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COMBATTING METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) IN THE FOOD INDUSTRY BY HARNESSING THE POWER OF NATURE: A SYSTEMATIC REVIEW

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Abstract

Antibiotic resistance is a critical global health concern, with *Methicillin-resistant Staphylococcus aureus (MRSA)* posing a significant challenge due to its resistance to commonly used antibiotics. Recent research has revealed the potential of natural compounds and microorganisms in combatting *MRSA* and other antibiotic-resistant bacteria. In this systematic review, we studied the effect of essential oils, bacteriophages, bacteriocins, and probiotics on *S. aureus,* including *MRSA* in particular, in the food industry. Essential oils (EOs) have gained significant attention because of their antimicrobial properties, inhibiting *MRSA* growth by damaging bacterial cells and inhibiting essential enzymes and compounds. Cinnamon oil liposomes caused the most significant decrease in *MRSA* populations among our reviewed essential oils. Bacteriophages can lyse the bacterial host. They encode peptidoglycan hydrolases called endolysins that target the bacterial cell wall. In our study, *S. aureus* phage (containing *CHAPLysGH15* and *LysGH15*), and phage *SA11* endolysin *(LysSA11*) were the most effective against *S. aureus*. Bacteriocins, antimicrobial peptides produced by bacteria, also show potential in combatting *MRSA*, mainly by generating organic acids that interfere with bacterial metabolism. According to our review, the

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most effective bacteriocins against *S. aureus* were *Enterocin AS-48* with phenolic compounds or with *2NPOH*, Bacteriocin isolated from *Lactobacillus pentosus - Pentocin JL-1*, and bacteriocin produced by *S. pasteuri RSP-1,* respectively. Probiotics can compete with pathogens by producing antimicrobial compounds that disrupt *MRSA* cell production and ultimately lead to bacterial death. In our review, the most effective probiotics were *Streptomyces griseus*, *Pediococcus acidilactici strains A11 and C12*, *Lactococcus lactis*, and *Lactobionic acid* respectively. A multi-hurdle approach combining these natural agents has shown promising results in targeting and eliminating *MRSA* cells. By harnessing the power of nature, we can potentially overcome the challenges posed by *MRSA* and other antibiotic-resistant bacteria.

Key words: *Methicillin-resistant Staphylococcus aureus (MRSA)*, Essential oils, Bacteriophage, Bacteriocin, Probiotic

BORBA PROTIV STAPHILOCOCCUS AUREUS-a (MRSA) OTPORNOG NA METICILIN U PREHRAMBENOJ INDUSTRIJI KORIŠĆENJEM SNAGE PRIRODE: SISTEMATSKI PREGLEDNI RAD

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Kratak sadržaj

Otpornost na antibiotike je globalni zdravstveni problem, a meticilin rezistentan *Staphilococcus aureus* (MRSA) predstavlja značajan izazov zbog otpornosti na antibiotike koji se obično koriste. Skorija istraživanja otkrila su potencijal prirodnih jedinjenja i mikroorganizama u borbi protiv MRSA i drugih bakterija otpornih na antibiotike. U ovom preglednom radu proučavan je efekat eteričnih ulja, bakteriofaga, bakteriocina i probiotika na *S. aureus*, uključujući i izolate MRSA, u prehrambenoj industriji. Eterična ulja (EO) privukla su značajnu pažnju zbog svojih antimikrobnih svojstava, inhibirajući rast MRSA tako što oštećuju bakterijsku ćeliju i inhibiraju njihove esencijalne enzime i jedinjenja. Od svih ispitanih eteričnih ulja, lipo-

zomi ulja cimeta doveli su do najznačajnijeg smanjenja populacije MRSA. Bakteriofagi mogu da liziraju bakteriju koju napadaju. Oni sintetišu enzime peptiodoglikan hidrolaze koji su poznati pod nazivom - endolizini, koji oštećuju bakterijski zid. U našoj studiji, *S. aureus* fage (koje sadrže CHAPLisGH15 i LisGH15) i fag SA11 endolizin (LisSA11) bili su najefikasniji protiv *S. aureus*. Bakteriocini, antimikrobni peptidi koje proizvode bakterije, takođe pokazuju potencijal u borbi protiv MRSA, uglavnom stvaranjem organskih kiselina koje ometaju metabolizam bakterija. Na osnovu rezultata našeg preglednog rada, najefikasniji bakteriocini protiv *S. aureus* su bili Enterocin AS-48 sa fenolnim jedinjenjima ili sa 2NPOH, Bacteriocin izolovan iz *Lactobacillus pentosus* - Pentocin JL-1 i bakteriocin proizveden od *S. pasteuri* RSP-1. Probiotici mogu da deluju na patogen tako što proizvode antimikrobna jedinjenja koja ometaju proizvodnju MRSA ćelija i na kraju dovode do smrti bakterija. U našem pregledom radu, najveću efikasnost pokazali su probiotici *Streptomices griseus*, *Pediococcus acidilacti* sojevi A11 i C12, *Lactococcus lactis* i *Lactobionic acid*. Pristup koji kombinuje ove prirodne agense pokazao je zadovoljavajuće rezultate u prepoznavanju i eliminaciji MRSA ćelija. Koristeći snagu prirode, razvijamo potencijal za prevazilaženje infekcija uzrokovanih sa MRSA-ma i drugim bakterijama koje su otporne na antibiotike.

Ključne reči: *Staphilococcus aureus* otporan na meticilin (MRSA), eterična ulja, bakteriofag, bakteriocin, probiotik

INTRODUCTION

Staphylococcus aureus is a gram-positive pathogenic bacterium. The ability of *S. aureus* to adhere to specific host substrates and evade host defenses (Eom, et al. 2014; Lu, et al. 2021), as well as its ability to survive in various environmental conditions while posing different virulence factors (de Oliveira, et al. 2010; Eom, et al. 2014; Burris, et al. 2015; Lu, et al. 2021), makes it highly virulent and capable of causing life-threatening infections in both humans and animals (Zhu, et al. 2015; Catteau, et al. 2017; Lalouckova, et al. 2021). Foodborne diseases caused by *S. aureus* (Lee, et al. 2009; de Oliveira, et al. 2010; Keyvan and Tutun 2019; Prastiyanto, et al. 2020; Lalouckova, et al. 2021) are generally limited to food poisoning and gastroenteritis, resulting from enterotoxins produced by *S. aureus* (Lee, et al. 2009; Zhu, et al. 2015; AL-Saadi 2016; Prastiyanto, et al. 2020).

Antibiotic resistance is one of the most significant health challenges of the

century (Lee, et al. 2009; Chang, et al. 2017; Chang, et al. 2017; Prastiyanto, et al. 2020). Antibiotic-resistant forms of *S. aureus*, such as methicillin-resistant *Staphylococcus aureus (MRSA)*, are multi-drug-resistant (Eom, et al. 2014; AL-Saadi 2016; Lu, et al. 2021) to β-lactam antibiotics (Eom, et al. 2014; Redwan et al. 2016; Catteau, et al. 2017; Lestari, et al. 2019; Prastiyanto, et al. 2020). Foodborne *MRSA* is a major concern for public health worldwide (Lee, et al. 2013; Redwan, et al. 2016; Kang, et al. 2020; Lu, et al. 2021), because it can enter the food chain as animal based food (Vaiyapuri, et al. 2019; Kang, et al. 2020) or by colonizing in food handlers and transferring from them to food (Eom, et al. 2014). A high rate of morbidity and mortality by *MRSA* have been reported worldwide (Zhu, et al. 2015; Redwan, et al. 2016; Zouhir, et al. 2016; Salem 2017; Zihadi, et al. 2019). *MRSA* has already been isolated from food, indicating that it is present as a contaminant in the food production chain (Ansari, et al. 2020; Afshari, et al. 2022). The presence of *MRSA* has been reported mainly in meat such as pork, beef, lamb, chicken, rabbit, and turkey, as well as in dairy products such as milk and cheese (Mohammed-Ali, et al 2015). This means that the food production chain is a pathway of transmission between resistant microorganisms and humans (Mohammed-Ali, et al 2015). Food safety is an important global concern in the food industry and public health. Many preservatives that are used to control microbial growth in foods not only increase the shelf-life of food products, but they also reduce the incidence of foodborne diseases (Xu, et al. 2016; Chang, et al. 2017). Due to consumer worries regarding safety of chemical preservatives utilized in food, there is an increasing need for natural alternatives that can function as food preservatives. (Gyawali, et al 2014). Therefore, it is critical to use natural agents that control or prevent foodborne pathogens, including *MRSA*, in food (Kang, et al. 2020). By utilizing these natural antimicrobials as food preservatives, the need for excessive physical and chemical food processing can be reduced while ensuring microbial safety and environmental preservation (Yusuf, 2018).

