus aureus (MRSA) possessing the tet(K) determinant. Phytother Res. 2000 Mar; 14(2): 139-40. doi: https://10.1002/(sici)1099-1573(200003)14:2. PMID:10685116.
31. Ramalhete C, Spengler G, Martins A, Martins M, Viveiros M, Mulhovo S, et al. Inhibition of efflux pumps in methicillin-resistant Staphylococcus aureus and Enterococcus faecalis resistant strains by triterpenoids from Momordica balsamina. Int J Antimicrob Agents. 2011 Jan; 37(1): 70-4. doi: https://10.1016/j. ijantimicag.2010.09.011. PMID:21075604.
32. Smith E, Williamson E, Zloh M, Gibbons S. Isopimaric acid from Pinus nigra shows activity against multidrug-resistant and EMRSA strains of Staphylococcus aureus. . Phytother Res. 2005 Jun; 19(6): 538-42. doi: https://10.1002/ptr.1711. PMID:16114093.
33. Monteiro KLC, de Aquino TM, Mendonça Junior FJB. An Update on Staphylococcus aureus NorA Efflux Pump Inhibitors. Curr Top Med Chem. 2020 Sept; 20(24): 2168-85. doi: https://10.2174/ 1568026620666200704135837.
34. Alhadrami HA, Hamed AA, Hassan HM, Belbahri L, Rateb ME, Sayed AM. Flavonoids as potential anti-MRSA agents through modulation of PBP2a: a computational and experimental study. Antibiotics. 2020 Aug; 9(9): 562. doi: 10.3390/ antibiotics9090562. PMID:32878266.
35. Bernal P, Lemaire S, Pinho MG, Mobashery S, Hinds J, Taylor PW. Insertion of epicatechin gallate into the cytoplasmic membrane of methicillin-resistant Staphylococcus aureus disrupts penicillin-binding protein (PBP) 2a-mediated beta- lactam resistance by delocalizing PBP2. J Biol Chem. 2010 Jul; 285(31): 24055-65. doi: https://10.1074/jbc.M110.114793. PMID:20516078.
36. Liu C, Huang H, Zhou Q, Liu B, Wang Y, Li P, et al. Pithecellobium clypearia extract enriched in gallic acid and luteolin has antibacterial activity against MRSA and reduces resistance to erythromycin, ceftriaxone sodium and levofloxacin. J Appl Microbiol. 2020 Oct; 129(4): 848-59. doi: https://10.1111/jam.14668. PMID:32301544.
37. Mun S-H, Kim S-B, Kong R, Choi JG, Kim YC, Shin DW, et al. Curcumin reverse methicillin resistance in Staphylococcus aureus. Molecules. 2014 Nov; 19(11): 18283-95. doi: https://10.3390/molecules191118283. PMID:25389660.
38. Mun S-H, Lee Y-S, Han S-H, Lee SW, Cha SW, Kim S bae, et al. In vitro Potential Effect of Morin in the Combination with β-Lactam Antibiotics Against Methicillin- Resistant Staphylococcus aureus. Foodborne Pathog Dis. 2015 Jun; 12(6): 545-50. doi: https://10.1089/fpd.2014.1923. PMID:26067230.
39. Rani N, Vijayakumar S, P T V L, Arunachalam A. Allosteric site-mediated active site inhibition of PBP2a using Quercetin 3-O-rutinoside and its combination. J Biomol Struct Dyn. 2016 Aug; 34(8): 1778-96. doi: https://10.1080/07391102.2015.1092096. PMID:26360629.
40. Santiago C, Pang EL, Lim K-H, Loh HS, Ting KN. Inhibition of penicillin-binding protein 2a (PBP2a) in methicillin resistant Staphylococcus aureus (MRSA) by combination of ampicillin and a bioactive fraction from Duabanga grandiflora. BMC Complement Altern Med. 2015 Jun; 15: 178. doi: https://10.1186/s12906-015-0699-z. PMID:26060128.
