



A review on medicinal plant extracts and their active ingredients against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus*

Marzieh Askarinia^{1,2}, Ali Ganji^{3,4}, Farhad Jadidi-Niaragh^{5,6,7}, Sajad Hasanzadeh⁸, Bahram Mohammadi², Farideh Ghalamfarsa², Ghasem Ghalamfarsa^{2*}, Hassan Mahmoudi^{9*}

¹Student Research Committee, Yasuj University of medical sciences, Yasuj, Iran

²Medicinal Plants Research Center, Yasuj University of Medical Sciences, Yasuj, Iran

³Molecular and Medicine Research Center, Arak University of Medical Sciences, Arak, Iran

⁴Department of Microbiology and Immunology, School of Medicine, Arak University of Medical Sciences, Arak, Iran

⁵Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁶Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁷Department of Immunology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁸Department of Internal Medicine, Yasouj University of Medical Sciences, Yasouj, Iran

⁹Department of Microbiology, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

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ABSTRACT

Staphylococcus aureus is among the pathogens capable of developing a broad spectrum of infections in human beings. In addition to the hospital, the bacterium is present in the community and has a high resistance to antibiotics, which is also increasing on an ongoing basis. Resistance to β -lactam antibiotic family is one of the concerns about the bacterium that has encountered the treatment of such infections with difficulty. Due to the increased resistance and importance of this bacterium, new strategies are needed to control this pathogen. One of these approaches is the use of medicinal plants, which has attracted many researchers in the last decade. Several studies have been carried out or are being designed using various herbs to find active ingredients to deal with this bacterium. The aim of this study was to present the antibacterial activity of different medicinal plants and the effects of their active ingredients on methicillin-resistant and methicillin-sensitive *S. aureus* (MRSA, MSSA), and to clarify the pathway to further studies in this regard.

Implication for health policy/practice/research/medical education:

Due to the increased resistance and importance of this bacterium, new strategies are needed to control this pathogen. One of these approaches is the use of medicinal plants, which has attracted many researchers in the last decade.

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Introduction

Staphylococcus aureus is a gram-positive bacterium colonized on the skin, and present in the nose of 25% to 30% of healthy people (1). In general, the nose, armpit and groin before the invasive infection with *S. aureus* are sites where the bacteria are colonized (2). A broad spectrum of infections, ranging from minor skin infections to postoperative wound infections are caused by *S. aureus* (3). This bacterium is one of leading human pathogens that has high resistance to antibiotics and is the main

source of hospital-acquired and community-acquired infections (4,5). Nosocomial infections with *S. aureus*, in particular methicillin-resistant *S. aureus* (MRSA), are of the major causes of hospitalization, which imposes a high economic burden on the patients and the hospital (6). The MRSA is one of the opportunistic pathogens considered to be a serious threat to public health (7). The bacterium was described for the medical community through a prominent article published for the first time in a British Medical Journal (8). After the introduction of

*Corresponding authors: Ghasem Ghalamfarsa, Tel: +98-9177746921, Email: Ghasem_Ghalamfarsa@yahoo.com; Hassan Mahmoudi, Tel: +989189539458, Hassanmahmoudi24@gmail.com

methicillin to the medical arena in 1960, the MRSA was first identified in Europe. Natural resistant strains have been isolated without the use of methicillin or related agents in some countries (9). Methicillin resistance occurs due to the presence of the *mecA* gene encoding PBP2a (penicillin-binding protein 2a) molecule that has a slight affinity for binding to β -lactam antibiotics. The PBPs are trans-peptidases that catalyze the interaction between the peptide bridges of the bacterial cell wall. The mutation in this molecule causes antibiotic resistance of the bacterium (10).

A similar PBP2a has been described recently, encoding by *mecC*, and is homogeneous by 70% with *mecA* (11). The SCC (Staphylococcal cassette chromosomes) elements have been so far described as the only carrier for the *mecA* gene. These elements are classified into different types according to the type of recombinases they carry and their overall genetic composition. Coagulase-negative staphylococci with *mecA* are of the potential reservoir of these elements (12). The first strain of community-acquired MRSA (CA-MRSA) was reported in 1990. In recent years, it has been unclear the distribution of hospital-acquired MRSA (HA-MRSA) and CA-MRSA strains. Both strains are endemic in hospitals in many areas. The changes in the MRSA evolution have made these bacteria a serious threat to public health. The CA-MRSA develops a series of skin and soft tissue infections and sometimes severe infections (3,13-14). Indiscriminate administration of antibiotics is one of the causes of antibiotic resistance. The high level of antibiotic resistance and the presence of SCC *mec* types indicate that infections caused by these strains require more advanced care and also newer antibiotics (15). The antibiotic resistance is the biggest challenge for the medical area in the treatment of infectious diseases. The resistance has been documented not only against natural and semi-synthetic antibiotics, but also against fully synthesized compounds (such as fluoroquinolones) or antibiotics that do not even penetrate through the cells (such as vancomycin) (16). This study was aimed to review the antibacterial activity of different medicinal plants and the effects of their active ingredients on MRSA and MSSA, and to clarify the pathway to further studies in this regard.