Several natural compounds from plants, animals, and microorganisms have been studied and applied in order to inhibit or control the growth of foodborne microorganisms, including *MRSA*. Plant-derived essential oils are commonly used as flavoring and preservation agents in food and drinks have antimicrobial and antioxidative activity (Cui, et al. 2018; Yuan, et al 2018).

Bacteriophages are viruses that infect bacteria and can exhibit inhibitory activity against *S. aureus*, particularly *MRSA*. Furthermore, since gram-positive bacteria lack an outer membrane, bacteriophages can directly lyse the cell wall from the outside (Lysis from without) (Lu, et al. 2021). Bacteriocins are proteins that exhibit bactericidal effects on a variety of bacteria, including *S. aureus*. They are considered as alternatives to traditional antibiotics (Zhu, et al.

2015; Chauhan, et al. 2017; Lestari, et al. 2019) and an effective approach for use in food against *MRSA* (Arumugam, et al. 2019). Probiotics are living organisms used as food additives to help maintain a healthy microbial balance in the gastrointestinal tract, leading to better health in humans (Lee, et al. 2021).

This review focuses on the effective natural antimicrobials originating from plants and microorganisms against *MRSA*, including essential oils, bacteriophages, bacteriocins, and probiotics. The mechanisms of action, as well as their effectiveness, are also surveyed. Our main aim was to review the efficiency of natural antimicrobial agents in combating *MRSA* in food.

MATERIAL AND METHODS

Study Design

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were applied to conduct this systematic review. The main objective of this study was to review the literature on natural approaches for controlling *MRSA* in food.

Search Strategy

In this study, the main databases, including Scopus, PubMed, Google Scholar, and Science Direct, were searched. The literature review was limited to studies published from 2000 to 2023. The search was independently conducted for each database, focusing on controlling *Methicillin-resistant Staphylococcus aureus* OR *MRSA* in any food product worldwide. The keywords used were "*Methicillin-resistant Staphylococcus aureus*" OR "*MRSA*" AND "Dairy" OR "Milk" OR "Meat" OR "Food" AND "Essential Oils" OR "Probiotic" OR "Bacteriophage" OR "Bacteriocin" AND "Control".

Inclusion and Exclusion Criteria

This review included articles (n = 83) that reported on the natural types of effective antimicrobials, including essential oils, bacteriophages, bacteriocins, and probiotics, against *MRSA*. The selection for inclusion eligibility was conducted by scanning the titles, abstracts, and full texts of retrieved articles. The focus of our study was on livestock-associated *(LA) MRSA*. All review studies, duplicate publications, as well as clinical reports and trials on healthcare-associated *(HA) MRSA*, were excluded.

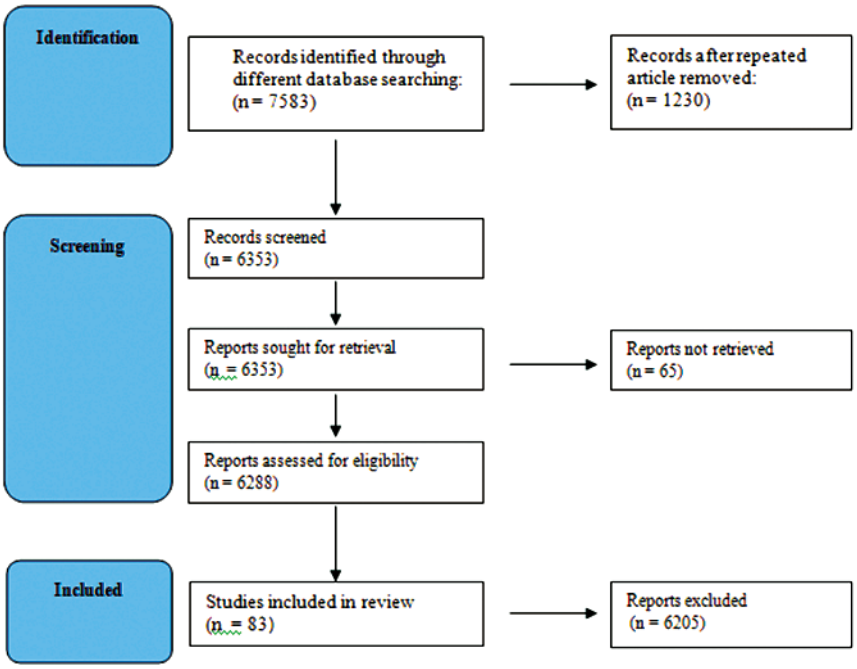

Figure 1. PRISMA flowchart for studies selection

RESULTS

Essential Oils

Essential oils have shown an antimicrobial effect against *S. aureus* and *MRSA* in particular. For instance, Cinnamon oil, Thyme oil, and Lemongrass oil reduced the *MRSA* population in minced meat by 7.6, 6.53, and 5.94 log CFU/g, respectively, when applied at a concentration of 1.5% (Eom, et al. 2014). Cinnamon oil was bactericidal against the biofilm activity of *MRSA*. A concentration of 1.0 mg/mL of cinnamon oil was sufficient to eliminate *MRSA* biofilm (Cui, et al. 2016). *Syzygium aromaticum (CLV)* and *Cinnamomum zeylanicum (CIN)* exhibited bactericidal activity at a concentration of 200 µg/mL against *S. aureus* and reduced the population of *S. aureus* by 4.50 log10 CFU/mL and 3.97 log10 CFU/mL, respectively (Mandal, et al. 2011).*Cuminum cyminum (CMN)* exhibited bactericidal activity at 300 µg/mL and caused a reduction of 0.59 log10 CFU/mL in *MRSA* after 24 hrs (Mandal, et al. 2011). The MIC concentration of the polyphenolic components of green tea, neem leaves extract, and a combination of green tea and neem were 15.62, 31.25,

and 46.87 mg/mL, respectively (Zihadi, et al. 2019). Allicin liquid was active against *S. aureus* strains, and all *MRSA* strains were inhibited by *allicin* at 32 µg/mL (Cutler, et al 2004). The indigenous cinnamon B leaf oil *(Cinnamomum osmophloeum)* had antibacterial effect against *MRSA* with an MIC of 250 µg/mL (Chang, et al. 2001). The *ethanolic* extract of *Elettaria cardamomum* displayed antibacterial activity against *MRSA*, with a minimum inhibitory concentration (MIC) of 0.25 mg/disk and minimum bactericidal concentration (MBC) of 0.50 mg/disk against *S. aureus* (Yassin, et al. 2022). *Nigella sativa* oil extract was effective against *MRSA*, with inhibition zones of 7 ± 1 mm and 10 ± 0.9 mm observed at concentrations of 400 µl and 800 µl, respectively (Abdullah, et al. 2021). *Litsea cubeba* essential oil *(LC-EO)* contained high percentages of *aldehydes*, *primarily β-Citral* (39.25%) and *α-Citral* (30.89%). *LC-EO* caused a steady decrease in *MRSA* populations, with a 99.99% reduction observed after 2 hours of treatment with 0.25 mg/mL of *LC-EO* (Hu, et al. 2019). *Red propolis* extracts *(RPE)* had an inhibition zone of 16.5 ± 0.5 mm and 19.3 ± 0.5 mm against *S. aureus* and *MRSA*, respectively (Zhang, et al. 2022). The essential oil extracted from *Carum carvi L.* seeds completely prevented *MRSA* biofilm formation at a concentration of 1.28%, with decreasing inhibitory effects observed at lower concentrations (Liu, et al. 2023). The *ethanol* extract from *Psoralea corylifolia* seeds exhibited antibacterial activity against Gram-positive bacteria, with inhibition zones of 14 mm and 16 mm for *S. aureus* and *MRSA,* respectively. *MRSA* cells treated with 1600 µg/mL of the extract were deformed and collapsed (Li, et al. 2019). *Backhousia citriodora* essential oil significantly inhibited 90.01% to 93.39% of *S. aureus* biofilms (Lim, et al. 2022). Oregano *(Origanum vulgare)* and clove *(Eugenia caryophyllata)* essential oils were effective against *S. aureus* and *MRSA*, with complete inhibition at concentrations of 0.63 µg/mL and 10 µg/mL, respectively (Debiagi, et al. 2020). Finally, *Lippia micromera* and *Plectranthus amboinicus* exhibited potent antibacterial activity against *MRSA*, with large inhibition zones of 23.7 - 35.7 mm (Bugayong, et al. 2019). The MIC of a combination of *oregano* and *thyme* essential oils was found to be 320 µg/mL (Boskovic et al. 2015) .Other studies reporting the effectiveness of essential oils are summarized in Table 1. According to Table 1, the most effective compound against *MRSA* is the *liposome* containing cinnamon oil, with a MIC of 0.25 mg/mL and MBC of 0.25 mg/mL, this compound resulted in a 99.99% decrease in *MRSA* populations after 4 hours and a decrease of 2.83 logs after 24 hours at a concentration of 1.0 mg/mL. Other most effective EOs against *MRSA* are *Cinnamomum zeylanicum*, *Syzygium aromaticum*, *Cuminum cyminum*, respectively. Additionally, *allicin*, *glabrol*, *clove buds*, and *Backhousia citriodora* essential oil s < 0, have shown significant effectiveness against *MRSA* with low MIC values.

