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Review

Effects of tannins and related polyphenols on methicillin-resistant *Staphylococcus aureus*

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) often acquires multi-drug resistance and is involved in many cases of disease in hospitals. We investigated natural substances directly effective against MRSA or that influence antibiotic resistance. Aloe-emodin, an anthraquinone, and several licorice flavonoids showed potent antibacterial effects against MRSA. Like some hydrolysable tannins (corilagin and tellimagrandin I) and a tea polyphenol [(−)-epicatechin gallate], the licorice flavonoid licoricidin also restored the effects of oxacillin, a β-lactam antibiotic against MRSA. Further study revealed that theasinensin A, a polyphenol formed from (−)-epigallocatechin gallate, proanthocyanidins obtained from fruits of *Zizyphus jujuba* var. *inermis*, and polymeric proanthocyanidins from fruit peels of *Zanthoxylum piperitum* also suppressed the antibiotic resistance of MRSA.

Keywords: Tea; *Camellia sinensis* (Theaceae); *Zizyphus jujuba* var. *inermis* (Rhamnaceae); *Zanthoxylum piperitum* (Rutaceae); Polyphenol; Tannin; Proanthocyanidin; MRSA; Antibiotic resistance; Antibacterial

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1. Introduction

Although the use of antibiotics has greatly reduced the incidence of infectious diseases, it has also led to the appearance of drug-resistant bacteria. Among infectious diseases caused by antibiotic-resistant bacteria, the most frequently encountered in Japan is that caused by methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA often acquires multi-drug resistance (Shiota et al., 1999) and causes severe problems in clinical medicine.

Various plant phenolics, including flavonoids and tannins, have been shown to have antibacterial effects (Mitscher et al., 1980; Kolodziej et al., 1999), and some flavonoids and xanthones are effective against MRSA (Sakagami et al., 1998; Iinuma et al., 1996). This report reviews our recent investigations, which have revealed that several types of phenolics isolated from medicinal plants are effective against MRSA, acting either directly or by restoring the antibacterial effects of antibiotics.

2. Effects of phenolic compounds of low molecular weight on MRSA: anthraquinones, naphthalenes, and licorice flavonoids

The MRSA strains used in these studies, OM481, OM505, OM584, and OM623, were clinical isolates from Okayama University Hospital (Shiota et al., 2004). The antibiotic resistance of MRSA is mainly attributed to the production of penicillin binding protein (PBP) 2a, which interacts with β-lactams, although much less strongly than other PBPs. Two of the strains, OM481 and OM623, express PBP 2a constitutively, and in OM505 and OM584 it is induced in the presence of β-lactam antibiotics. The latter two also express *blaZ* and produce β-lactamase. The development of drug-excretion systems, and of mechanisms that make it difficult for antibiotics to penetrate bacterial colonies, such as the formation of biofilms, also contribute to antibiotic resistance in some bacterial species and strains. The role of such mechanisms in the resistance of MRSA strains has not been determined.

Minimum inhibitory concentrations (MICs) of representative antibiotics against MRSA strains are shown in Table 1. These strains are resistant to the β-lactam antibiotics such as ampicillin and cefmetazole, to the aminoglycoside antibiotic streptomycin, and to the macrolide antibiotic erythromycin.

Some phenolic constituents of *Cassia tora* and of licorice (the underground portion of *Glychyrrhiza uralensis* and related species) have been reported to have antibacterial activity (Kitanaka and Takido, 1986; Demizu et al., 1988); we investigated their effects on MRSA.

Several anthraquinone and naphthalene glycosides, including some new compounds, were isolated from seeds of *C. tora*, but their antibacterial effects on MRSA were negligible. On the other hand, the unglycosylated naphthalenes torachrysone (**1**) and toralactone (**2**) had MIC values of 32 or 64 μg/ml against the MRSA strains, and therefore the effects of unglycosylated anthraquinones isolated from rhubarb were also examined. Aloe-emodin (**3**) was a potent antibacterial with a MIC of 2 μg/ml (Hatano et al., 1999). Aloe-emodin (**3**) (Fig. 1) did not show noticeable synergistic effects with oxacillin on MRSA (unpublished data).