41. Saravanakumar K, Chelliah R, Hu X, Oh DH, Kathiresan K, Wang MH. Antioxidant, Anti-Lung Cancer, and Anti-Bacterial Activities of Toxicodendron vernicifluum. Biomolecules. 2019 Mar; 9(4):127. doi: https://10.3390/biom9040127. PMID:30934938.

42. Wang A, Xu Y. Synthesis and antibacterial activity of novel icariin derivatives. Die Pharmazie. 2019 Feb; 74(2): 73-78. 2019/02/21. doi: https://10.1691/ph.2019.8866. PMID:30782254.
43. Verma AK, Ahmed SF, Hossain MS, Bhojiya AA, Mathur A, Upadhyay SK, et al. Molecular docking and simulation studies of flavonoid compounds against PBP-2a of methicillin-resistant Staphylococcus aureus. J Biomol Struct Dyn. 2021 Jul;40(21): 1-17. doi: https://10.1080/07391102.2021.1944911. PMID:34243699.
44. Zoraghi R, Worrall L, See RH, Strangman W, Popplewell WL, Gong H, et al. Methicillin-resistant Staphylococcus aureus (MRSA) pyruvate kinase as a target for bis-indole alkaloids with antibacterial activities. J Biol Chem. 2011 Dec; 286(52): 44716-25. doi: https://10.1074/jbc.M111.289033. PMID:22030393.
45. Kumar NS, Dullaghan EM, Finlay BB, Gong H, Reiner NE, Jon Paul Selvam J, et al. Discovery and optimization of a new class of pyruvate kinase inhibitors as potential therapeutics for the treatment of methicillin-resistant Staphylococcus aureus infections. Bioorg Med Chem. 2012 Dec; 20(24): 7069-82. doi: https://10.1016/j.bmc.2012.10.002. PMID:23141418.
46. El-Sayed MT, Zoraghi R, Reiner N, Suzen S, Ohlsen K, Lalk M, et al. Novel inhibitors of the methicillin-resistant Staphylococcus aureus (MRSA)-pyruvate kinase. J Enzyme Inhib and Med Chem. 2016 Dec; 31(6): 1666-71. doi: 10.3109/14756366.2015.1118685. PMID:26653005.
47. Ates-Alagoz Z, Kisla MM, Goker H, Yildiz S. Synthesis, Molecular Docking Studies and Antibacterial Activities of Novel Monocationic Indole- benzimidazole Derivatives. Med Chem. 2020 Aprl;17(7): 699-706. doi: https://10.2174/1573406416666200420080459. PMID:32310051.
48. Chan BCL, Ip M, Lau CBS, Lui SL, Jolivalt C, Ganem-Elbaz C, et al. Synergistic effects of baicalein with ciprofloxacin against NorA over-expressed methicillin-resistant Staphylococcus aureus (MRSA) and inhibition of MRSA pyruvate kinase. J Ethnopharm. 2011 Jul;137:767-773. doi: https://10.1016/j. jep.2011.06.039.
49. Chan BCL, Ip M, Gong H, Lui SL, See RH, Jolivalt C, et al. Synergistic effects of diosmetin with erythromycin against ABC transporter over-expressed methicillin- resistant Staphylococcus aureus (MRSA) RN4220/pUL5054 and inhibition of MRSA pyruvate kinase. Phytomedicine. 2013 April;20:611-14. doi: https://10.1016/j.phymed.2013.02.007.
50. Kim A, Kim MJ, Noh TH, Hong J, Liu Y, Wei X, et al. Synthesis and antibacterial evaluation of hamacanthin B analogues. Bioorg Med Chem Lett. 2016 Sept; 26: 5013-17. doi: https://10.1016/j.bmcl.2016.08.095.