Table 1. Effectiveness of essential oils against *MRSA*

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Cinnamon oil, Thyme oil and Lemongrass oil	*Cinnamaldehyde, eugenol, Alpha* and *beta-citral, mycrene*	The initial count of *MRSA* after inoculation (at zero time) was 10.28(log CFU/g) which at a concentration of 1.5% Cinnamon oil, Thyme oil and Lemongrass oil reduced *MRSA* population by 7.6, 6.53, 5.94 log CFU/g, respectively.	(Salem 2017)
Liposome containing cinnamon oil	*Cinnamon oil*	After 4h there was a decrease of around 99.99% in the *MRSA* populations and after 24 h, the population of *MRSA* decreased by 2.83 logs using 1.0 mg mL^{-1}. MIC (mg/mL): 0.25, MBC (mg/mL): 0.25	(Cui, et al. 2016)
Indian Spices	*Syzygium aromaticum (CLV), Cinnamomum zeylanicum (CIN) and Cuminum cyminum (CMN)*	After 24 h the *CIN* and *CLV* showed bactericidal activity at concentration 200 μg/mL against *S. aureus* reducing 4.50 log10 cfu/mL and 3.97 log10 cfu/mL, respectively; *CMN* exhibited bactericidal effects at 300 μg/mL, leaving 0.59 log10 cfu/mL. Effectiveness order: *C.zeylanicum* > *S.aromaticum* > *C. cyminum*	(Mandal, et al. 2011)

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Polyphenolic components of *Green tea,* Neem leaves extract of *Camellia sinensis* and *Azadirachta indica leaves*	*Catechin*	MIC (mg/mL): *Green tea*: 15.62 *Neem*: 31.25 *Green tea + Neem*: 46.87 (*green tea* extract is more potent than *neem* against *MRSA*)	(Zihadi, et al. 2019)
Allicin	NR	MIC: 32 µg/Ml, MBC: 128 µg/mL	(Cutler, et al 2004)
Cinnamomum osmophloeum leaf	*Cinnamaldehyde*	MIC: 250 µg/mL	(Chang, et al. 2001)
Thyme (Tymus vulgaris) and Oregano (Origanum vulgare)	*Thymol* from *Thyme and Carvacrol* from *Oregano*	MIC of *Oregano* and *Thyme*: 320 µg/mL MBC of *Oregano*: 1280 µg/mL MBC of *Thyme*: 640 µg/mL	(Boskovic, et al. 2015)
PFF (phlorofucofuroecko, a marine-derived polyphenol found in brown algae)	NR	MIC: 64 µg/mL	(Eom, et al. 2014)
URS (ursolic acid 3-O-α-L arabinopyranoside was isolated from the leaves of A. henryi (Oliv) with oxacillin	Ursolic acid 3-O-α-L-arabinopyranoside with (URS) oxacillin	MIC: 6.25 µg/mL After 24 h, treatment with 1/2 MIC OXA and 3/4 MIC URS in combination resulted in combined group bacteria counts that decreased to 3 log10.	(Zhou, et al. 2017)

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Pink oyster mushroom Pleurotus flabellatus	The terpenoid compound group	MIC: 62.5 mg/mL MBC: 250 mg/mL	(Ghosh, et al. 2016)
Carvacrol	NR	MIC: 0.11 mg/mL	(Keyvan, and Tutun 2019)
Bulb Eleutherine Americana	Naphtho-quinone	MIC: 125-500 g/mL, MBC: 250-1000 g/mL	(Ifesan, et al. 2009)
Aloysia citriodora essential oils from Baqa al-Gharbiyye and Umm al-Fahm	lipophilic structures like α- citral and α-curcumene	MIC: 2.5 µg/mL	(Arumugam, et al. 2019)
Garlic	Allicin (allyl 2-propenethiosulphinate)	MIC: 256 g/mL	(Prastiyanto, et al. 2020)
Cinnamon (Cinnamomum verum)	Cinnamaldehyde, eugenol	Against MSSA: MIC of 250 µg/mL Against MRSA: MIC of 250 µg/mL	(Prastiyanto, et al. 2020)
Thyme (Thymus vulgaris L.)	Thymol, carvacrol	MIC of 0.25% (v/v)	(Prastiyanto, et al. 2020)
Clove (Eugenia caryophyllata)	Eugenol, Cariofilene	MIC of 0.25% (v/v)	(Prastiyanto, et al. 2020)
Rosemary (Rosemarinus officinalis)	Borneol, 1, 8-cineole	MIC of 1.0% (v/v) MIC of 0.5% (v/v)	(Prastiyanto, et al. 2020)
Sage (Salvia officinalis)	Thujone, cineol, thymol	MIC of 1.0 (% v/v)	(Prastiyanto, A et al. 2020)
Tea tree (Melaleuca alternifolia)	Terpene	MIC of 0.5% (v/v)	(Prastiyanto, et al. 2020)

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Flavonoids from licorice	glabrol, licochalcone A, licochalcone C, and licochalcone E	After 3 h, at 8 mg/mL killed both MRSA T144 and MSSA ATCC29213 completely and after 1 h, all MRSA T144 and MSSA ATCC29213 cells were killed after exposure to glabrol at 4–16 mg/mL.	(Burgos, et al. 2015)
Clove buds	Eugenol	MIC: 0.62 mg/mL	(Xu, et al. 2016)
Chuzhou chrysanthemum	B-Eudesmene, L-Borneol, Camphor	MIC: 5 mg/mL, MBC: 10 mg/mL	(Cui, et al. 2018)
Syzygium antisepticum plant	b-caryophyllene	MIC: 0.12 mg/mL MBC: 0.5 mg/mL	(Yuan, et al 2018)
Sanguisorba officinalis strains	Ethanol	At the concentration of 10 mg/mL S. officinalis the growth of the MRSA was inhibited. at a low concentration (<2.5 mg/mL), inhibitory effect of S. officinalis on biofilm formation in the MRSA strain was obvious.	(Chen, et al. 2015)
Korean soybean fermented product doenjang	Methanolic	MIC: 2048 μg/mL	(Lalouckova, et al. 2021)

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Bisdemethoxycurcumin with three antibiotics (gentamicin, ampicillin and oxacillin)	NR	MIC: 7/8 µg /mL for all S. aureus strains including MRSA. The combination of BDMC with antibiotics caused more than 3 log10 cfu/mL reductions on all the three S. aureus strains.	(Hermawati, et al. 2016)
Thymol and carvacrol with organic acids (lactic acid)	NR	Combination of thymol and carvacrol with organic acids results a reduction over two log cycles in initial bacterial after 24 h.Thymol and carvacrol showed MIC of 0.6 and 1.25 µL/mL and MIC of lactic acid was 2.5 µL/mL	(de Oliveira, et al. 2010)
Elettaria cardamomum ethanolic extract	a-terpinyl acetate and 1,8 cineole	MIC: 0.25 mg/disk, MBC: 0.50 mg/disk	(Yassin, et al. 2022)
Nigella sativa (Black seed) Oil	Heptanal, Benton 2,3-dimethyl, 1-OCTAN-1,1-D2-OL and Pentane, 2-cyclopropyl	MIC shows that at the concentration of 400 µl with (7± 1) mm of inhibition zone and 800mL concentration was (10± 0.9) mm	(Abdullah, et al. 2021)
Litsea cubeba essential oil	β-Citral and α-Citral	MIC 0.5 mg/ mL, MBC 1.0 mg/ mL	(Hu, et al. 2019)
Red Propolis	Pinobanksin, pinobanksin-3-acetate	MIC: of 50 µg/mL MBC: 200 µg/mL	(Zhang, et al. 2022)

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Essential Oil Extracted from Carum carvi L. seeds (CEO)	Carvone and limonene	MIC: 6.4 µg/mL	(Liu, et al. 2023)
Ethanol Extracts of Psoralea corylifolia Seeds	Phenol, hydrazine, aldehyde, and ketone	MIC: 50 µg/mL MBC: 100 µg/mL	(Li, et al. 2019)
Black seed (Nigella sativa) oil	Heptanal, Benton 2,3-dimethyl, 1-OCTAN-1,1-D2-OL and Pentane, 2-cyclopropyl	MIC: 32.8 mg/mL MBC 42.2 mg/mL	(Abdullah, et al. 2021)
Backhousia citriodora Essential Oil (BCEO) leaves	oxygenated monoterpenes and neral phytocompounds	MIC: 6.25 µL/mL, MBC: 50 µL/mL	(Lim, et al. 2022)
Pelargonium graveolens Oil	citronellol, citronellyl formate	MIC: 1.56 µg/mL.	(Jaradat, et al. 2022)
Origanum-vulgare and Eugenia caryophyllata oil	phenols components	MIC CEO: 10 µg/mL MIC OEO: 0.63 µg/mL	(Debiagi, et al. 2020)
Essential Oils from Leaves of Some Aromatic Plants	Monoterpenes	MIC :2.00 %, MBC>4.00 %	(Bugayong, et al. 2019)

