

Antibiotics and bioactive natural products in treatment of methicillin resistant *Staphylococcus aureus*: A brief review

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ABSTRACT

Infections caused by *Staphylococcus aureus* strains with Methicillin resistance are associated with increased mortality and morbidity, aggressive course, multiple drug resistance and hospital outbreaks. Several first and second line antibiotics are rapidly becoming ineffective for treatment due to emergence of resistance. Extracts of medicinal plants are rich source of unique phytochemicals. Plants used in traditional medicine have been reported to have significant anti-MRSA activity. The objective of this review is to provide a brief overview of antibiotics as well as anti-MRSA natural products and their future prospect.

Key words: Methicillin resistant *Staphylococcus aureus* (MRSA), phytochemicals, plant extracts

INTRODUCTION

Staphylococcus aureus is one of the prominent medically important bacterial pathogen. Its potential to cause wide spectrum of pyogenic lesions involving several organs, hospital outbreaks and community acquired infections are well recognized. *S. aureus* infections are often fatal in nature and are associated resistance to several beta-lactam antibiotics used in hospitals.^[1] These strains are known as MRSA (methicillin resistant *S. aureus*).^[2] Historically, it had drawn special attention since 1970 due to its association with several nosocomial outbreaks and cross infections.^[3] The epidemiology of this organism has changed over years. Life-threatening infections which were limited only in hospitals are now becoming widespread in community.^[4] High usage of antibiotics in hospitals and selection pressure of these antibiotics has been implicated in development of multidrug resistance (MDR) in hospital acquired

MRSA (HA-MRSA) strains. Likewise, increased use of antibiotics in animal feed has resulted in emergence of a new MRSA strain (livestock associated MRSA or LA-MRSA) with multiple non-beta lactam drug resistance.

Pertaining to the difference in virulence, pathogenicity, risk factors and drug resistance, MRSA strains are highly variable in different geographical areas. Even within a country, there may be local variation in MRSA strains.^[5,6] MRSA prevalence varies from 20% to 54.8% in different parts of India,^[7-9] while a recent study shows 29.1% prevalence in South India.^[10] Antibiotic susceptibility pattern indirectly correlate with pathogenicity and therefore may be helpful in tracing the dissemination of the predominant MRSA strain or emergence of new MRSA strain. The transmission of Staphylococcal infection can be effectively reduced by stringent infection control measures and judicious use of antibiotics.^[11] Conventional anti-MRSA antibiotics like Vancomycin, Teicoplanin, Linezolid and Daptomycin are currently in clinical use. However, development of resistance to many of these drugs has been identified worldwide. Vancomycin resistant and intermediate MRSA strains (VRSA and VISA) have been reported sporadically. Furthermore, it has also shown increase in the minimum inhibitory concentration (MIC) to Glycopeptides over years indicating reduced susceptibility. With the emergence of resistance to these drugs along with scarcity of newer anti-MRSA in the pipeline, the therapeutic options are likely to be further narrowed in future. Conversely, novel bioactive natural products have been identified to display anti-MRSA activity. Current research suggests these natural products have the prospect of being considered for treatment of MRSA infections.

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This review critically appraises conventional antibiotics and bioactive natural products with anti-MRSA activity.

Anti-MRSA antibiotics and their resistance mechanisms

Methicillin

Methicillin (originally called Celbenin) was the first beta lactamase resistant semisynthetic penicillin developed in 1960 to treat infections with penicillin resistant *S. aureus*. However, methicillin resistant strains of *S. aureus* emerged within one year of its clinical use.^[12] The early reports of MRSA among European countries were from UK and Denmark.^[13] MRSA has also been reported from India as early as 1964.^[14] Methicillin exerts its antimicrobial activity by inhibiting transpeptidase mediated peptidoglycan cross-links by after binding with cell wall PBPs.

Methicillin resistance is mediated by an additional PBP (PBP2a) with low affinity for beta-lactam agents and it confers resistance to methicillin as well as other beta-lactam antibiotics. The *mecA* gene coding PBP2a along with two regulator genes (*mecI* and *mecR1*) is carried by SCCmec. Expression of *mecA* gene is usually inducible and regulated by *mecI*, *mecR1* and additional genes like *blaI*, *blaR1*, *femB*, *aux*.^[15] Apart from *mecA* mediated resistance, other resistance mechanisms which are not associated with treatment failure are also described.^[16] Alteration of existing PBP by mutation in the beta lactam drug binding domain may give rise to resistance in *S. aureus* which are termed as MODSA (moderately oxacillin resistant *S. aureus*). Similarly few penicillinase hyper-producer *S. aureus* strains described as BORSA (borderline oxacillin resistant *S. aureus*) can slowly hydrolyse methicillin/oxacillin by type-A staphylococcal beta-lactamase resulting in borderline MIC and low level resistance.