Medicinal plants

Herbal medicines embrace a wide range of practices and therapies outside the realm of traditional Western medicine. Although herbal medicines are not risk free, they can still be safer than synthetic drugs. The potential benefits of herbal medicines include high acceptance by patients, effectiveness, relative safety and relatively low costs (17). Due to the increasing use of herbal medicines around the world, their safety has often become a medical issue (18). Many consumers are demanding food that is free of harmful and chemically synthetic materials, including food antimicrobial preservatives. As a result, the passion

for natural antimicrobial substances has been increased as potential alternative to commonly used antimicrobial agents to increase half-life and control the food pathogens (19). The complementary and alternative medicine practices are increasingly being employed to detect or treat allergic diseases, and numerous studies have been reported on the benefits of this type of medication (20). Conventional drugs usually provide antibiotic treatment for bacterial infections, but the problem of increasing antibiotic resistance reveals the need for new therapies. Over the past few years, the use of natural ingredients has attracted further attention to promote human and animal health. Hence, increased antibiotic resistance has encouraged healthcare providers to be in the wake of alternatives, including botanical and herbal medicines to manage the invasive microorganisms (21, 22).

Huge consideration has been directed to determine the antimicrobial activity of the plant extracts in traditional medicine, essential oils or other isolated ingredients, such as alkaloids, flavonoids, diterpenes, triterpenes or naphthoquinones, sesquiterpene lactones, and the like. Some of these compounds have been separated after detecting the antimicrobial activity of the plant (23). The flavonoids are compounds present in photosynthetic cells and commonly found in fruits, vegetables, stems, seeds, flowers, and so on. Many studies have been conducted to identify the antibacterial mechanisms of the flavonoids. For example, quercetin activity is partly responsible for inhibiting DNA gyrase. It has been observed that sophoraflavone G and epigallocatechin gallate hamper the energy metabolism of membrane cell function and licochalcones A and C (24). Flavonostilbenes have shown special antibacterial and antibiofilm activity against *Staphylococcus epidermidis* with minimum inhibitory concentration (MIC) values of 3.1 to 12.5 μ g/mL (25). Phenolic acids exist in our various diets such as foods made thanks to Fungi, which owing to their biological properties have been widely investigated so that there is evidence of their role in disease prevention. However, these compounds are metabolized in vivo, circulating as glucuronidated, sulfated and methylated metabolites and indicating higher or lower biological activity (26). The essential oils are complex compounds among the various types of volatile molecules such as terpenoids, aromatic compounds derived from phenols and aliphatic compounds, which have found many fans in pharmaceutical, health, cosmetic, agriculture and food industries (27). The essential oils have been used since the middle ages as bactericides, virucides, fungicides, disinfectants, insecticides and other purposes such as analgesics, sedatives, anti-inflammatory agents, spasmolytics and local anesthetics (28). Terpenoids and phenylpropanoids are the main components of essential oils that provide their biological properties (29). Sesquiterpenoids, and especially sesquiterpene lactones,

from family Asteraceae play a pivotal role in human health as part of a balanced diet and pharmaceutical agents. Some sesquiterpene lactones have antimicrobial properties and can impair fungal and bacterial cell wall (30).

The active ingredients of medicinal plants against *S. aureus*

This article attempts to highlight the findings of previous studies regarding the antimicrobial effects of various herbal compounds on bacteria, including *S. aureus* and MRSA, in order to clarify the effects of medicinal plants on these bacteria. A comprehensive description of medicinal plants with antibacterial activities is presented below and a summary of them are listed in Table 1.