Essential oils			
Name	**Active Components**	**Effectiveness**	**References**
Essential Oils from Elettaria Cardamomum fruit capsules	monoterpenes and sesquiterpenes	MIC: 250 μg/mL.	(Jha, et al. 2022)

NR: not reported

Bacteriophage

A phage endolysin, *LysP108*, was able to decrease viable *MRSA* cells by approximately 2 log units within 30 minutes at an optimal concentration of 250 μg/mL. At an MIC of 100 μg/mL, while the antibiofilm activity of the endolysin resulted in the removal of 66% of *MRSA* biofilm (Lu, et al. 2021). Endolysin *LysSA11*, at a concentration of 450 nM, reduced the optical density of the *S. aureus* culture after 30 minutes. However, the efficacy of *LysSA11* declined by 50% at temperatures of 4 °C or 65 °C (Chang, et al. 2017). Two other endolysins, *CHAPLysGH15* and *LysGH15*, that were isolated from *S. aureus*, showed a rapid antibacterial effect on *MSSA* and *MRSA* strains. Although they became inactive when exposed to heat treatment, *CHAPLysGH15* demonstrated high activity at pH 7.0–10.0, and *LysGH15* was active in high-salt environments. Therefore, they can be used in salty foods, as well as alkaline foods, including raw beef, pork, fish, and chicken, which are prone to contamination with *S. aureus* (Yan, et al. 2021). A well-studied, *S. aureus*-specific bacteriophage, Phage K, demonstrated a good inhibitory effect on *S. aureus* strains, including *MRSA*. Furthermore, when this phage was combined with essential oils, such as *a-pinene*, the inhibitory effect was greater than either the phage or the essential oil alone (Ghosh, et al. 2016). When Phage *SapYZU11* was applied at a multiplicity of infection (MOI) of 100, it resulted in the maximum reduction of *MRSA JCSC 4744* and *S. aureus* cocktail after 4 days, with reductions of 0.33 log CFU/mL and 0.29 log CFU/mL, respectively. These findings suggest that *SapYZU11* could be utilized as a biocontrol agent to effectively combat *S. aureus* contamination in the food industry (Wen, et al. 2023). Good results have been reported for combinations of phages and other antimicrobials, such as bacteriocins. For example, a combination of phage *SAP84* and a bacteriocin from *L. lactis CJNU* demonstrated significantly better *anti-S. aureus* activity

compared to each one alone *(Kim, et al. 2019)*. The synergistic inhibition of the combination of phage *SAP84* and bacteriocin against *S. aureus* caused a reduction of more than 5 log in viable counts, while the phage alone led to only about a 2 log cfu/mL reduction in *S. aureus* counts (Kim, et al. 2019). In another study, a lower concentration of endolysin *LysH5* was required in combination with subinhibitory concentrations of nisin to achieve complete inhibition of *S. aureus Sa9* (Arumugam, et al. 2019). After the treatment with 1 μM of recombinant *SAP8* endolysin, the initial *MRSA* count of 5.93 log CFU/mL was reduced to 3.64 log CFU/mL. In addition, the combination of 0.01 μM of recombinant *SAP8* endolysin and 18 IU/mL of nisin completely prevented the growth of *MRSA* (Hassan, et al. 2020). Also, the combination of bacteriophage endolysin *LysSA97* with *carvacrol* was found to significantly decrease the number of viable *S. aureus* cells (Chang, et al. 2017). When a combination of *S. aureus* phage (MOI 10) and 1% thyme oil was used, a greater reduction (87.22%) in *S. aureus* was achieved compared to using each treatment alone (Abdallah, et al. 2021). These examples indicate that phages can have a synergistic effect with other antibacterials. The effects of different bacteriophages and endolysins against *S. aureus*, including *MRSA*, have been reported in studies that are summarized in Table 2. Based on Table 2, the most effective phage compounds are *S. aureus* phage (containing *CHAPLysGH15* and *LysGH15)*, phage *SA11* endolysin *LysSA11*, endolysin *LysSA97* with *carvacrol*, and phage *endolysin LysH5* and *nisin*, respectively.

Table 2. Effect of bacteriophages and endolysins against *MRSA*

Bacteriophage			
Name	**Active Components**	**Effectiveness**	**References**
Endolysin *LysP108*	NR	MIC: 100 μg /mL	(Lu, et al. 2021)
Staphylococcus aureus bacteriophage	*CHAPLysGH15 and LysGH15*	*MRSA* was completely cleaved by 0.4 nmol/cm2 of *CHAPLysGH15*. 1.0 Log10 cfu/cm2 of *MRSA* declined after adding 0.4 nmol/cm2 of *LysGH15*	(Li, et al. 2011)

Bacteriophage			
Name	**Active Components**	**Effectiveness**	**References**
Endolysin *LysSA97* (an endolysin encoded by the bacteriophage *SA97*) with *carvacrol*	NR	The numbers of *S. aureus cells* were decreased by 0.8 ± 0.2 log cfu/mL and 1.0 ± 0.0 log cfu/mL at concentrations of 376 nm and 3.33 mm, respectively.	(Chang, et al. 2017)
EOCs (*a-pinene and 3-carene*) combined with two types of *S. aureus* bacteriophage, *phage K (ATCC 19685-B1)* and *phage 92 (ATCC 33741-B1)*	NR	Both phage of *S. aureus*-specific bacteriophage alone and EO *(a-pinene)* alone at 1.5 and 3.28 % yielded similar inhibition trends. However, with *phage K* and EOC (essential oil compounds) combinations, *phage K* with 3.28 % *a-pinene* inhibited *S. aureus* growth better than other combinations of EOCs and phage depending on the strain.	(Jaradat, et al. 2021)
Phage SA11 endolysin *LysSA11*	NR	The highest dose of Phage *SA11 endolysin LysSA11*(450 nM of endolysin) yielded a 50% reduction in optical density in less than 20 min and a 70% reduction within 30 min. *LysSA11* treatment (3.37μM, 1 h) reduced the number of *staphylococcal cells* in milk by about 2.53 log/mL	(Chang, et al. 2017)
Phage endolysin *LysH5* and *nisin*	NR	The MICs of *nisin* and *LysH5* were 3μg/mL and 50u/mL, respectively but in the presence of subinhibitory concentrations of *nisin*, a lower endolysin concentration was needed to fully inhibit *S. aureus Sa9*. These values implied up to a 64-fold and 16-fold reduction of the *nisin* and endolysin MICs, respectively, when used in combination.	(Arumugam, et al. 2019)

NR: not reported

Bacteriocins

According to studies, the growth of gram-positive pathogens, including *S. epidermidis*, *S. aureus*, and *MRSA*, was effectively inhibited by *NX371*, a novel class III bacteriocin gene. When *NX371* was added to milk, it moderately but significantly inhibited the growth of pathogens from day 1 to day 7, with reductions of 3.5 - 4.0 log in milk and 5.0 - 7.0 log in cheese, indicating its effectiveness as a food additive for controlling *S. aureus* in dairy products (Meng, et al. 2021). *Colicin* and *interocin* bacteriocins produced by *Escherichia coli* strains and *Enterococcus* species were found to have bactericidal effect against *MRSAs* and other *Staphylococcal* isolates, with complete bactericidal action achieved after 18-24 hours of incubation (Bajlan, et al. 2018). Bacteriocin produced by *Lactobacillus plantarum ZJ217 (plantaricin ZJ217)* was found to significantly decrease the colony forming units (Log10 CFU) of *S. aureus*, with viable cell counts decreasing from 6.5 ± 0.1 to 3.7 ± 0.04 log CFU/mL within 2 hours of incubation (Zhu, et al. 2015). Bacteriocin *KTH0-1S* produced by *Lactococcus lactis KTH0-1S* was found to significantly reduce the viable cell counts of *S. aureus* within 2 hours of incubation, with a higher proportion of dead cells compared to the control treatment (Saelao, et al. 2017). Bacteriocin *Paracin 54* produced by *Lactobacillus paracasei ZFM54*, was found to have a strong inhibitory effect on *Staphylococci*, with minimum inhibitory concentration values of 3.00 - 4.50 μg/mL (Zhu, et al. 2021). Bacteriocin producing *Pseudomonas aeruginosa TA6*, isolated from soil, was found to decrease the cell density of *S. aureus* rapidly, with cell lysis eventually occurring at concentrations of 100 AU/mL (Arumugam, et al. 2019). *Plantaricin 827*, produced by *Lactobacillus plantarum 163*, was found to quickly decrease *S. aureus* cells within 150 minutes of treatment with 64 μg/mL, and all *S. aureus* cells were destroyed within 90 minutes of treatment with 128 μg/mL. Moreover, *plantaricin 827* exhibited a certain preservation effect in skimmed milk and significantly extended the shelf life of skimmed milk (Zhao, et al. 2022). Bacteriocins produced by two strains, *Lactobacillus helveticus (BLh)* and *Lactobacillus plantarum (BLp*), had significant activity against *S. aureus* and *MRSA*. *L. helveticus (BLh)* was the most effective against *MRSA* after 18 to 24 hours of incubation at 37°C, while *L. plantarum (BLp)* had a similar effect against *MRSA* after 24 to 48 hours of incubation at 37°C under anaerobic conditions. The bacteriocin extracted from *L. plantarum (BLp)* was active even after passing through high temperature and pressure during sterilization, but the bacteriocin synthesized by *L. helveticus (BLh)* was more labile to heat (Hassan, et al. 2020). *Nisin*, a bacteriocin produced by the *Lactococcus lactis subsp. lactis* bacterium, exhibited