Vancomycin

Vancomycin is currently the antibiotic of choice for treating MRSA infections. It is a branched glycosylated tricyclic peptide belonging to the glycopeptide antibiotic class. It binds to the growing ends of peptide chains and prevents their interaction with transpeptidase enzyme. Although reports of MRSA strains with diminished susceptibility to this antibiotic are not infrequent,^[17] only few reports of vancomycin resistant *S. aureus* (VRSA) showing MIC ≥ 32 $\mu\text{g}/\text{ml}$ have been documented. Four VRSA carrying *vanA* gene were reported from USA between 2002 and 2006.^[18] Later Tiwari *et al.* reported *vanA* negative VRSA in 2006^[19] and recently Saha *et al.* recovered one isolate of VRSA from Kolkata.^[20] Vancomycin intermediate *S. aureus* (VISA) is characterized by MIC between 8-16 $\mu\text{g}/\text{ml}$. It was first reported in Japan in 1997.^[21] Subsequently it was reported from United States and Europe. Intermediate sensitivity among MRSA has also been reported from South India.^[22]

Linezolid

It is a new drug class, the *Oxazolidinones*. It binds to domain V of 23s RNA and prevents correct protein synthesis. Linezolid resistance occurs when at least 2 copies of 23s RNA genes are mutated specially with increased clinical use and the control

measure is aggressive antibiotic stewardship (reducing its clinical use).^[23] First case of linezolid resistance in MRSA was reported in 2001^[24] and subsequently 8 cases in the US, 2 in Germany and 1 each in Brazil, Colombia and the UK. Spanish outbreak of linezolid resistant *S. aureus* had a different cause, the importation of the *efr* gene carrying plasmid, which also mediates resistance to the older drugs clindamycin and chloramphenicol.^[25]

Daptomycin

It is a calcium-dependent cyclic lipopeptide anti MRSA drug which act by depolarization of the bacterial cell membrane. However, due to its lipophilic nature it gets incorporated in alveolar surfactant and deposited in alveoli instead of bacterial cell membrane and results in eosinophilic pneumonia limiting its therapeutic use.^[26] There is no defined resistance breakpoints for *S. aureus*, isolates are either categorized as susceptible or nonsusceptible.^[27] Since vancomycin prolonged exposure is related to decreased daptomycin susceptibility, it should be ruled out by rechecking daptomycin MIC when a patient is unresponsive to this combination.^[28]

Streptogramin antibiotics

These are derivative of *Streptomyces pristinaespiralis*. They are categorized into - group A (e.g. dalfopristin) and group B (e.g. quinupristin).^[29] It is available for therapeutic use as combination of quinupristin and dalfopristin (30:70 ratio) which is more potent than single agent and may be active even when there is resistance to one component. Both quinupristin and dalfopristin bind to 50S ribosome at different sites to form a stable tertiary complex, and inhibit protein synthesis of bacteria. Genes coding *Streptogramin* inactivating enzymes (*erm*, *msr*, *vat*) can occur on transmissible elements. Drug elimination by efflux has also been described.^[30] The first report of resistance to this antibiotic in MRSA was from France in 1975.^[31] Diverse range of the resistance ranging from 0% to 31% has been detected in different studies globally.^[32] Different groups in India have reported variable rate of resistance with the maximum of 64% as observed by Deep *et al.*^[29,33]

Clindamycin and inducible clindamycin resistance

Clindamycin is a lincosamide antibiotic classically used for infections by aerobic Gram-positive cocci and anaerobes. Clindamycin resistance in *S. aureus* may be classified in one of the three phenotypes, designated as MLSBi, MLSBc and MS respectively.^[34] Inducible resistance to *Streptogramin* B, macrolide and lincosamide in *S. aureus* is attributed to *erm* gene encoding an enzyme which methylate adenine residue of 23s rRNA.^[34] This inducible clindamycin resistance has been found more frequently among MRSA strains and it often leads to treatment failure as it is not detected in routine antibiotic susceptibility tests.^[35] It requires detection by a simple test, frequently described as D-test.