On the other hand, several flavonoids with C_5 aliphatic residues were isolated as the effective constituents of licorice against MRSA (Hatano et al., 2000). The MICs of licochalcone A (**4**) (a chalcone), gancaonin G (**5**) and isoangustone A (**6**) (isoflavones), glyasperins C (**7**) and D (**8**), glabridin (**9**), and licoricidin (**10**) (isoflavans), glycycoumarin (**11**) (3-arylcoumarin), and licocoumarone (**12**) (2-arylbenzopyran) were 16 μg/ml, and

Table 1
Effects of antibiotics against MRSA strains[a] (data from Shiota et al., 1999)

Antibiotics	Minimum inhibitory concentration (MIC) for the MRSA strains (μg/ml)			
	OM481	OM505	OM584	OM623
β-Lactams				
Oxacillin	512	128	256	256
Penicillin G	32	32	16	32
Ampicillin	128	128	128	128
Cefmetazole	64	32	64	64
Imipenem	32	4	16	16
Aminoglycoside				
Streptomycin	8	16	4	16
Others				
Ofloxacin	2	1	4	8
Tetracyclin	4	0.24	64	64
Erythromycin	>128	>128	>128	>128
Fosfomycin	>1024	256	>1024	>1024

[a] MRSA strains were clinical isolates from Okayama University Hospital.