51. Liu Y, Cui Y, Lu L, Gong Y, Han W, Piao G. Natural indole-containing alkaloids and their antibacterial activities. Arch Pharm (Weinheim) 2020 Oct; 353(10):e2000120. doi: https://10.1002/ardp.202000120.
52. Rehberg N, Sommer GA, Drießen D, Kruppa M, Adeniyi ET, Chen S, et al. Nature-Inspired (di)Azine- Bridged Bisindole Alkaloids with Potent Antibacterial In Vitro and In Vivo Efficacy against Methicillin-Resistant Staphylococcus aureus. J Med Chem. 2020 Oct; 63: 12623-41. doi: https://10.1021/acs. jmedchem.0c00826.
53. Mu D, Xiang H, Dong H, Wang D, Wang T. Isovitexin, a Potential Candidate Inhibitor of Sortase A of Staphylococcus aureus USA300. J Microbiol Biotechnol. 2018 Sep; 28(9): 1426-1432. doi: https://10.4014/jmb. 1802.02014. PMID:30369109.
54. Zhang B, Teng Z, Li X, Lu G, Deng X, Niu X, et al. Chalcone Attenuates Staphylococcus aureus Virulence by Targeting Sortase A and Alpha-Hemolysin. Front Microbiol. 2017 Sep; 8: 1715. doi: https://10.3389/fmicb.2017.01715. PMID:28932220.
55. Yang T, Zhang T, Guan X-N, Dong Z, Lan L, Yang S, et al. Tideglusib and Its Analogues As Inhibitors of Staphylococcus aureus SrtA. J Med Chem. 2020 Aug;63(15): 8442-57. doi: https://10.1021/acs.jmedchem.0c00803. PMID:32639734.
56. Kang SS, Kim J-G, Lee T-H, Oh KB. Flavonols inhibit sortases and sortase-mediated Staphylococcus aureus clumping to fibrinogen. Bio Pharm Bul. 2006 Aug;29(8): 1751-1755.. doi: https://10.1248/bpb.29.1751. PMID:16880637.
57. Ouyang P, He X, Yuan Z-W, Yin ZQ, Fu H, Lin J, et al. Erianin against Staphylococcus aureus Infection via Inhibiting Sortase A. Toxins. 2018 Sep;10(10):385. doi: https://10.3390/toxins10100385.
58. Wang G, Wang X, Sun L, Gao Y, Niu X, Wang H. Novel Inhibitor Discovery of Staphylococcus aureus Sortase B and the Mechanism Confirmation via Molecular Modeling. Molecules. 2018. Apr;23(4): 977. doi: 10.3390/ molecules23040977.
59. Wang L, Wang G, Qu H, Wang K, Jing S, Guan S, et al. Taxifolin, an Inhibitor of Sortase A, Interferes With the Adhesion of Methicillin-Resistant Staphylococcal aureus. Frontiers in Microb. 2021 Jul;12:686864. doi: https://10.3389/fmicb.2021.686864. PMID:34295320.
60. Quave CL, Plano LRW, Bennett BC. Quorum sensing inhibitors of Staphylococcus aureus from Italian medicinal plants. Planta Med. 2011 Jul;77(2): 188-95. doi: https://10.1055/s-0030-1250145.
61. Muhs A, Lyles JT, Parlet CP, Nelson K, Kavanaugh JS, Horswill AR, et al. Virulence Inhibitors from Brazilian Peppertree Block Quorum Sensing and Abate Dermonecrosis in Skin Infection Models. Sci Rep. 2017 Feb;7: 42275. doi: https://10.1038/ srep42275.
62. Kuo D, Yu G, Hoch W, Gabay D, Long L, Ghannoum M, et al. Novel quorum-quenching agents promote methicillin-resistant Staphylococcus aureus (MRSA) wound healing and sensitize MRSA to β-lactam antibiotics. Antimicrob Agents Chemother. 2015 Feb; 59(3): 1512-18. doi: https://doi.org/10.1128/ aac.04767-14.