Family Asteraceae

The plants in family Asteraceae are of great interest owing to compounds such as flavonoids, saponins, steroids, alkaloids and glycosides. The active compounds in this family are sesquiterpene lactones, which are key secondary metabolites responsible for the antibacterial activity of this family (52,53). *Xanthium strumarium* extract showed significant effect on MSSA (25 mm) and MRSA (20 mm), which had more effect on MSSA. The results exhibited correlation of dose and sensitivity between the plant extract concentrations and bacterial growth inhibition. The antibacterial activity of this plant may be due to the presence of phenolic acids, flavonoids, tannins and terpenoids in the methanolic extracts (54). Hasson et al examined the antibacterial activity of ethanolic extract of *Saussurea lappa* root against multidrug resistant (MDR) bacteria, including MRSA. The results showed bacteriostatic effects at a concentration of 2000 µg/mL and a bactericidal effect at a concentration of 6000 µg/mL on the MRSA. Therefore, this study investigated the herb as an antibiotic because one of the reasons may be attributed to the presence of a new source of antimicrobial agents with new potential mechanisms.

Systematic screening of molecules such as antibacterial agents may lead to the discovery of new active ingredients (55). Different extracts of *Senecio tenuifolius* Burm plant were evaluated on MRSA and MSSA. The results showed that the methanolic extract of this plant significantly reduced the growth of these bacteria. Then, the active ingredients of this plant were purified by column chromatography. Four fractions were obtained and the fraction 3 had an inhibitory effect on the strains studied, which showed the zone of inhibition (ZOI) diameter of 15.09, 13.25, 14.12 mm, and the MIC values of 88.16, 128.11 and 116.12 µg/mL, respectively (56). These studies show the benefits of *S. tenuifolius* in treating skin infections. Talib et al investigated the antibacterial activity of 14 plants on various gram-positive and gram-negative bacteria. These plants displayed antibacterial effect on both bacterial groups, while their impacts were

higher on gram-positive bacteria. One of the bacteria was MRSA. The results of the study showed that the MIC value was 500 µg/mL for butanol and aqueous extracts of *Rosa damascena* receptacles and 250 µg/mL for butanol extract of *Inula viscosa* flowers. The bacterium was sensitive to butanol extract of *Rosa damascena* receptacles (95% inhibition), *I. viscosa* flowers (92% inhibition) and *Verbascum sinaiticum* flowers (70% inhibition) (57). Investigating different fractions of methanolic extract of *Atractylodes japonica* root showed that the fraction of CHCl₃ had a good antibacterial effect on *S. aureus* strains. The MIC value for the fraction of CHCl₃ exhibited the antibacterial effect as equal as ampicillin (32 µg/mL) against MRSA ATCC33591. Purification of this fraction gave four compounds; the compound 4 (6E, 12E)-tetradecadiene-8, 10-diyne-1, 3-diol) possessed anti-MRSA activity at a MIC value of 4-32 µg/mL. These results provide a promising basis for the potential use of this extract as well as the separation of its compounds for the treatment of bacterial infections (58).

During a research on *Gynoxys verrucosa* Wedd, which is one of the traditional southern Ecuadorian herbs, the results showed that the extract of this plant had a poor antibacterial activity. Purification and examination of the compounds of this plant extract showed that compound 1 (sesquiterpene lactones leucodine) had no antibacterial activity, but compound 2 (dehydroleucodine) had moderate antibacterial activity (MIC₅₀ between 49 and 195 µg/mL). This conclusion suggests that exocyclic conjugated methylene in the lactone ring is essential for the antibacterial activity of sesquiterpene lactones. In the compound 2, in addition to the lactone ring carbonyl, there is a carbonyl in the opposite direction to the cycloheptane ring and perhaps the second hydrogen bonding site is required for this activity (59).

Family Apocynaceae

One of the folk Indian medicines used to treat skin infections is leaf and stem bark of *Tabernaemontana alternifolia* (Roxb). In studies, the MIC value was 600-800 µg/mL for MRSA. The aqueous extract of this plant has shown antibacterial activity against MRSA and VRSA, and it has no cytotoxic effect that confirms the validity of this plant in traditional medicine and introduces it as a candidate for the treatment of MRSA infections (47). The methanolic extract of *Tabernaemontana stapfiana* Britten root and stem had good antibacterial activity. The zone of inhibition diameter of this extract was 9 to 19 mm higher than other bacteria, which showed the highest inhibitory effect on *S. aureus* (ZOI=19 mm). The lowest MIC value was 15.6 mg/ml, which was related to *S. aureus*. This potent antibacterial effect of methanolic extract can be attributed to the presence of alkaloids and saponins, which are antibacterial compounds. There are also other antibacterial compounds such as flavonoids