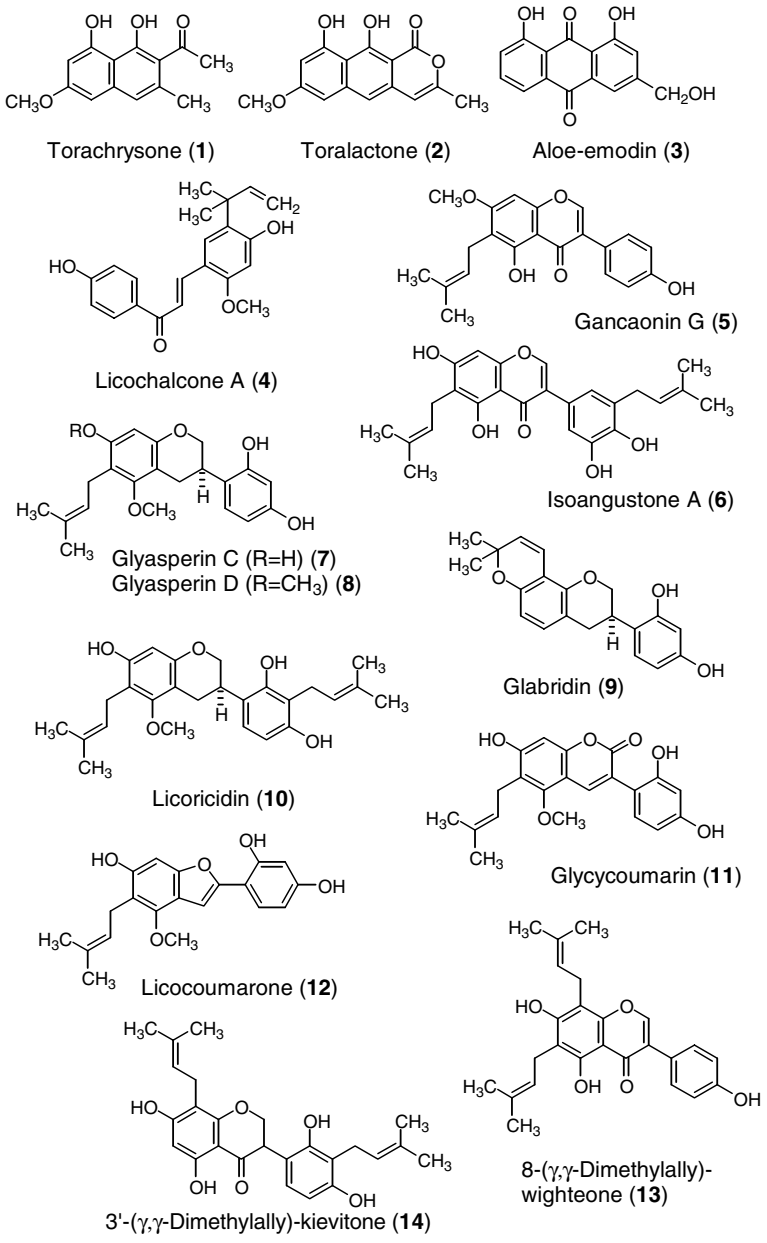

Fig. 1. Structures of low molecule polyphenols effective against MRSA.

those of 8-(γ,γ-dimethylallyl)-wighteone (**13**) and 3′-(γ,γ-dimethylallyl)-kievitone (**14**) were 8 μg/ml. All of these compounds have phenolic hydroxyl groups and C_5 side chains. The requirement for the lipophilic C_5 group suggests that interactions between the MRSA cell membrane and the aliphatic residues participate in the antibacterial effect.

Several licorice flavonoids also reduced the MIC values for oxacillin against MRSA (Hatano et al., 2000). The addition of 4 μg/ml of licoricidin (**10**) (Fig. 1), an isoflavan, shifted the MIC of oxacillin from 128–256 to 8–16 μg/ml, and 8 μg/ml licoricidin reduced it to less than 0.5 μg/ml. The order of potency of licorice flavonoids in suppressing oxacillin resistance was not the same as for direct antibacterial effects, suggesting that different mechanisms participate in each effect. Perturbation of the cell membrane by the aliphatic residues of the flavonoids does not explain the oxacillin synergism satisfactorily. Licoricidin did not affect the production of PBP 2a in an MRSA strain, although it might still alter PBP 2a's inhibitory effect on cell wall production in some way. The bacteriostatic suppression of cell growth by the combination of oxacillin and licoricidin continued for at least 24 h.

3. Effects of oxidation products of a tea polyphenol on MRSA

Various pharmacological properties have been reported for the major tea polyphenol (−)-epigallocatechin gallate (EGCG) (**15**) (Philpott and Ferguson, 2004; Okuda et al., 1983; Yoshizawa et al., 1987), including effects on the β-lactam resistance of MRSA (Stapleton et al., 2004). Interaction of EGCG with various biomolecules has been investigated (Charlton et al., 2002; Jobstl et al., 2004; Hatano et al., 2003a). On the other hand, this compound is easily converted into a number of products, even in neutral solution (Hatano et al., 2003b). At pH 7.4, the half-life of EGCG was 0.56 h. Addition of a metal chelator, diethylene-triamine-pentaacetic acid, prolonged the half-life, and the addition of ferric iron shortened it, suggesting that metal ions participate in the breakdown of EGCG in solution. We identified products present during the rapid breakdown of EGCG. Their structures indicated that the changes in EGCG were: (1) hydrolysis to give gallic acid (**16**), (2) epimerization at C-2 to give (−)-gallocatechin gallate (**17**), (3) oxidative cleavage of the trihydroxy B-ring to give EGCG-MOx-M1 (**18**) and M2 (**19**), (4) oxidative coupling of B-rings between the two molecules of EGCG to give theasinensins A (**20**) and D (**21**), and (5) the production of dimeric products with B-ring oxidation, such as EGCG-MOx-D1 (**22**), D2 (**23**) and D3 (**24**) (Fig. 2) (Hatano et al., 2004).