63. Rubini D, Banu SF, Nisha P, Murugan R, Thamotharan S, Percino MJ, et al. Essential oils from unexplored aromatic plants quench biofilm formation and virulence of Methicillin resistant Staphylococcus aureus. Microb Pathog. 2018 Jun;122: 162-173. doi: https://10.1016/j.micpath.2018.06.028.
64. Merghni A, Noumi E, Hadded O, Dridi N, Panwar H, Ceylan O, et al. Assessment of the antibiofilm and antiquorum sensing activities of Eucalyptus globulus essential oil and its main component 1,8-cineole against methicillin-resistant Staphylococcus aureus strains. Microb Pathog. 2018 May;118: 74-80. doi: https://10.1016/j.micpath.2018.03.006. PMID:29522803.
65. Perez AP, Perez N, Lozano CMS, Altube MJ, de Farias MA, Portugal RV, et al. The anti MRSA biofilm activity of Thymus vulgaris essential oil in nanovesicles. J Phymed. 2019 Mar;57: 339-351. doi: https://10.1016/j.phymed.2018.12.025.
66. Saddiq AA, Al-Ghamdi H. Aloe vera extract: A novel antimicrobial and antibiofilm against methicillin resistant Staphylococcus aureus strains. Pak J Pharm. 2018 Sep;31(5): 2123-30. PIMD: 30393222.
67. Al-Mousawi AH, Al-Kaabi SJ, Albaghdadi AJH, Almulla AF, Raheem A, Algon AAA. Effect of Black Grape Seed Extract (Vitis vinifera) on Biofilm Formation of Methicillin-Resistant Staphylococcus aureus and Staphylococcus haemolyticus. Curr Microbiology. 2020 Feb;77(22): 238-45. doi: https://10.1007/s00284-019-01827-0. PMID:31807848.
68. Mutmainnah B, Ni'matuzaroh N. Inhibitory Effectiveness of Ethyl Acetate Extract of Abrus precatorius on Methicillin-Resistant Staphylococcus aureus (MRSA) 22372 from Urine Samples of Catheterized Patients. Proceeding SNPBS National Seminar of Biology Education and Science Technology. Ke-2, 2017.
69. Santiago C, Lim K-H, Loh H-S, Ting KN. Inhibitory effect of Duabanga grandiflora on MRSA biofilm formation via prevention of cell-surface attachment and PBP2a production. Molecules. 2015 Mar;20(3): 4473-82. doi: https://10.3390/molecules20034473. PMID: 25764489.
70. Quelemes PV, Perfeito MLG, Guimarães MA, dos Santos RC, Lima DF, Nascimento C, et al. Effect of neem (Azadirachta indica A. Juss) leaf extract on resistant Staphylococcus aureus biofilm formation and Schistosoma mansoni worms. J Ethnopharmacol. 2015 Dec; 175:287-94. doi: 10.1016/j.jep.2015.09.026.
71. Sarkar P, Acharyya S, Banerjee A, Patra A, Thankamani K, Koley H, et al. Intracellular, biofilm-inhibitory and membrane-damaging activities of nimbolide isolated from Azadirachta indica A. Juss (Meliaceae) against meticillin-resistant Staphylococcus aureus. J Med Microbiol. 2016 Oct;65(10): 1205-14. doi: https://10.1099/jmm.0.000343. PMID:27553840.

72. Gangwar B, Kumar S, Darokar MP. Glabridin Averts Biofilms Formation in Methicillin-Resistant Staphylococcus aureus by Modulation of the Surfaceome. Front MicrobIol. 2020 Sep;11: 1779. doi: https://10.3389/fmicb.2020.01779. PMID:33071991.