bacteriostatic activity against *MRSA* alone and had no effect against *S. aureus ATCC 25937*, while some strains of *Lactobacillus reuteri* produced *reuterin (β-hydroxypropionaldehyde)* under anaerobic conditions, which was considered to have bactericidal effects against *MRSA* and *S. aureus ATCC25937*. The combination of *nisin* at a concentration of 25.6 and *reuterin* at a concentration of 5.2 mg/mL exerted a bactericidal effect on *MRSA* and *S. aureus ATCC 25937* (Yehia, et al. 2022). Combinations of bacteriocins with other antimicrobials can increase their antibacterial efficacy. For instance, co-treatment of drinks with *enterocin* and phenolic compounds *(2NPOH)* resulted in the eradication of viable *staphylococci* after 24 hours (Burgos, et al. 2015). The effects of different types of bacteriocins against *S. aureus*, including *MRSA*, have been reported in studies that are summarized in Table 3. According to Table 3, the most effective bacteriocins against *S. aureus* are *Enterocin AS-48* with phenolic compounds or with *2NPOH*, Bacteriocin isolated from *Lactobacillus pentosus – Pentocin JL-1*, bacteriocin producing *Pseudomonas aeruginosa TA6*, and bacteriocin produced by *S. pasteuri RSP-1,* respectively.

Table 3. Effect of some bacteriocins against *MRSA*.

Bacteriocins			
Name	**Active Components**	**Effectiveness**	**References**
Bovine myeloid antimicrobial peptide (BMAP-28)	NR	20 mg/mL of *BMAP-28* could inhibit the growth of the two kinds of bacteria (*MRSA* and *MSSA*). MIC range (mg/mL): 5–20	(Takagi, et al. 2012)
Cell-free extracts of *Bifidobacterium*	*b1, b2, BL* and *BI*	MIC: 1.0 mg/mL	(AL-Saadi 2016)
Bacteriocin Produced by *B. cereus TSH5*	NR	MIC: 80 μg/mL	(Chauhan, et al. 2017)
Bacteriocin produced by *Staphylococcus pasteuri RSP-1 (S. pasteuri RSP-1)*	NR	MIC: 5 AU/mL	(Hong, et al. 2018)

Bacteriocins			
Name	**Active Components**	**Effectiveness**	**References**
Bacteriocin isolated from *Lactobacillus pentosus*	*Pentocin JL-1*	MIC: 7.5 µg/mL	(Jiang, et al. 2017)
Enterocin *AS-48* with phenolic compounds or with *2NPOH*	NR	No viable *staphylococci* were detected after 24 h incubation with the combination of *enterocin AS-48* and *2NPOH*	(Murray, et al. 2021)
Bacteriocin from *Lactococcus lactis KU24*	*Bacteriocin KU24*	*S. aureus ATCC 33591* was inhibited *by bacteriocin KU24* at 2 Log cfu/mL after 10 h of incubation. MIC: 400 to 800 AU/mL	(Lee, et al. 2013)
Bacteriocin producing *Pseudomonas aeruginosa TA6*	NR	MIC: 50 AU/mL the cell density of *S. aureus* decreased rapidly, and cell lysis occurred at 100 AU/mL concentrations	(Zhou, et al. 2017)
Bacteriocin producing *Lactobacillus acidophilus*	*bacteriocin gene NX371*	MIC90 was ranged from 20 to 160 µg/mL	(Meng, et al. 2021)
Bacteriocins produced by *Escherichia coli* and *Enterococcus species*	*Colicin and interocin*	The incubation times for complete bactericidal action were 18-24h.	(Bajlan, et al. 2018)
Bacteriocin produced of *Lactococcus lactis KTH0-1S*	*Bacteriocin KTH0-1S*	The proportion of dead cells was significantly higher since viable cell counts decreased from 6.5±0.1 to 3.7±0.04 log CFU/mL within 2 h of incubation	(Saelao, et al. 2017)
Bacteriocin produced of *Lactobacillus paracasei ZFM54*	*Bacteriocin Paracin 54*	MIC: 3.50 µg/mL	(Zhu, et al. 2021)

Bacteriocins			
Name	**Active Components**	**Effectiveness**	**References**
Bacteriocin producing from *Pseudomonas aeruginosa TA6*	NR	Maximum bacteriocin activity (100AU/mL) was observed at 37 °C in 24 h time duration.	(Arumugam, et al. 2019)
Bacteriocin produced by *Lactobacillus plantarum 163*	*Plantaricin 827*	MIC: 64 μg/mL.	(Zhao, et al. 2022)
Bacteriocin produced by Lactobacillus helveticus and Lactobacillus plantarum		L. helveticus showed the activity against MRSA after 18 to 24 hours of incubation at 37°C. In comparison, L. plantarum showed similar activity against MRSA after 24 to 48 hours of incubation at 37°C under anaerobic conditions.	(Hassan, et al. 2020)
Bacteriocin produced by Lactococcus lactis subsp. lactis. and Lactobacillus reuteri	*Nisin and reuterin*	MIC of nisin: 51.2 mg/ mL, MIC of reuterin: 5.2mg/mL MBC of nisin: 5 mg/mL, MBC for reuterin: 5 mg/mL	(Yehia, et al. 2022)

NR: not reported

Probiotics

The most common probiotics are *lactic acid bacteria (LAB)* strains, and they are considered safe. *LAB* can produce bactericidal bioactive peptides and enzymes that have antibacterial and antibiofilm effects (Hermawati, et al. 2016). For instance, *Lactobacillus* can inhibit *Staphylococcal cells*, including *MRSA* (Hermawati, et al. 2016). Several probiotics such as *Lactobacillus plantarum* (Lee, et al. 2021, Afshari, et al. 2022), *Lactobacillus acidophilus*, *Lactobacillus casei* (Hermawati, et al. 2016), *Streptomyces griseus*, *Lactococcus lactis*, *Streptococcus*, *Leuconostoc*, and *Pediococcus* (Li, et al. 2011) have demonstrated

inhibitory effects on *S. aureus* strains, including *MRSA*. Table 4 shows the effects of different probiotics on *MRSA*. According to Table 4, the most effective probiotics were *Streptomyces griseus*, *Pediococcus acidilactici strains A11 and C12, Lactococcus lactis*, and *Lactobionic acid*, respectively.

Table 4. Effect of some probiotics against MRSA

Probiotic			
Name	**Active Components**	**Effectiveness**	**References**
Lactobacillus acidophilus and probiotic *Lactobacillus casei*	NR	MIC: 3.12% for *Lactobacillus acidophilus* and 2% *Lactobacillus casei*	(Karska-Wysocki, et al. 2010)
Probiotic *Lactobacillus plantarum KU200656*	NR	MIC :12.5%	(Lee, et al. 2021)
Pseudomonas fluorescens	*Pseudomonic acids and Mupirocin*	MIC of 8-256 µg/mL for low level resistance and 512 µg/mL for high level resistance	(Prastiyanto, et al. 2020)
Streptomyces griseus	*Treptose, streptydine, and Nmethyl- L –glycosamine and Streptomycin*	MIC: 1.56-6.25 µg/mL	(Prastiyanto, et al. 2020)
Lactococcus lactis	*Lnathionine (Lan), methyllanthionine (MeLan), didehydroalanine (Dha) and didehydroaminobutyric acid (Dhb) and Nisin*	MIC: 1.5 to > 1.6 mg/L	(Prastiyanto, et al. 2020)
Streptococcus, Leuconostoc, Lactobacillus, and *Pediococcus*	*Diacetyl*	MIC: 1.00 µg/mL	(Prastiyanto, et al. 2020)
Pediococcus acidilactici strains A11 and C12	NR	MIC: 25%, MBC: 12.5%	(Lestari, et al. 2019)