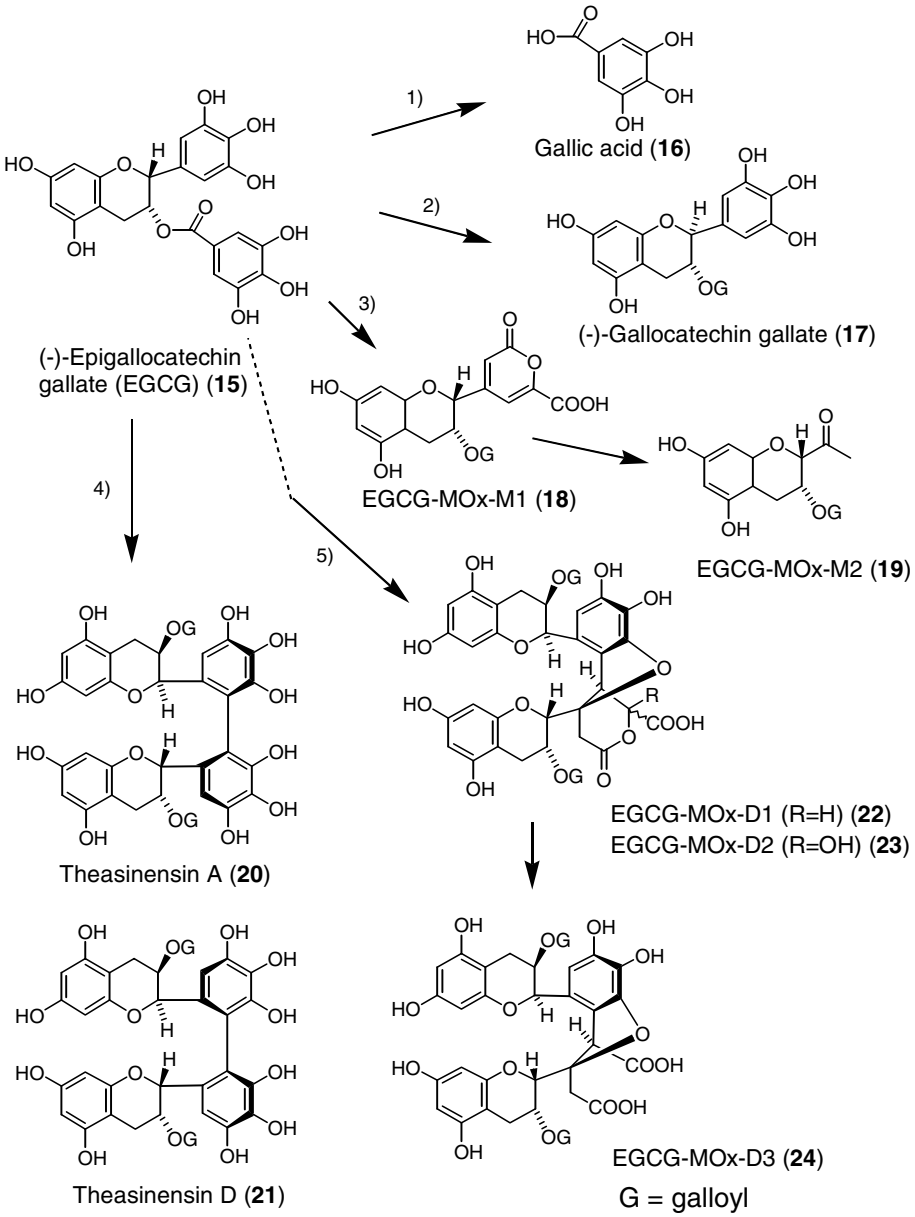

Fig. 2. Structural changes to (−)-epigallocatechin gallate (**15**) in neutral solution (1)–(5) are explained in the text.

We found that several dimeric products showed antibacterial activity against MRSA (MIC values of 64 or 128 μg/ml), and we examined the effect of theasinensin A (**20**), the major product of EGCG breakdown, on antibiotic resistance. It caused a noticeable reduction in MIC values of oxacillin for the MRSA strains (Table 2) (Hatano et al., 2003b; Hamilton-Miller and Shah, 2000). Oxacillin in the presence theasinensin A (**20**) completely inhibited cell growth over 10 hrs. Analogous inhibition was observed for the tea polyphenol (−)-epicatechin gallate (**25**), and for the hydrolysable tannins tellimagrandin I (**26**) and corilagin (**27**), as shown previously (Fig. 3) (Shiota et al., 1999; Shiota et al., 2000; Shimizu et al., 2001).