73. Yong YY, Dykes G, Lee SM, Choo WS. Biofilm inhibiting activity of betacyanins from red pitahaya (Hylocereus polyrhizus) and red spinach (Amaranthus dubius) against Staphylococcus aureus and Pseudomonas aeruginosa biofilms. J App Microbiol. 2019 Jan;126(1): 68-78. doi: https://10.1111/jam.14091. PMID:30153380.
74. Wang S, Kang O-H, Kwon D-Y. Bisdemethoxycurcumin Reduces Methicillin-Resistant Staphylococcus aureus Expression of Virulence-Related Exoproteins and Inhibits the Biofilm Formation. Toxins (Basel). 2021 Nov;13(11):804. doi: https://10.3390/toxins13110804. PMID:34822588.
75. Kifer D, Mužinić V, Klarić MŠ. Antimicrobial potency of single and combined mupirocin and monoterpenes, thymol, menthol and 1,8-cineole against Staphylococcus aureus planktonic and biofilm growth. J Antibiot (Tokyo). 2016 Feb;69: 689-96. doi: https://doi.org/10.1038/ja.2016.10.
76. Cheypratub P, Leeanansaksiri W, Eumkeb G. The Synergy and Mode of Action of Cyperus rotundus L. Extract Plus Ampicillin against Ampicillin-Resistant Staphylococcus aureus. Evidence-Based Complementary and Alternative Medicine 2018 Aprl;2018: 3438453. doi: https://doi.org/10.1155/2018/3438453.
77. Cui Z-H, He H-L, Wu S-B, Dong CL, Lu SY, Shan TJ, et al. Rapid Screening of Essential Oils as Substances Which Enhance Antibiotic Activity Using a Modified Well Diffusion Method. Antibiotics. 2021 Aprl;10(4): 463. doi: https://doi. org/10.3390/antibiotics10040463.
78. Wang M, Ma B, Ni Y, Xue X, Li M, Meng J, et al. Restoration of the Antibiotic Susceptibility of Methicillin-Resistant Staphylococcus aureus and Extended- Spectrum β-Lactamases Escherichia coli Through Combination with Chelerythrine. Microbial Drug Resist. 2021 Mar;27(3): 337-41.doi: https://doi.org/10.1089/mdr.2020.0044.
79. Zhou L-N, Ge X-L, Dong T-T, Gao HY, Sun BH. Antibacterial steroidal alkaloids from Holarrhena antidysenteriaca. Chin J Nat Med. 2017 Jul;15(7): 540-45.doi: https://doi.org/10.1016/S1875-5364(17)30080-8.
80. Yap JKY, Tan SYY, Tang SQ, Thien VK, Chan EWL. Synergistic Antibacterial Activity Between 1,4-Naphthoquinone and β-Lactam Antibiotics Against Methicillin-Resistant Staphylococcus aureus. Microb Drug Resist. 2021 Feb;27(2): 234-40. doi: https://doi.org/10.1089/mdr.2020.0178.
81. Kępa M, Miklasińska-Majdanik M, Wojtyczka RD, Idzik D, Korzeniowski K, Smoleń-Dzirba J, et al. Antimicrobial Potential of Caffeic Acid against Staphylococcus aureus Clinical Strains. Biomed Res Int. 2018 Jul;2018: 7413504.doi: https://doi.org/ 10.1155/2018/7413504.
82. Garcia MAR, Theodoro RS, Sardi JCO, Santos MB, Ayusso GM, Pavan FR, et al. Design, synthesis and antibacterial activity of chalcones against MSSA and MRSA planktonic cells and biofilms. Bioorg Chem. 2021 Nov;116: 105279. doi: https:// doi.org/10.1016/j.bioorg.2021.105279.
83. Vivekanandan L, Sheik H, Singaravel S, Thangavel S. Ameliorative effect of silymarin against linezolid-induced hepatotoxicity in methicillin- resistant Staphylococcus aureus (MRSA) infected Wistar rats. Biomed Pharmacother. 2018 Dec;108: 1303-12. doi: https://doi.org/ 10.1016/j.biopha.2018.09.133.