Table 1. The list of medicinal plants and their antibacterial activities

Source	Active compounds	Antibacterial assay method	Type extraction	Active against bacteria	MIC($\mu\text{g/mL}$)	Ref.
<i>Laennecia confusa</i> (Cronquist) G. L. Nesom (Asteraceae).	Triterpenes Saponins Flavonoids Tannins	MIC	N-hexane (hexane)	<i>E.coli</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i> MRSA <i>Staphylococcus aureus</i>	NA NA NA 1000 1000	(31)
<i>Laennecia confusa</i> (Cronquist) G. L. Nesom (Asteraceae).	Triterpenes Saponins Flavonoids Tannins	MIC	Chloroform	<i>E.coli</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i> MRSA <i>Staphylococcus aureus</i>	NA NA NA NA 1000	(31)
<i>Laennecia confusa</i> (Cronquist) G. L. Nesom (Asteraceae).	Triterpenes Saponins Flavonoids Tannins	MIC	Methanol	<i>E.coli</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i> MRSA <i>Staphylococcus aureus</i>	NA NA 1000 200 1000	(31)
<i>Psidium guineense</i> Swartz	Tannins, flavonoids, condensed proanthocyanidins, leucoanthocyanidins, and sugar	MIC MBC	Aqueous extract	MRSA	Between 250 and 500 $\mu\text{g/mL}$	(32)
Goldenseal (<i>Hydrastis canadensis</i>)	Alkaloid and flavonoid	MIC, Quorum quenching assays with fluorescent reporters, Quorum quenching assay with lux reporter, Human skin epithelia toxicity assay	Hydroethanolic extract	MRSA	75	(33)
<i>C. circinalis</i> and <i>C. revoluta</i> leaflets	Biflavonoids	MIC MBC IC50	Methanolic extract	<i>Staphylococcus aureus</i> MRSA	17.5/ 35.9/ 37 NA/35.9/ 37	(34)
<i>Abrus schimperi</i>	Amorphaquinone and pendulone	MIC IC50	Etoh extract	<i>Staphylococcus aureus</i> MRSA	10/2.5 20/2.5	(35)
<i>Bersama engleriana</i> Gurke	Flavonoids Phenols Triterpenes Anthraquinones	MIC MBC Preliminary phytochemical investigations Antitumor assays Antioxidant assay Acute oral toxicity study	Methanolic extracts	<i>Citrobacter freundii</i> , <i>Enterobacter cloacae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumonia</i> , <i>Morganella morganii</i> , <i>Proteus mirabilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Shigella dysenteriae</i> , <i>Salmonella typhi</i> , <i>Streptococcus faecalis</i> , <i>Staphylococcus aureus</i> , <i>Bacillus cereus</i> , <i>Bacillus stearothermophilus</i> , <i>Bacillus subtilis</i>	9.76 to 156.25	(36)
<i>Xanthium strumarium</i>	Phenolic acids, flavonoids tannins, triterpenoids	Disc diffusion method Paired diene method	Methanolic extract	MSSA, MRSA	-	(37)
<i>Holoptelea integrifolia</i>	Alkaloids, flavonoids tannins, terpenoids, glycosides	MIC MMC Agar well diffusion method Folin-Ciocalteu Colorimetric method	Methanolic extracts	<i>Bacillus cereulences</i> , <i>Pseudomonas aeruginosa</i> , <i>Bacillus subtilis</i> , <i>Klebsiella aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	62.5 to 1250	(38)