NR: not reported

DISCUSSION

Essential oils

Several possible mechanisms have been proposed for antibacterial activity of essential oils. Table 4 shows the mechanisms of action of reported EOs. Essential oils can inhibit enzymes and compounds that are needed for the growth of *MRSA* (Eom, et al. 2014; Burris, et al. 2015). For example, *cinnamaldehyde* in cinnamon oil inhibits *N-3-oxohexanoyl-L-homoserine lactone (3-oxo-C6-HSL)* and *AI-2* (Salem 2017) while allicin liquid can inhibit sulfhydryl enzymes, thereby inhibiting DNA and protein synthesis (Cutler, et al 2004; Li, et al. 2011). Some EOs can cause the release of intracellular components (Eom, et al. 2014; Jaradat, et al. 2021), such as brown algae, which lead to the release of intracellular components via phlorofucofuroeckol (PFF) (Eom, et al. 2014). Inhibition of enzymes by EOs can occur through participation in electron transport with the cell components and binding to bacterial adhesions and cell walls (Ifesan, et al. 2009). *Aloysia citriodora* EO can participate in the lipophilic lipids of the mitochondria and cytoplasmic membrane due to their lipophilic ability (Jaradat, et al. 2021). The lipophilic characteristics of EOs make them capable of easily penetrating the bacterial cell (Prastiyanto, et al. 2020). For example, *terpenoids* in mushroom *Pleurotus flabellatus* have this ability and can interfere with protein synthesis and DNA replication (Prastiyanto, et al. 2020). Additionally, some EOs such as EOs derived from *Chuzhou chrysanthemum* and *clove buds* increase the permeability of the cell membrane, resulting in the leakage of intracellular essential substances such as electrolytes, protein, and nucleic acids (Xu, et al. 2016; Cui, et al. 2018). Many EOs such as *carvacrol* are safe to apply in foods as a natural food preservative and are 'Generally Recognized as Safe' (GRAS) by the US Food and Drug Administration (FDA) (Chang, et al. 2017). EOs can have an enhanced effect when they are used at high concentrations (Higginbotham, et al. 2014). Furthermore, if they are applied in processed foods such as hot dogs, chemicals like potassium lactate, sodium lactate, sodium diacetate, and sodium nitrite, they can improve the antimicrobial activity of the Eos (Higginbotham, et al. 2014). Black seed *(Nigella sativa*) is a type of medicinal herb that contains bioactive substances of medical importance. The GC-MS analysis of *N. sativa* shows that it contains five essential compounds, all of which are a unique mix of organic compounds and alkaloids that possess high biological activity, such as *Heptanal, Benton 2,3-dimethyl, 1-OCTAN-1,1-D2-OL, and Pentane, 2-cyclopropyl* (Abdullah, et al. 2021). *Litsea cubeba* essential oil *(LC-EO)* can cause *MRSA* cell rupture, which results in the leakage of cellular content and ultimately

leads to the bacteria's death. LC-EO treatment decreases the activity of four ATPases, including the Na+/K+ ATPase, Ca2+/ Mg2+ATPase, Ca2+ATPase, and Mg2+ATPase (Hu, et al. 2019). *Chinese Red Propolis* is rich in *pinobanksin* and *pinobanksin-3-acetate*, and its antibacterial activity may be the result of the synergistic effect of polyphenols (Zhang, et al. 2022). *Carum carvi L.* disrupts *MRSA* biofilm and amino acid metabolism, and it also hinders DNA and RNA synthesis (Liu, et al. 2023). *Psoralea corylifolia* seed ethanol extract *(PCEE)* is composed of *phenol*, *hydrazine*, *aldehyde*, and *ketone*, which can destroy the cell structure and reduce enzymes, ultimately killing bacteria (Li, et al. 2019). *Backhousia citriodora* Essential Oil *(BCEO)* contains large amounts of *oxygenated monoterpenes*, which disrupt the microbial cytoplasmic wall, improve cell permeability, and lead to cell death (Lim, et al. 2022). Oregano essential oil (OEO) and cinnamon essential oil (CEO) increase cell permeability and cause leakage of intracellular constituents, leading to the disruption of the cell respiration system and microbial enzyme system (Debiagi, et al. 2020). *L. micromera* and *P. amboinicus* essential oils contain *monoterpenes* such as *carvacrol*, *γ-terpinene*, and *β-cymene*, which are responsible for their antibacterial activity against *Staphylococcus species* including *MRSA* (Bugayong, et al. 2019). *Elettaria cardamomum* essential oil blurs the surface barrier of the cell wall, altering the structure of the cells, and causing bacterial mortality (Jha, et al. 2022). The combination of EOs can enhance the efficacy of their antibacterial activity. For instance, when *carvacrol* and *thymol* are combined with organic acids, a significant reduction in the number of *S. aureus* is observed on food samples. On one hand, these EOs disrupt the bacterial cell membrane and make the bacteria more susceptible to the acidic environment. On the other hand, organic acids enhance the hydrophobicity of EOs and make the EOs bind better to hydrophobic regions of the membrane proteins (de Oliveira, et al. 2010). Thyme oil, when combined with lytic *S. aureus* phage, is a promising biocontrol agent and antimicrobial alternative in the food industry to control and reduce *MRSA* or other *antibiotic-resistant S. aureus* contamination in food (Abdallah, et al. 2021). Some plant extracts can increase the effectiveness of antibiotics against *MRSA*. For instance, *ursolic acid 3-O-α-L-arabinopyranoside (URS)* from the leaves of *Acanthopanax henryi* (Oliv.) can enhance the *anti-MRSA* effect of oxacillin (Zhou, et al. 2017).

Bacteriophages

Bacteriophages encode peptidoglycan hydrolases, known as endolysins or lysins, which lyse bacterial cells by targeting their cell wall, particularly in Gram-positive bacteria, due to their naturally exposed peptidoglycan layer (Murray,

et al. 2021). Bacterial death by endolysins is in accordance with the typical phenomenon of osmotic-mediated cell lysis, which occurs in Gram-positive bacteria following a phage attack (Lu, et al. 2021). For instance, *LysP108* causes disintegration of the *MRSA* cell wall (Lu, et al. 2021). It has been reported that a combination of endolysin *LysSA97* with *carvacrol* can cleave bacterial peptidoglycan layers and destroy the structure of the cell wall (Chang, et al. 2017). Combining endolysins with antibiotics causes better accessibility of antibiotics to *MRSA* cells through initial lysing of the biofilm by endomysia (Linden, et al. 2015). Combining endolysins with bacteriocins can result in a higher sensitivity of *S. aureus* cells to these antibacterials. The mechanism might be attributed to the prevention of peptidoglycan breaks produced by endolysins from contraction (Arumugam, et al. 2019). Moreover, bacteriocins can cause a partial activation of autolysins that allows for better activity of the endolysin (Arumugam, et al. 2019). The combination of synthetic *SAP8 endolysin* and *nisin* can effectively restrain various types of Gram-positive bacteria by creating openings in the bacterial cell membrane and blocking the production of cell walls (Kim, et al. 2022).

Bacteriocin

Bacteriocins can cause damage to the cell wall or induce cell lysis (Lee, et al. 2013). They target the cytoplasmic membrane of bacterial cells and inhibit the proton motive force (PMF), leading to inhibition of protein or nucleic acid production (Lestari, et al. 2019). The *anti-MRSA* activity of bacteriocins is mainly due to the generation of organic acids such as *lactic acid* and *acetic acid*. These acids enter bacterial cells and interfere with essential metabolic processes (AL-Saadi 2016). Bacteriocins against *MRSA* can change the cell surface from smooth to rough. Therefore, the suggested mechanism is related to the bacterial cell membrane (Takagi, et al. 2012). Several bacteriocins have been reported to have *anti-MRSA* activity, leading to the disruption in the integrity and uniformity of *MRSA* (Zhu, et al. 2015; Jiang, et al. 201; Taggar, et al. 2021). Through bioinformatic analysis of *Lactobacillus acidophilus*, a new class III bacteriocin gene called *NX371* was discovered, which demonstrated high antimicrobial activity across a wide range of pH values (3.0-8.0). This bacteriocin was able to disrupt the cell wall of gram-positive bacteria and induce membrane leakage in gram-negative bacteria, leading to separation of the cell wall and membrane (Meng, et al. 2021). Other bacteriocins such as *colicins* and *enterocins* also exhibit antibacterial effect against Gram-positive bacteria, with *colicins* acting as transmembrane proteins that depolarize the cytoplasmic