84. Liu T, Luo J, Bi G, Du Z, Kong J, Chen Y. Antibacterial synergy between linezolid and baicalein against methicillin-resistant Staphylococcus aureus biofilm in vivo. Microb Pathog. 2020 Oct;147: 104411. doi: https://doi. org/10.1016/j.micpath.2020.104411.
85. Gallique M, Wei K, Maisuria VB, Okshevsky M, McKay G, Nguyen D, et al. Cranberry-Derived Proanthocyanidins Potentiate β-Lactam Antibiotics against Resistant Bacteria. Appl Environ Microbiol. 2021 Aprl;87: e00127-00121. doi: https://doi.org/10.1128/AEM.00127-21.
86. Sheppard JG, McAleer JP, Saralkar P, Geldenhuys WJ, Long TE. Allicin-inspired pyridyl disulfides as antimicrobial agents for multidrug-resistant Staphylococcus aureus. Eur J Med Chem. 2018 Jan;143: 1185-1195. doi: https://doi.org/10.1016/j.ejmech.2017.10.018.
87. Jones SM, Morgan M, Humphrey TJ, Lappin-Scott H. Effect of vancomycin and rifampicin on meticillin-resistant Staphylococcus aureus biofilms. The Lancet. 2001 Jan; 357(9249): 40-1. doi: 10.1016/S0140-6736(00) 03572-8. PMID:11197363.
88. Li J, Liu D, Tian X, Koseki S, Chen S, Ye X, et al. Novel antibacterial modalities against methicillin resistant Staphylococcus aureus derived from plants. Crit Rev Food Sci and Nutr. 2019; 59(sup 1): S153-S161. doi: 10.1080/ 10408398.2018.1541865. PMID:30501508.
89. Hodille E, Rose W, Diep BA, Goutelle S, Lina G, Dumitrescu O. The Role of Antibiotics in Modulating Virulence in Staphylococcus aureus. Clin Microbiol Rev. 2017 Oct; 30(4): 887-917. doi: 10.1128/CMR.00120-16. PMID:28724662.
90. Kelesidis T, Humphries R, Ward K, Lewinski MA, Yang OO. Combination therapy with daptomycin, linezolid, and rifampin as treatment option for MRSA meningitis and bacteremia. Diagn Microbiol Infect Dis. 2011 Nov; 71(3): 286-90. doi: 10.1016/j.diagmicrobio.2011.07.001. PMID:21855248.
91. Rodvold KA, McConeghy KW. Methicillin-resistant Staphylococcus aureus therapy: past, present, and future. Clin Infect Dis. 2014 Jan; 58(Sup 1): S20-7.
92. Azhar A, Rasool S, Haque A, Shan S, Saeed M, Ehsan B, et al. Detection of high levels of resistance to linezolid and vancomycin in Staphylococcus aureus. J Med Microbiol. 2017 Sep; 66(9): 1328-31. doi: 10.1099/jmm.0.000566. PMID:28857738.
93. Fernández-Barat L, Motos A, Panigada M, Álvarez-Lerma F, Viña L, Lopez-Aladid R, et al. Comparative efficacy of linezolid and vancomycin for endotracheal tube MRSA biofilms from ICU patients. Crit Care. 2019 Jul; 23(1): 251.doi: 10.1186/ s13054-019-2523-5. PMID:31291978.
94. Li J, Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, et al. Linezolid vs. vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis. Eur Rev Med Pharmacol Sci. 2017 Oct; 21(17):3974-9. PMID:28975963.
95. Hashem AA, Abd El Fadeal NM, Shehata AS. In vitro activities of vancomycin and linezolid against biofilm-producing methicillin-resistant staphylococci species isolated from catheter-related bloodstream infections from an Egyptian tertiary hospital. J Med Microbiol. 2017 Jun; 66(6): 744-52. doi: 10.1099/jmm.0.000490. PMID:28598310.