Table 1. Continued

<i>Piper umbellatum</i>	Flavonoid, alkaloid, terpene, and sterolclasses	MIC Outer membrane permeability IntracellularKp efflux Nucleotide leakage	Hydroethanolic extract	<i>E.coli, K. pneumoniae, P. aeruginosa, S. typhimurium, Shigella flexneri, E. faecalis, S. aureus, S.pyogenes, S. epidermidis</i>	12.5 to 25 mg/mL >100 mg/mL	(39)
Lemongrass, oregano, rosemary thyme, neem, tulsi, aloe vera bryophyllum	Sugars, alkaloids, anthraquinones, glycosides flavonoids tannins, steroids, saponins, triterpenoids, phlobatanins	MIC agar well diffusion method	Hexane, Chloroform, Methanol, ethanol water extract	Multi-drug resistant <i>Staphylococcus aureus</i> <i>K. pneumoniae, E. coli.</i>	1.56-6.25 6.25-25	(40)
<i>Helicanthus elastica</i>	Phenolic composition	MIC agar well diffusion method	Ethanol extract	<i>A. hydrophila, K. pneumoniae, E.coli, V. fischeri, B. subtilis, MRSA, P. aeruginosa, S. pyogenes,</i>	250 to 500	(41)
<i>Ephedra procera</i>	Phenolic compound	MIC MBC	Ethanol extract	<i>Proteus vulgaris</i> <i>P. aeruginosa</i> <i>Enterobacter aerogenes</i> <i>B. cereus</i> <i>S. aureus</i>	250 500 250 250 500	(42)
<i>Blechnum orientale</i> Linn	Flavonoids, terpenoids, Tannins	Disc diffusion test MIC MBC	Methanol extract	<i>B. cereus, Micrococcus luteus, MSSA, MRSA, S. epidermidis</i>	15.6-250	(43)
<i>Cocos nucifera</i>	Procyanidins	Agar diffusion method MIC, MBC	Aqueous crude extract	<i>S. aureus</i> MRSA	1024 1024	(44)
<i>Clausena heptaphylla</i>	Flavonoids, alkaloids, saponins, steroids, glycoside, carbohydrate	Disc diffusion method MIC	Ethanol extract	<i>B. subtilis, S. aureus, B. cereus, B. polymyxa, B. megaterium, E. faecalis, S. typhi, Klebsiella sp, S. flexneri, S. sonnei, Proteus sp, E. coli</i>	2.000 to 3.500	(45)
<i>Pupalia lappacea</i> Juss	Steroids, glycosides, saponins, flavonoids, alkaloids, sugar and phenol	MIC, MBC	Methanolic extract	<i>P. aeruginosa, S.aureus, B. subtilis</i>	9000, 4000, 3000	(46)
<i>Tabernaemontana alternifolia</i>	Alkaloids, flavonoids, coumarins, saponins and steroids	Disc diffusion method MIC	Aqueous extracts	<i>B. subtilis, S.aureus</i> (ATCC 6538P), <i>S. epidermidis</i> (ATCC 12228), <i>E. coli</i> (ATCC 8739), MRSA (ATCC 43300), VRSA	600–800	(47)
<i>Chelidonium majus</i> Linn	Alkaloids	MICs MBCs	Methanolic extract (crude extract and fractions)	MRSA	0.49-15.63	(48)
<i>Premna resinosa</i>	Flavonoids, Anthraquinones, Terpenoids, Phenols, Alkaloids	Disc diffusion method MIC MBC	Methanol crude extracts and fractions)	<i>S. aureus, MRSA, E. coli, K. pneumoniae, P. aeruginosa, S. typhi, S. sonnei, M. tuberculosis</i>	31.25-125 >6.25 - 50	(49)
<i>B. citriodora, T. ferdinandiana, C. australasica, L. ponticum</i>	Phenolic compounds	Well diffusion assay MIC MBC	Aqueous, ethanolic and peptides extracts	<i>S. aureus,</i> <i>E. coli,</i> <i>B. cereus</i>	>125- 1.17 125-1.17 31.25-0.58	(50)
<i>Terminalia fagifolia</i>	Terpenoidsglucocorticoids, flavonoids polyphenols	MIC MBC	Ethanol extract, Hydroalcoholic fraction, Aqueous fraction, Water soluble fraction	<i>S. aureus</i> (ATCC 29213), <i>S. aureus</i> COL, <i>S. aureus</i> WB69, <i>S.epidermidis</i> (ATCC 12228), <i>S. epidermidis</i> H111, <i>S. epidermidis</i> 70D	25-200	(51)

and coumarin that have synergistic effects (60). Wang et al examined the *Alstonia scholaris* plant and concluded that the plant had six pentacyclic terpenoids. Two compounds of oleanolic and ursolic acid have antibacterial activity limited to gram-positive bacteria. The ursolic acid had a synergistic effect along with ampicillin and tetracycline on two bacteria of *S. aureus* and *Bacillus cereus*. The ability of this compound to enhance the activity of antibiotics can be one of the most important therapeutic agents in the future (61).

Family Labiatae (Lamiaceae)

The ethanol extract of tulsi, thyme, oregano and rosemary plants belonging to Family Lamiaceae have promising broad spectrum antibacterial properties on MDR bacteria. The ZOI is between 6 to 20 mm in tulsi, 4 to 18 mm in oregano and rosemary, and 4 to 21 mm in thyme. The presence of tannins and saponins has been confirmed in all herbs. The MIC value in the *Ocimum tenuiflorum* plant was ≤ 3.12 mg/ml for *S. aureus* and MRSA, which could be due to the fact that flavonoids and tannins are the main components of this plant against MRSA (40).