Bioactive natural products anti-MRSA activity

Indian medicinal plants

Indian continent is blessed with 120 families and 130000 species of plants. Many of these are known to have medicinal properties.

From historical time, various parts of these plants have been used in treatment of communicable as well as non-communicable diseases. However, the bioactive phytoconstituents contributing to antimicrobial properties are yet to be discovered.

Recent research has identified *Acorus calamus*, *Lawsonia inermis*, *Hemidesmus indicus*, *Holarrhena antidysenterica*, *Punica granatum*, *Plumbago zeylanica*, *Camellia sinensis*, *Delonix regia*, *Terminalia chebula*, *Emblca officinalis* and *Terminalia bellerica* have *in vitro* antimicrobial action against MRSA. *A. calamus* also known as sweet flag, calamus and bach, grows throughout India, especially in hills of Manipur and Nagaland. Its rhizome has effect on nervous system and has been used as antihypertensive, sedative, antianxiety, antispasmodic, anticonvulsant as well as for bronchial infection, chronic diarrhoea and dysentery. Several studies reported bactericidal activity of its rhizome and leaf extracts.^[36-38]

Emblca officinalis, *Terminalia chebula* and *Terminalia bellerica* fruits are constituents of a polyherbal Ayurvedic medicinal formulation known as *Triphala*. Its antioxidant, antimicrobial, anticancer, anti-allergic, cardiogenic, hypocholesterolemic and hepatoprotective properties are well recognized and it has been used in treatment of malabsorption, constipation, dyspepsia and hyperglycemia for its multiple health benefits.^[39] Although human clinical trials have not been conducted to support its use in infections, evidence from *in vitro* studies and animal models suggests each component of *Triphala* have anti-MRSA property.^[39-41]

Likewise, leaves of *Camellia sinensis* (tea),^[40,41] *Lawsonia inermis* (mehndi)^[41] and *Azadirachta indica* (neem),^[40,42,43] *Holarrhena antidysenterica* (Kurachi) bark,^[36] *Delonix regia* (Gulmohar) flowers,^[41] *Punica granatum* (Pomegranate) rind,^[41,44] *Hemidesmus indicus* (Anantamul) stem^[36] and *Plumbago zeylanica* (Chitra) root^[36] has shown *in vitro* activity against MRSA [Table 1].

Miscellaneous medicinal plants

With the increase in awareness of medicinal value of plants and herbal component, several studies have investigated the antibacterial properties of herbal plants against MDR pathogens in current years. This trend is seen worldwide and developed countries are no exception. Significant activity against MRSA have been documented in studies which used extract of plants mentioned in traditional medicine of Thailand (*Garcinia mangostana*, *Quercus infectoria*),^[44] Nigeria (*Terminalia avicennioides*, *Phyllanthus discoideus*, *Ocimum gratissimum*, *Acalypha wilkesiana*)^[45] and Australia (*Eremophila alternifolia*, *Amyema quandong*, *Eremophila duttonii*, *Lepidosper mariscidum*).^[46] Voravuthikunchai *et al.* found that *Quercus infectoria*, *Garcinia mangostana* and *Punica granatum* had highest antibacterial activity and MICs for MRSA were 0.2-0.4 mg/mL, 0.05-0.4 mg/mL and 0.2-0.4 mg/mL respectively.^[44] In another study, the MICs of ethanol extracts of four Nigerian plants *i.e.* *A. wilkesiana*, *P. discoideus*, *T. avicennioides* and *O. gratissimum* ranged from 18.2 to 24.0 mcg/ml.^[45] While the leaf extract from *Eremophila duttonii* was most bactericidal among five Australian medicinal plants in reducing the number

of viable cells of MRSA,^[46] ten Italian plants exhibited MRSA biofilm inhibition with minuscule bacteriostatic activity.^[47]

Active phytoconstituents with anti MRSA activity

Despite ample research evidence of anti-MRSA activity of various plant products, there is lack of adequate information about precise phytoconstituents possessing anti MRSA activity. Most studies have investigated anti-MRSA activity of different plant parts (leaf, bark, flower, rind, fruit etc.) extracted in various solvents (aqueous, methanol, ethanol, ethyl acetate etc.) and expressed the result of phytochemical analysis of these extracts in terms of presence of alkaloids, terpenoids, flavonoids, phenols, steroids and glycosides. Since in most instances isolation of each phytochemical in pure form and re-testing their anti-MRSA activity not attempted and these phytochemicals are often unnamed or named generically (as alkaloids, terpenoids, flavonoids, etc.), it is difficult to assign the anti-MRSA activity to a particular component.