membrane and kill cells by producing pores or acting as a nuclease to chop up DNA or RNA (Bajlan, et al. 2018). Another example is *plantaricin ZJ217*, a novel bacteriocin produced by *Lactobacillus plantarum ZJ217*, which was inhibitory effect against a variety of gram-positive and gram-negative bacteria by forming pores in cells (Zhu, et al. 2015). Similarly, bacteriocin *KTH0-1S* produced by *Lactococcus lactis KTH0-1S* acted on sensitive cells by forming pores in membranes, leading to cell death due to the loss of essential intracellular substances (Saelao, et al. 2017). *Paracin 54*, a bacteriocin produced by *Lactobacillus paracasei ZFM54*, also formed pores in the cell membrane of *MRSA*, which disrupted the balance of ions inside and outside the membrane and led to the dissipation of proton driving force, inhibiting the synthesis of intracellular ATP and causing the disorder of intracellular energy metabolism (Zhu, et al. 2021). Another bacteriocin, *plantaricin 827*, produced by *Lactobacillus plantarum 163*, had antibacterial effects against *MRSA* by increasing the cell membrane permeability and integrity, resulting in the leakage of K+ and changes in cell morphology, inhibiting biofilm formation, and interacting with genomic DNA minor groove in AT-rich regions (Zhao, et al. 2022). The combination of *nisin* produced by *Lactococcus lactis subsp. lactis* and *reuterin* produced by *Lactobacillus reuteri* also disrupted membranes by forming pores, inhibiting energy production and biosynthesis of proteins and nucleic acids (Yehia, et al. 2022). Despite the fact that they are proteins, some bacteriocins can remain stable in harsh environmental conditions. For instance, *Paracin 54* retained 93.7% of its activity after treatment with lysozyme, indicating its potential for use in food preservation. Furthermore, *Paracin 54* maintained its inhibitory activity against *MRSA* at different temperatures, suggesting its potential use in pasteurized products (Zhu, et al. 2021). *Plantaricin* 827 also exhibited antibacterial activity at pH 7.0, while *plantaricin ZJ217* was stable at pH 2.0 to 6.0 but lost activity at pH 10.0 (Zhu, et al. 2015).

Probiotics

The major effects of probiotics include modulation of the immune system, inhibition of pathogen adhesion to epithelial cells, and generation of antimicrobial compounds (AL-Saadi 2016; Lee, et al. 2021). Antimicrobial compounds produced by probiotics can also demonstrate anti-adhesion ability (Lee, et al. 2021). These antimicrobial components include organic acids, oxygen catabolites, and proteinaceous compounds (Lee, et al. 2021). These components can inhibit the growth of *MRSA* cells in food products (Karska-Wysocki, et al. 2010). For instance, *Lactococcus lactis* can generate antibacte-

rial agents, including *didehydroaminobutyric acid (Dhb)* and *didehydroalanine (Dha)*, *methyllanthionine (MeLan)*, *Lanthionine (Lan)*, and bacteriocin *(Nisin)*. These substances can disrupt the uptake of amino acids by *S. aureus* cells and suppress the production of the cell wall. In addition, some metabolites will be released, leading to cell death (Li, et al. 2011). Generally, *LBA* can cause alkaline phosphatase leakage from *MRSA cells* to the extracellular medium, and in this way, they prevent the formation of biofilms (Kang, et al. 2020). A list of *anti-S. aureus* agents and their modes of action is in Table 5.

Table 5. Mechanisms of action of anti-MRSA EOs, bacteriophages, bacteriocins, and probiotics.

Name	Active Components	Mechanisms	References
Essential oils			
Essential oils: Cinnamon oil, Thyme oil and Lemongrass oil	*Cinnamaldehyde, eugenol, Alpha and beta-citral, mycrene*	These can inhibit *N-3-oxohexanoyl- Lhomoserine lactone (3- oxo-C6-HSL)* and *AI-2,* and certain enzymes needed for the growth of *MRSA*.	(Salem 2017)
Liposome containing cinnamon oil	NR	The damage of bacterial cell membrane is by their effect on morphology, structure, function, modification in the transport of nutrients, membrane disruption, extensive leakages from the bacterial cells leading to cell death.	(Cui, et al. 2016)
Indian Spices	*Syzygium aromaticum (CLV) and Cinnamomum zeylanicum (CIN) and Cuminum cyminum (CMN)*	These can affect the synthesis of the peptidoglycan layer of the cell wall and the mode of action of the spice extracts is cell wall related.	(Mandal, et al. 2011)

Name	Active Components	Mechanisms	References
Essential oils			
Camellia sinensis and Azadirachta indica leaves	*catechin*	The *catechin* has direct effects on the destruction of the bacterial cell membrane by binding with the lipid bilayer.	(Zihadi, et al. 2019)
Allicin	NR	Inhibit the acetyl coA forming system, to inhibit DNA and protein synthesis, and to target RNA polymerase.	(Cutler, et al 2004)
Cinnamomum osmophloeum leaf essential oils	*cinnamaldehyde*	NR	(Chang, et al. 2001)
Thyme (Tymus vulgaris) and Oregano (Origanum vulgare) essential oils	*Thymol* from *Thyme* and *Carvacrol* from *Oregano*	Phosphate ion leakage.	(Boskovic, et al. 2015)
PFF (phlorofucofuroeckol, a marine-derived polyphenol found in brown algae)	NR	Interfering with cell wall synthesis and the cell membrane and agents change membrane function and permeability, leading to cell damage or death.	(Eom, et al. 2014)

Name	Active Components	Mechanisms	References
Essential oils			
URS (ursolic acid 3-O-α-L arabinopyranoside was isolated from the leaves of A. henryi (Oliv) with oxacillin	Q	Deformation of bacterial cells. Cell membrane disintegration, cell lysis and release of cytoplasmic contents.	(Yan, et al. 2021)
Pink oyster mushroom Pleurotus flabellatus	The terpenoid compound group	These penetrate the bacterial cell and may interfere with protein synthesis and DNA replication.	(Ghosh, et al. 2016)
Amomum villosum Lour	Bornyl acetate	Leakage of intracellular macromolecular substances.	(Tang, et al. 2020)
Bulb Eleutherine Americana	Naphthoquinone	Inhibits electron transport with the cell components. They also can bind to bacterial adhesions and complex with cell wall, thus inactivating enzymes.	(Ifesan, et al. 2009)
Aloysia citriodora essential oils EOs from Baqa al-Gharbiyye and Umm al-Fahm	lipophilic structures like α- citral and α-curcumene	Their lipophilic ability to partition in the lipophilic lipids of the mitochondria and cytoplasmic membrane. They could also disturb the structures, resulting in leakage of bacterial cell contents.	(Arumugam, et al. 2019)

Name	Active Components	Mechanisms	References
Essential oils			
Garlic	Allicin (allyl 2-propenethiosulphinate)	1) The primary mechanism of allicin centers on its ability to inhibit sulfhydryl enzymes common for pathogenic bacteria. 2) Inhibiting enzymes associated with DNA and protein synthesis and limiting RNA polymerase and alcohol dehydrogenase activities.	(Prastiyanto, et al. 2020)
flavonoids from licorice	glabrol, licochalcone A, licochalcone C, and licochalcone E	Disruption of membrane permeability. The binding of these to the cell wall or the cytoplasmic membrane is important for their action on the bacterial membrane.	(Burgos, et al. 2015)
Clove buds	Eugenol	The permeability of bacterial membrane would be increased, which caused the leakage of intracellular ingredient, especially losses of electrolytes including K+, Ca2+, Na+, as well as cell constituents such as protein, nucleic acids, and some essential molecules.	(Xu, et al. 2016)
Chuzhou chrysanthemum	B-Eudesmene, L-Borneol, Camphor	Disruption of the cell membrane and leakage of DNA, protein and ATP to the bulk solution.	(Cui, et al. 2018)

Name	Active Components	Mechanisms	References
Essential oils			
Syzygium antisepticum plant	b-caryophyllene	Membrane-disrupting effect was observed	(Yuan, et al 2018)
Korean soybean fermented product doenjang	Methanolic	Inhibits the respiratory metabolism and protein synthesis of the bacteria and prevents nucleic acid synthesis. Thus, it affects the integrity of the cell wall and membrane.	(Lalouckova, et al. 2021)
Bisdemethoxycurcumin with three antibiotics (gentamicin, ampicillin, and oxacillin)	NR	The polyphenol structure can destroy the cell wall of bacteria and thus increases the efficiency of antibiotics entering the cell.	(Wang, et al. 2020)
Thymol and carvacrol with organic acids (lactic acid)	NR	Phenolic compounds can damage cellular membrane changing their structure and function and causing it to become more susceptible to acid environments. On the other hand, at low pH the molecules of thymol and carvacrol are mostly dissociated, more hydrophobic, and bind better to hydrophobic regions of the membrane proteins resulting in better partition into the lipid phase of the bacterial membrane.	(de Oliveira, et al. 2010)

Name	Active Components	Mechanisms	References
Essential oils			
Litsea cubeba essential oil	β- Citral and α-Citral	The LC-EO could lead to the rupture of MRSA cells and the loss of cellular contents and eventually to the death of bacteria.	(Hu, et al. 2019)
Red Propolis	Pinobanksin, Pinobanksin-3-acetate	The mechanism of action of RPE due to loss of membrane integrity.	(Zhang, et al. 2022)
Ethanol Extracts of Psoralea corylifolia Seeds	phenol, hydrazine, aldehyde, and ketone	PCEE could change the membrane integrity of MRSA, releasing nucleic acids and proteins, resulting in bacterial death.	(Li, et al. 2019)
Manuka EO was extracted from manuka leaves	Sesquiterpenes	MIC: 0.233 mg/mL, MBC: 0.466 mg/mL	(Pedonese, et al. 2022)
Essential Oils from Elettaria Cardamomum fruit capsules	Monoterpenes and sesquiterpenes	Elettaria cardamomum EO damages the biofilm barrier, causing the bacteria to lose metabolic activity.	(Jha, et al. 2022)
Bacteriophages			
Phage Endolysin *LysP108*	NR	*LysP108* disintegrated the cell wall of *MRSA*.	(Lu, et al. 2021)