96. Okazaki F, Tsuji Y, Seto Y, Ogami C, Yamamoto Y, To H. Effects of a rifampicin pre-treatment on linezolid pharmacokinetics. PLoS One. 2019 Sep; 14(9): e0214037. PMID:31518346.
97. Aktas G, Derbentli S. In vitro activity of daptomycin combined with dalbavancin and linezolid, and dalbavancin with linezolid against MRSA strains. J Antimicrob Chemother. 2017 Feb; 72(2): 441-3. doi: 10.1093/jac/dkw416. PMID:28073963.
98. Romero YG, Gómez-Garcés J-L. In vitro activity of ceftaroline in combination with other antimicrobials active against Staphylococcus spp. Enferm Infecc Microbiol Clin (Engl ed). 2020 Jan; 38(1): 25-27. doi: 10.1016/j.eimc.2019.03.007. PMID:31072712.
99. Parra-Ruiz J, Bravo-Molina A, Pena-Monje A, Hernández-Quero J. Activity of linezolid and high-dose daptomycin, alone or in combination, in an in vitro model of Staphylococcus aureus biofilm. J Antimicrob Chemother. 2012 Nov; 67(11): 2682-5. doi: 10.1093/jac/dks272. PMID:22796888.
100. Lekshmi M, Ammini P, Adjei J, Sanford LM, Shrestha U, Kumar S, et al. Modulation of antimicrobial efflux pumps of the major facilitator superfamily in Staphylococcus aureus. AIMS Microbiol. 2018; 4(1): 1-18. doi: https://10.3934/ microbiol.2018.1.1. PMID:31294201.
101. Gibbons S. Phytochemicals for Bacterial Resistance - Strengths, Weaknesses and Opportunities. Planta Med. 2008 Mei; 74: 594-602. doi: https://10.1055/s-2008-1074518.
102. Shalaby M-AW, Dokla EME, Serya RAT, Abouzid KAM. Penicillin binding protein 2a: An overview and a medicinal chemistry perspective. Eur J Med Chem. 2020 Aug; 199: 112312. doi: https://doi.org/10.1016/ j.ejmech.2020.112312. PMID:32442851.
103. Kumar NS, Amandoron EA, Cherkasov A, Finlay BB, Gong H, Jackson L, et al. Optimization and structure-activity relationships of a series of potent inhibitors of methicillin-resistant Staphylococcus

aureus (MRSA) pyruvate kinase as novel antimicrobial agents. Bioorg Med Chem. 2012 Dec; 20(24): 7069-82. doi: https://10.1016/j.bmc.2012.10.002. PMID:23141418.
104. Bradshaw WJ, Davies AH, Chambers CJ, Roberts AK, Shone CC, Acharya KR. Molecular features of the sortase enzyme family. FEBS J. 2015 Jun; 282(11): 2097-114. doi: https://10.1111/febs.13288. PMID:25845800.
105. Maresso AW, Schneewind O. Sortase as a target of anti-infective therapy. Pharmacol Rev. 2008 Mar; 60(1): 128-41. doi: https://10.1124/pr.107.07110. PMID:18321961.
106. Foster TJ. Surface Proteins of Staphylococcus aureus. Microbiol Spect. 2019 Jul; 7 doi: https://10.1128/microbiolspec.GPP3-0046-2018.
107. Cascioferro S, Raffa D, Maggio B, Raimondi MV, Schillaci D, Daidone G. Sortase A Inhibitors: Recent Advances and Future Perspectives. J Med Chem. 2015 Dec; 58(23): 9108-23.
108. Ha MW, Yi SW, Paek S-M. Design and Synthesis of Small Molecules as Potent Staphylococcus aureus Sortase A Inhibitors. Antibiotics (Basel). 2020 Oct; 9(10):706 doi: https://10.3390/antibiotics9100706. PMID:33081148.