The two compounds of oleanolic acid and ursolic acid from *Salvia officinalis* (Sage) leaves showed antibacterial activity on vancomycin-resistant enterococci, *Streptococcus pneumoniae* and MRSA. The antimicrobial activity of ursolic acid on vancomycin-resistant enterococci suspension and *S. pneumoniae* and MRSA were twice as strong as oleanolic acid, which was calculated from the values obtained from MIC (62). Although the antibacterial activity of oleanolic acid and ursolic acid is not as strong as the antimicrobial drugs used in the clinic, its antibacterial activity is relatively acceptable as a plant-derived compound. *Premna resinosa* is one of the traditional herbs used for respiratory diseases. The findings highlighted the anti-*Mycobacterium tuberculosis*, anti-bacterial and antifungal activity of this plant. The fraction of dichloromethane had the highest MIC on MRSA (31.25 μ g/mL) and the fraction of ethyl acetate had the highest ZOI diameter (22.3 \pm 0.3 mm) on *S. aureus*. The effects of this plant can be related to its alkaloids, flavonoids, terpenoids, anthraquinones and phenols (49). Reports suggest an inhibitory effect of the 5-hydroxy-1,4-naphthalenedione composition of the Teak leaf on *Listeria monocytogenes* and MRSA (63). The leaves of *Rosmarinus officinalis* and *Tecoma capensis* have a moderate anti-quorum sensing activity (64). Family Labiatae can be widely used as a natural source derived from plants against MRSA (65).

Family Ranunculaceae

The goldenseal (*Hydrastis canadensis* L.) plant is traditionally used for skin diseases (66). LC-MS method was used to detect alkaloids and flavonoids in this extract as inhibitors of efflux pump. The extract of this plant has anti-quorum sensing activity on MRSA, which can be

due to the reduction of cell signaling through the two-component regulatory system (TCS) of AgrCA. This extract also inhibits the production of MRSA toxin and damage to keratinocytes, in vitro (33-67).

Family Polygonaceae

Polygonum aviculare and *Polygonum cuspidatum* are the plants from family Polygonaceae with antibacterial activity on *S. aureus* (68). The ethanolic extract of *Rumex nervosus* has an inhibitory effect on gram-positive and gram-negative bacteria, while the hexane extract of this plant has a relatively mild antibacterial activity on gram-negative bacteria such as *E. coli* and *Pseudomonas aeruginosa*, but both extracts inhibit *Candida albicans*. The aqueous extract of this plant has a dose-dependent inhibitory effect on *S. aureus* and MRSA (69). In the essential oils extracted from *Polygonum minus*, GCMS showed different compounds, including aliphatic compounds such as decanal and dodecanal. The antibacterial activity of non-polar extracts (n-hexane) showed higher antimicrobial activity on MRSA compared to polar extracts (70).

Family Solanaceae

Methanolic extract of *Withania somnifera* leaves from family Solanaceae on gram-positive bacteria including *S. aureus* and Enterococcus showed the ZOI diameters of 20.6 and 19.4 mm, respectively, at a concentration of 2 mg/mL (71). The antimicrobial activity of methanolic extracts of various organs of *Bersama engleriana* (family Melianthaceae) on different microorganisms including gram-positive bacteria, gram-negative bacteria, *Candida* and mycobacterium showed that the MICs were between 9.76 to 156.25 μ g/mL. These activities were attributed to the presence of flavonoids, terpenoids, anthraquinones and phenols (36).

Family Urticaceae

The methanolic extract of *Urtica dioica* (family Urticaceae) has antibacterial properties, which can be due to the presence of antibacterial compounds (208.37 \pm 4.39 = phenols, 20.29 \pm 0.48 = flavonoids, and 22.83 \pm 0.30 = flavonols). The reported MICs for this extract were 9.59 to 149.93 mg/ml (72,73).

Family Piperaceae

The hydroalcoholic extract of *Piper umbellatum* (family Piperaceae) leaves has antibacterial activity and low toxicity in vitro and in vivo. Its mechanism of action is related to the change in the cell membrane and wall permeability that can be linked at least to the presence of flavonoid spresentin (39).