Although the effectiveness of the inhibition by theasinensin A (**20**) continued over 10 h, bacterial growth was observed after prolonged incubation. A second addition of theasinensin A (**20**) at 10 h, however, led to further inhibition of growth. Theasinensin A (**20**) was also effective in reducing the MIC values of the other β-lactams, penicillin G and ampicillin. Streptomycin, an aminoglycoside antibiotic, also showed a reduced MIC in the presence of theasinensin A (**20**), not only against MRSA strains but also against the methicillin-sensitive strain 209P (Hatano et al. 2003). The aminoglycoside antibiotics have adverse side effects, inhibiting renal and some acoustic-nerve functions. Co-administration of aminoglycosides with these polyphenols may help to reduce doses and their associated risks.

4. Effects of proanthocyanidin constituents of *Zizyphus jujuba* var. *inermis* and *Zanthoxylum piperitum* on MRSA

Fruits of *Zizyphus jujuba* var. *inermis* (Rhamnaceae) and fruit peel of *Zanthoxylum piperitum* (Rutaceae) have been used in traditional medicine in Japan.

Our investigation of the constituents of *Zizyphus* fruits identified two dimeric procyanidins, procyanidin B3 (**28**) and B4 (**29**) (Fig. 4). Although the MICs of these polyphenols were 512–1024 μg/ml, procyanidins B3 (**28**) and B4 (**29**) both reduced the MIC for oxacillin to 1/2–1/16 of those in the absence of the polyphenols, as shown

Table 2
Effect of theasinensin A (**20**) on the antibiotic resistance of MRSA (data from Hatano et al., 2003b)

Antibiotics	Minimum inhibitory concentration (MIC) for the MRSA strains (μg/ml)			
	OM481	OM505	OM584	OM623
Oxacillin alone	256	64	256	256
Oxacillin + theasinensin A (16 μg/ml)	128	64	32	128
Oxacillin + theasinensin A (32 μg/ml)	4	4	4	4
Penicillin G alone	32	32	32	32
Penicillin G + theasinensin A (16 μg/ml)	4	8	4	4
Penicillin G + theasinensin A (32 μg/ml)	0.125	0.5	0.25	0.25
Theasinensin A alone	64	64	64	64

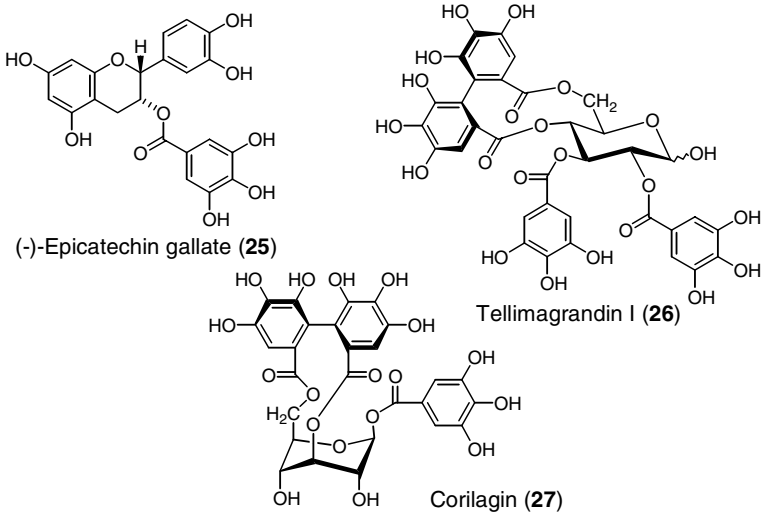

Fig. 3. Structures of a tea catechin and hydrolyzable tannins that restored the effects of antibiotics against MRSA.