Name	Active Components	Mechanisms	References
Bacteriophages			
Bacteriophage *endolysin plygrcs*	*PlyGRCS*	The endolysin *plygrcs* would provide the initial disturbance to the biofilm structure.	(Linden, et al. 2015)
Carvacrol and lyssa97	NR	*LysSA97* cleaving bacterial peptidoglycan layers is likely to render the cell wall structure less rigid so that *carvacrol* may more readily reach the cytoplasmic membrane of S. *aureus*.	(Chang, et al. 2017)
Phage endolysin lysh5 and nisin	NR	*LysH5 activity might be increased by the permeabilization of the cytoplasmic membrane by nisin. Also, partial activation of autolysins by nisin may occur and facilitate LysH5 activity.*	(García, et al. 2010)
SAP8 endolysin	NR	*Forms pores in bacterial cytoplasmic membrane and inhibits cell wall synthesis*	(Kim, et al. 2022)
Bacteriocins:			
Bovine myeloid antimicrobial peptide (BMAP-28)	NR	1) Cell wall permeation is made by the activity of *BMAP-28* as it is diffusing inside the bacteria. 2) Bacterial smooth surface somehow changes into a rough surface by the activity of *BMAP-28*. 3) *BMAP-28* can break *MRSA* cell membranes.	(Takagi, et al. 2012)

Name	Active Components	Mechanisms	References
Bacteriocins			
Pediococcus acidilactici strains A11 and C12	NR	The initial bacteriocin reaction is to damage membrane permeability and eliminate proton motive force *(PMF)* thereby inhibiting energy production and biosynthesis of proteins or nucleic acids. 2) bacteriocin molecules are in direct contact with cell membranes, this contact process is able to disrupt membrane potential in the destabilizing cytoplasmic membranes so that cells become less strong, and membrane instability is capable of producing holes in cell membrane through the process of interference with PMF (Proton Motive Force).	(Lestari, et al. 2019)
Cell-free extract of *Bifidobacterium Species of LAB*	*b1, b2, BL* and *BI*	The acids produced by *LAB* enter the sensitive bacterial cells and interfere with the necessary metabolic process such as substrate translocation and oxidative phosphorylation, which leads to a decrease in the internal pH of bacterial cells.	(AL-Saadi 2016)

Name	Active Components	Mechanisms	References
Bacteriocins			
bacteriocin produced by *Staphylococcus pasteuri RSP-1 (S. pasteuri RSP-1)*	*Pasteuricin*	*Pasteuricin* rapidly damaged the membrane of viable cells.	(Hong, et al. 2018)
Bacteriocin isolated from *Lactobacillus pentosus*	*Pentocin JL-1*	*Pentocin JL-1* targets the cell membrane of *MRSA GIM 1.771*, causing a loss of PMF in only a few minutes, and that has a dramatic impact on the structure and integrity of the *MRSA* cell and finally leads to cell death.	(Jiang, et al. 2017)
Bacteriocin from *Lactococcus lactis KU24*	*Bacteriocin KU24*	The bacteriocin *KU24* damages the cell wall or induces cell lysis and has an impact on the bacterial cytoplasmic membrane.	(Lee, et al. 2013)
Bacteriocin from Lactobacillus plantarum ZJ217	*NR*	Bacteriocin produced by Lactobacillus plantarum can cause the formation of pores on bacterial cells and releasing ATP, and bacterial death	(Zhu, et al. 2015)
Bacteriocin isolated from the natural inhabitant of Allium cepa	*Peptide-Ba49*	Peptide-Ba49 can result in the rupturing and uniformity of MRSA.	(Taggar, et al. 2021)

Name	Active Components	Mechanisms	References
Bacteriocins			
Bacteriocin producing Lactobacillus acidophilus	*Bacteriocin gene NX371*	The leakage of intracellular ATP, disrupt the cell wall, and induce membrane leakage.	(Meng, et al. 2021)
Bacteriocin produced by Escherichia coli strains and Enterococcus species	*Colicins and Enterocin*	These depolarize the cytoplasmic membrane, leading to dissipation of cellular energy and killing domain may produce a pore in the target cell membrane, or act as a nuclease to chop up the DNA or RNA of the target cell	(Bajlan, et al. 2018)
Bacteriocin produced by Lactobacillus plantarum ZJ217	*Plantaricin ZJ217*	The Plantaricin ZJ217 had activity against biofilm cells of MRSA by forming pores to release ATP.	(Zhu, et al. 2015)
Bacteriocin produced of Lactococcus lactis KTH0-1S	*Bacteriocin KTH0-1S*	The KTH0-1S can have an impact on sensitive cells, causing pores formation in the membrane, resulting in cell death due to loss of essential intracellular substances	(Saelao, et al. 2017)
Bacteriocin produced by Lactobacillus paracasei ZFM54	*Bacteriocin Paracin 54*	The treatment with Paracin 54 enhanced the permeability of the cell membrane, damaged the cell membrane, and led to electrolyte outflow.	(Zhu, et al. 2021)

Name	Active Components	Mechanisms	References
Bacteriocins			
Bacteriocin produced by Lactobacillus plantarum 163	*Plantaricin 827*	Its antibacterial mechanism increased the cell membrane permeability and integrity, resulting in the leakage of K+ and changes in cell morphology.	(Zhao, et al. 2022)
Bacteriocin produced by Lactococcus lactis subsp. lactis. and Lactobacillus reuteri	*Nisin and reuterin*	The combination of nisin and reuterin may change the permeability of the outer membrane and cause a lethal effect.	(Yehia, et al. 2022)
Probiotics			
Lactobacillus plantarum KU200656	NR	It can inhibit the adherence of pathogens by competing for nutrition and host intestinal cell-binding sites, e.g., receptor exclusion. bolites (e.g. hydrogen peroxide), and proteinaceous compounds.	(Lee, et al. 2021)
Lactobacillus acidophilus and *Lactobacillus casei*	NR	They produce antimicrobial components that can inhibit the growth and eliminate of the *MRSA* cells.	(Karska-Wysocki, et al. 2010)

NR: not reported.

CONCLUSION

According to our review, the most effective EO against *MRSA* was a liposome containing cinnamon oil, which resulted in a significant decrease in *MRSA* populations. Additionally, essential oils from *Cinnamomum zeylanicum*, *Syzygium aromaticum*, *Cuminum cyminum*, allicin, *glabrol, clove buds,* and *backhousia citriodora* have shown significant effectiveness against *MRSA*. Another potential solution against *MRSA* is the use of bacteriophages. Based on our review, promising phage compounds include *S. aureus* phage containing *CHAPLysGH15* and *LysGH15* and *phage SA11 endolysin*. Bacteriocins have also shown promise in combatting *MRSA*. Bacteriocins such as *Enterocin AS-48, Pentocin JL-1*, bacteriocin-producing *Pseudomonas aeruginosa TA6*, and bacteriocin produced by *S. pasteuri RSP-1* were effective against *S. aureus*. Probiotics have also shown antimicrobial properties against *MRSA*. *Streptomyces griseus*, *Pediococcus acidilactici* strains *A11 and C12, Lactococcus lactis*, and *Lactobionic acid* are among the most effective probiotics against *MRSA*. In the fight against *MRSA*, the combination of above-mentioned antibacterials has also shown promising results. These natural compounds and microorganisms possess unique mechanisms of action that can effectively target and eliminate *MRSA* cells. Furthermore, their use in combination with other antimicrobial agents including chemicals can enhance their efficacy, providing a multi-hurdle approach in combatting antibiotic-resistant bacteria. However, in food matrices, the results might be different from in vitro experiments because natural compounds can interact with food compounds like proteins and lipids, potentially reducing the availability of the natural compound as an antimicrobial agent. Additionally, processing steps can diminish the antimicrobial activity of such compounds. Furthermore, before the application of natural antimicrobials in food products, health and safety risks associated with them should be thoroughly assessed. The impact of EOs on the organoleptic characteristics of food should also be taken into account, as they may have negative effects. Nevertheless, the application of nanotechnology can mitigate these effects.

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Author's Contribution:

Z.A. made contributions to conception and design of the study, was involved in data collection and drafting the manuscript. G.S. revised the manuscript critically and together with Z.A., M.H., and A.A. prepared the final draft of the manuscript etc. All authors read and approved the final manuscript.

Competing interest

The authors declare that they have no competing interests.

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