Family Poaceae

Dahiya showed that hexane and chloroform extracts of lemongrass were not effective on the tested bacteria (*S. aureus*, MRSA, *E. coli*, *Klebsiella pneumoniae* and *Proteus*

mirabilis). *S. aureus* ATCC 25923 had the most sensitivity to the tested extracts (neem, tulsi, oregano, rosemary, aloe vera, thyme) except for hexane and chloroform extracts of lemongrass. The highest MIC of Lemongrass extract against *S. aureus* was 12.5 mg/mL (42). *Eleusine indica* (Poaceae) is a tropical plant. It is resistant to environmental conditions and is used for many diseases, including influenza, increased blood pressure and so on. In addition to antioxidant, it showed to have anti-bacterial properties and its hexane extract exhibited significant activities against MRSA and *P. aeruginosa* (74). Another species of this family is *Bromus inermis* Leyss, which contains flavonoids. The hexane extract of this plant (MIC = 8 µg/mL) had significant effects on MRSA (75).

Family Rosaceae

The *Rosa canina* L. (red rose) plant contains compounds such as tellimagrandin I and rugosin B that decrease MIC values of L-lactam antibiotics against MRSA (76). The Fructus crataegi (hawthorn) also contains catechin, epicatechin gallate and epigallocatechin, which increase the effect of β -lactam antibiotics whose mechanism of action is through the suppression of genes (nor A, nor C and abc A) involved in the efflux pump (77). *Rosa damascena* Mill is another plant in this family, whose anti-MRSA effect has been confirmed in previous researches (36).

Family Myrtaceae

The essential oils obtained from various species of *Melaleuca* plant have been effective against *S. aureus* isolated from the ulcer of patients (78). In a study by Razmavar et al on *Baeckea frutescens* L. plant from this family, the findings revealed that the leaf extract of this plant has active ingredients, including flavonoids, alkaloids, steroids, terpenoids, phenols and carbohydrates. The antibacterial activity of this extract is related to these compounds (79). The ethanol extract of *Rhodomyrtus tomentosa* showed good antibacterial activity. Proteome analyzes revealed the effects of this plant on the expression of several major functional classes of MRSA cell proteins, including proteins responsible for biosynthesis of cell wall and cell division, surface antigens, and virulence factors. The effects of this plant on morphology and superstructure changes in treated bacteria were confirmed using transmission electron micrographs. Significant changes were observed, including changes in the cell wall, abnormal septum, cellular collapse and lysis (80). The combination of aqueous extract of *Psidium guineense* Swartz with β -lactam antibiotics, fluoroquinolones and carbapenems showed synergistic effects against the MRSA strains (32).

Family Rutaceae

The ethanolic extract of *Clausena heptaphylla* (from family Rutaceae) stem bark has alkaloids, flavonoids,

saponins and steroids, but lacks tannins, anthraquinones and resins. This extract was effective on a large number of bacteria, including *S. aureus*. In addition to strong antioxidant properties, this plant showed better effects on gram-positive (ZOI = 6.5-9.0 mm) than gram-negative (ZOI = 3.0-4.5 mm) bacteria (45).

Family Lauraceae

Falodun et al suggested that the *Persea americana* plant is effective on both fungi and bacteria (81). The petroleum ether extract of the plant has an excellent antibacterial activity against MRSA with an IC₅₀ value of 7.8 µg/mL (82). The extract of *Laurus nobilis* leaves has also shown a potent anti-MRSA activity (ZOI = 25 mm) and an anti-quorum sensing activity (>17 mm) (46). Ethyl acetate fraction from *Cinnamomum iners* standardized leave has a strong antibacterial activity, especially against MRSA and *E. coli* with the MIC values of 100 and 200 µg/mL, respectively. Xanthorrhizol (5- (1,5-dimethyl-4-hexenyl) -2-methylphenol) was identified by different spectroscopic techniques in this plant, as the mentioned properties can be due to the presence of this compound (83).

Family Combretaceae

Ethanol extract and stem bark fractions of *Terminalia fagifolia* exposed good anti-MRSA activity (MIC=25-200 µg/mL and minimum bactericidal concentration (MBC) = 200-400 µg/mL). They also inhibited more than 80% biofilm formation. The images of Atomic Force Microscopy (AFM) also showed the morphological changes of the aqueous fraction of this plant on the surface of the *S. aureus* ATCC29213 (51). *Terminalia ivorensis* has traditionally been used to treat dermatological disorders, which can be due to the presence of tannins, saponins, flavonoids, coumarins and polyphenols (84).

Family Theaceae

Camellia sinensis plant from family Theaceae has antibacterial activity against MDR bacteria such as MRSA and MDR *P. aeruginosa* (85-86).