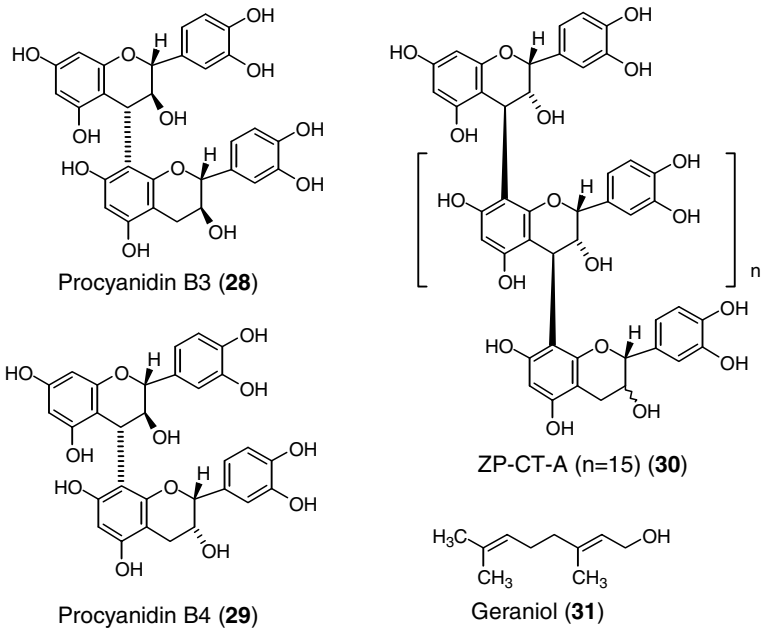

Fig. 4. Structures of proanthocyanidins and a monoterpene isolated from *Zizyphus* fruits and *Zanthoxylum piperitum* fruit peels.

Table 3
Effect of dimeric procyanidins on the antibiotic resistance of MRSA

Antibiotics	Minimum inhibitory concentration (MIC) for the MRSA strains (μg/ml)			
	OM481	OM505	OM584	OM623
Oxacillin alone	256	64	256	512
Oxacillin + procyanidin B3 (**28**) (64 μg/ml)	128	32	32	64
Oxacillin + procyanidin B4 (**29**) (64 μg/ml)	64	32	16	32
Penicillin G alone	32	32	32	16
Penicillin G + procyanidin B3 (**28**) (64 μg/ml)	8	16	8	8
Penicillin G + procyanidin B4 (**29**) (64 μg/ml)	4	16	4	4
Procyanidin B3 (**28**) alone	512	1024	1024	1024
Procyanidin B4 (**29**) alone	512	512	512	512

in Table 3. These two dimers also lowered the MIC of penicillin G (Table 3).

Fruit peels of *Z. piperitum* contain polymeric proanthocyanidins, in addition to essential oil monoterpenes, aliphatic acid amides, and some low-molecular-weight phenolics. Fractionation of fruit peel extracts yielded a condensed tannin (proanthocyanidin) fraction (ZP-CT-A) (**30**), in addition to several other previously identified constituents. ^{13} C NMR spectroscopic analysis showed signals of oligomeric or polymeric procyanidins, and thiolytic cleavage indicated that the extension (upper) units were mainly composed of epicatechin, and that the terminal units were composed of epicatechin and catechin. The polymerization degree suggested by the SEC analysis was 17 (Fig. 4).

Although the MIC of ZP-CT-A (**30**) alone against the MRSA strains was 128 μg/ml, addition of 32–64 μg/ml of ZP-CT-A (**30**) markedly reduced the MIC of oxacillin, by 64–512-fold, or more (Table 4). It also affected the MIC of penicillin G, similarly.

The increased potency in restoring antibiotic sensitivity that accompanied the increase in molecular weight (from dimer to polymer) suggests that an affinity for binding to bacterial proteins such as PBP 2a, or to cell-wall building blocks, may be responsible for some of the effects of the proanthocyanidins. Recently, the effects of corilagin (**27**) and tellimagrandin I (**26**) on antibiotic resistance were correlated with their effects on PBPs (Shiota et al., 2004). Inhibitory effects of the hydrolyzable tannins on β-lactamase were also observed.