109. Chan AH, Wereszczynski J, Amer BR, Yi SW, Jung ME, McCammon JA, et al. Discovery of Staphylococcus aureus sortase A inhibitors using virtual screening and the relaxed complex scheme. Chem Biol Drug Des. 2013 Oct; 82(4): 418-28. doi: https://10.1111/cbdd.12167. PMID:23701677.
110. Chan AH, Yi SW, Weiner EM, Amer BR, Sue CK, Wereszczynski J, et al. NMR structure-based optimization of Staphylococcus aureus sortase A pyridazinone inhibitors. Chem Biol Drug Des. 2017 Sep; 90(3): 327-44. doi: https://10.1111/ cbdd.12962. PMID:28160417.
111. Zhang J, Liu H, Zhu K, Gong S, Dramsi S, Wang YT, et al. Antiinfective therapy with a small molecule inhibitor of Staphylococcus aureus sortase. Proc Natl Acad Sci U S A. 2014 Sep; 111(37): 13517-22. doi: https://10.1073/pnas.1408601111. PMID:25197057.
112. Zhao X, Yu Z, Ding T. Quorum-Sensing Regulation of Antimicrobial Resistance in Bacteria. Microorganisms. 2020 Mar; 8(3):425. doi: https://10.3390/microorganisms8030425. PMID:32192182.
113. Jiang T, Li M. Quorum sensing inhibitors: a patent review. Expert Opin Ther Pat. 2013 Mar; 23(7): 867-94. doi: htt ps://10.1517/13543776.2013.779674.
114. Scutera S, Zucca M, Savoia D. Novel approaches for the design and discovery of quorum-sensing inhibitors. Expert Opin Drug Discov. 2014 Jul; 9(4): 353-66. doi: https://10.1517/17460441.2014.894974.
115. Das R, Mehta DK. Microbial Biofilm and Quorum Sensing Inhibition: Endowment of Medicinal Plants to Combat Multidrug-Resistant Bacteria. Curr Drug Targets. 2018 Apr; 19(16): 1916-32. doi: https://10.2174/1389450119666180406111143.
116. McCarthy H, Rudkin JK, Black NS, Gallagher L, O'Neill E, O'Gara JP. Methicillin resistance and the biofilm phenotype in Staphylococcus aureus. Front Cell Infect Microbiol. 2015 Jan; 5:1. doi: https://10.3389/fcimb.2015.00001. PMID:25674541.
117. Schilcher K, Andreoni F, Dengler Haunreiter V, Seidl K, Hasse B, Zinkernagel AS. Modulation of Staphylococcus aureus Biofilm Matrix by Subinhibitory Concentrations of Clindamycin. Antimicrob agents Chemother. 2016 Sep; 60(10): 5957-67. doi: https://10.1128/aac.00463-16. PMID:27458233.
118. Mohammed YHE, Manukumar HM, Rakesh KP, Karthik CS, Mallu P, Qin HL. Vision for medicine: Staphylococcus aureus biofilm war and unlocking key's for anti-biofilm drug development. Microb Pathog. 2018 Oct; 123: 339-47. doi: https://10.1016/j.micpath.2018.07.002. PMID:30057355.
119. Song H-S, Choi T-R, Bhatia SK, Lee SM, Park SL, Lee HS, et al. Combination Therapy Using Low-Concentration Oxacillin with Palmitic Acid and Span85 to Control Clinical Methicillin-Resistant Staphylococcus aureus. Antibiotics (Basel). 2020 Oct;9(10):682. doi: https://10.3390/ antibiotics9100682.
120. Nurani LW, Soleha TU, Ramadhian MR. Potensi 7-O-Butylnaringenin sebagai Antibakteri pada Methicillin Resistant Staphylococcus aureus (MRSA). Majority; 7, http://repository.lppm.unila.ac.id/ id/eprint/7115 (2018, accessed 3 October 2024).