Family Fagaceae

One of the members of family Fagaceae is *Quercus infectoria*, which is traditionally used for skin and wound infections, probably due to the presence of more than 70% tannin. It contains ellagic acid, gallic acid, syringic acid and tannic acid. This plant has shown good antibacterial activity, which leads to an increased sensitivity of MRSA to high and low osmotic pressure (87). The synergistic effect of this plant with β -lactam antibiotics has been shown to interfere with staphylococcal enzymes such as autolysins and β -lactamase (88). This plant also had antibiofilm effects through its effect on the bacterial cell wall (89).

Family Fabaceae

The antibacterial compounds were obtained from the

polar fractions of *Ononis hirta* (a.p) and *Ononis sicula* (a.p). The antibacterial activity was well observed on many bacteria, including *S. aureus* and *Bacillus cereus*, which are causes of food poisoning. These plants contain flavonoids and terpenoids (36). Two new flavonoids, called bakuisoflavone and bakuflavanone, were identified in the *Psoralea corylifolia* fruit; these compounds exhibited significant anti-MRSA effects (90). In the genus *Abrus* from this family, amorphoquinone and pendulone compounds have been shown to be effective not only against *Leishmania donovani* and *Plasmodium falciparum*, but also on *S. aureus* and MRSA (35).

Family Loranthaceae

Helicanthus elastica (Desr.) Danser plant belonging to family Loranthaceae did not affect MRSA bacteria, but was more effective on gram-negative bacteria, especially *Klebsiella pneumoniae* (41). The plants of *Ephedra procera* (Ephedraceae) (42), *Eleutherine americana* Merr (Iridaceae) (91), *Blechnum orientale* Linn. (Blechnaceae) (43), *Cocos nucifera* (Arecaceae) (44), *Chelidonium majus* Linn (Papaveraceae) (48), *Labisia pumila* Benth (Myrsinaceae) (92), *Cytinus hypocistis* (Cistaceae) (93), *Sonneratia caseolaris* Linn (Sonneratiaceae) (94), *Turnera ulmifolia* (Turneraceae) (95), *Plectranthus amboinicus* (Lour.) Spreng (96), have been effective on different bacteria, including MRSA, which can be investigated as anti-MRSA candidates.

A large number of studies have been carried out on the identification of the antimicrobial effects of plant compounds on different microbial agents (97), which have also yielded favorable results. Wild plants have bioactive ingredients with potential activity against diseases associated with microorganisms (98). Zhang et al examined 58 traditional herbs and argued that their findings were consistent with the traditional use of these herbs. By detecting and isolating the potential substances of these plants, they can be used to discover a new antimicrobial agent for treatments (50).

Clinical trials

In addition to in vitro use of plants, researchers have investigated the in vivo effects of these plants on different bacteria, including MRSA; remarkable effects of these plants have been reported on inhibiting this bacterium (91,98). Yamada et al examined the inhaled effect of catechin tea on aged patients with cerebrovascular ailments whose sputum contained MRSA. These patients were exposed to the herb inhaled three times a day for three weeks. The results showed that the reduction in MRSA count in the sputum was 47% in the treatment group and 15% in the control group and this difference was significant. Although the inhalation of this plant has reduced the count of this bacterium, its use to control the MRSA-associated infections is controversial (99). Buenz

et al stated that the Atun tree (*Atuna racemosa*) is one of the plants identified in the 400-year book of plant history to heal the MRSA-related infections. They showed that the Atun tree extract at the doses of 10 times greater than MIC value are effective against MRSA for topical use in humans (100). Tea tree oil is one of the ingredients traditionally used to treat skin diseases, as researchers have confirmed the effects of these compounds. The body washing with these compounds can prevent colonization of microorganisms on the body (101-103).

Conclusion

The emergence of expanding antibiotic-resistance genes in the bacterial population has led to the identification of new antimicrobial drugs. The most promising of these compounds are drugs affecting microorganisms through various mechanisms to eliminate microorganisms with subsequent drug actions in case of resistance to a mechanism, hereby contributing to treat MDR bacterial infections. Consequently, there is a need for concentration to detect the active components of these compounds, as well as to pursue simultaneously the development of this product as a natural product. The results of this study showed that different plants belonging to various families have the ability to inhibit *S. aureus* and MRSA and can be used to achieve effective drugs against these bacteria. Considering the synergistic effects of some of these plants with antibiotics used in the clinic, it is suggested to be evaluated the combined effects of different parts of the plants in combination with antibiotics in future studies.

Authors' contributions

MA, HM GGH and AG contributed to the idea of the study, its design and interpretation. The manuscript was prepared by HM, FJN, FGH, SH and BM and the final version was approved by all authors.

Conflict of interest

None to declare.

Ethical considerations

Ethical issues have been observed by the authors.

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