On the other hand, geraniol (**31**), a monoterpene among the essential oil constituents of *Z. piperitum*, also decreased the MIC of oxacillin against MRSA (Table 5) (Hatano and Yoshida, 2003). Preliminary studies on the mechanism of the effects of ZP-CT-A (**30**) and geraniol (**31**) suggest that both the tannin and the monoterpene

Table 4
Effect of ZP-CT-A (**30**), condensed tannin (polymeric proanthocyanidin fraction) obtained from fruit peels of *Zanthoxylum piperitum* on the antibiotic resistance of MRSA

Antibiotics	Minimum inhibitory concentration (MIC) for the MRSA strains (μg/ml)			
	OM481	OM505	OM584	OM623
Oxacillin alone	256	64	256	512
Oxacillin + ZP-CT-A (32 μg/ml)	256	32	32	64
Oxacillin + ZP-CT-A (48 μg/ml)	1	8	2	4
Oxacillin + ZP-CT-A (64 μg/ml)	<0.5	1	1	1
Penicillin G alone	32	32	32	32
Penicillin G + ZP-CT-A (32 μg/ml)	16	16	8	8
Penicillin G + ZP-CT-A (48 μg/ml)	0.125	4	1	0.25
Penicillin G + ZP-CT-A (64 μg/ml)	<0.06	2	0.25	0.125
ZP-CT-A alone	128	128	128	128

Table 5
Effect of geraniol (**31**) on the antibiotic resistance of MRSA

Antibiotics	Minimum inhibitory concentration (MIC) for the MRSA strains (μg/ml)			
	OM481	OM505	OM584	OM623
Oxacillin alone	512	128	256	512
Oxacillin + geraniol (128 μg/ml)	16	2	4	4
Streptomycin alone	8	8	8	16
Streptomycin + geraniol (128 μg/ml)	1	4	4	8
Geraniol alone	512	512	512	512

lower stability of the bacterial cell membrane (unpublished results).

5. Conclusions

We have found two types of phenolics effective against MRSA: phenolics with low molecular weights (anthraquinones and prenylated flavonoids) and higher-molecular-weight polyphenols (theasinensin A (**20**) and proanthocyanidins, in addition to some hydrolyzable tannins).

The anthraquinones and prenylated flavonoids showed potent antibacterial effects, with MIC values of 2–8 μg/ml. Some prenylated flavonoids such as licoricidin (**10**) also effectively suppressed the antibiotic resistance of MRSA. The low effective concentration (4–8 μg/ml) of licoricidin, in addition to its prolonged effect (24 h), make its performance superior to that of other compounds. The requirement for dimethylallyl or equivalent substituents suggests the importance of affinity for the bacterial cell membrane. The combination of licoricidin (**10**) and oxacillin was bacteriostatic.

EGCG, the main constituent of tea polyphenols, is easily converted to various breakdown products. The main product, theasinensin A (**20**), also showed moderate antibacterial effect against MRSA, and markedly decreased MICs of oxacillin and other antibiotics. The production of PBP 2a was not suppressed by theasinensin A (**20**), and the mechanism of its suppression of antibiotic resistance is still unclear. The combination of oxacillin and theasinensin A (**20**) markedly decreased the bacterial cells, and the effect lasted for 10 h. Repeated administration of theasinensin A (**20**) effected sustained inhibition of bacterial growth.

Proanthocyanidins isolated from *Zizyphus* fruits and *Zanthoxylum* fruit peels were also effective suppressors of antibiotic resistance in MRSA, and this effect was more pronounced with polymeric procyanidins than with dimeric ones. Since geraniol (**31**), a monoterpene constituent isolated from *Zanthoxylum* fruit, also showed analogous suppression, essential oil constituents from other plant sources may be expected to have potent effects on MRSA.

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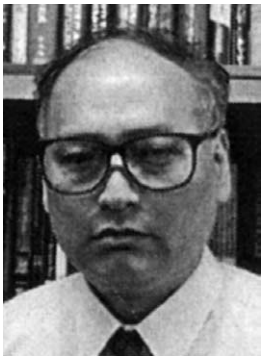

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