Among the compounds with reported anti-MRSA activity, β -asarone from *Acorus calamus* rhizome, mansonone F from *Ulmus davidiana* var. *japonica*, galloylated flavonol rhamnosides from *Calliandra tergemina* leaves, Prenylated flavonoids from *Desmodium caudatum* root, eupomatenoid-5 from *Piper regnellii* leaves are important.

Beta-asarone is cis-isomer of 2, 4, 5-trimethoxy-l-propenylbenzene, and the active constituent of *A. calamus*. Sujina *et al.* found that beta-asarone was the major constituent (92.4%) in *A. calamus* essential oil and showed 12 mm zone of inhibition and 2.5 mg/ml MIC value against MRSA.^[48] In contrast, Devi *et al.* reported minimal antibacterial activity of its extracts and β -asarone.^[49]

Mansonone F is an anti-MRSA sesquiterpenoid quinone compound of *U. davidiana* var. *japonica* present in the fourth fraction of root extract of *U. davidiana* obtained by silica gel column chromatography.^[50] It has been found to have potent antimicrobial activity against gram positive bacteria including MRSA. However, its activity against gram negative bacteria is insignificant.

Kaempferol-3-O-(2'',3'',4''-tri-O-galloyl)- α -L-rhamnopyranoside, quercetin-3-O-(3'',4''-di-O-galloyl)- α -L-rhamnopyranoside, and quercetin-3-O-(2'',3'',4''-tri-O-galloyl)- α -L-rhamnopyranoside are three novel galloylated flavonol rhamnosides from *C. tergemina* leaves. Chan *et al.* found these phytocompounds exert lytic effect on MRSA.^[51] Moreover, acylation of these rhamnosides is critical for their anti-MRSA activity. Likewise, seven prenylated flavonoids and one prenylated chromanochroman isolated from *Desmodium caudatum* also showed *in vitro* anti-MRSA activity.^[52] Prenyl or a 2,2-dimethylpyran group in these compounds are essential for their antimicrobial action.

Marcal *et al.* spectroscopically identified eupomatenoid-6, eupomatenoid-5, eupomatenoid-3 and conocarpan as the major constituents of *P. regnellii* leaf extract.^[53] Among these

Table 1: Medicinal plants in Indian traditional medicine with anti-MRSA properties

Medicinal plant	Habitat	Common name	Active phytochemicals	Studies which reported anti-MRSA activity
<i>Acorus calamus</i> (rhizome)	Manipur and Naga Hills	Bach	α and β -asarone	Aqil F, 2006 ^[36] Phongpaichit S, 2005 ^[37] Kar A, 1971 ^[38] Aqil F, 2006 ^[36]
<i>Hemidesmus indicus</i> (stem)	Throughout India; commonly in Bengal, Maharashtra	Anantamul	Pregnane glycosides, hemidine, hemidescine, emidine and indicine	Aqil F, 2006 ^[36]
<i>Holarrhena antidysenterica</i> (bark)	Tropical Himalayas	Kurachi	Conessin, curchin, holarrhine, tannins	Aqil F, 2006 ^[36]
<i>Plumbago zeylanica</i> (root)	Native to South Africa	Chitra	Naphthoquinone derivatives, Plumbagin	Aqil F, 2006 ^[36]
<i>Camellia sinensis</i> (leaves)	Assam, Darjeeling, Travancore, Nilgiris, Bengal, Dehra Dun	Tea	Caffeine, tannins, flavonoids, quercetin, kaempferol	Aqil F, 2005 ^[41] Mehrotra S, 2010 ^[40]
<i>Delonix regia</i> (flowers)	Native to Madagascar	Gulmohar	Zeaxanthin	Aqil F, 2005 ^[41]
<i>Lawsonia inermis</i> (leaves)	Native to Persia, now cultivated in Haryana and Gujarat	Mehndi	Naphthoquinones, in particular lawsone. Coumarins, flavonoids, luteolin	Aqil F, 2005 ^[41]
<i>Punica granatum</i> (rind of fruit)	Cultivated throughout India	Pomegranate	Granatin B, punicalagin, punicalin and ellagic acid	Voravuthikunchai SP, 2005 ^[44] Aqil F, 2005 ^[41]
<i>Terminalia chebula</i> (fruits)	Northern India- forests of Assam, West Bengal	Harir	Shikimic, gallic, triacontanoic and palmitic acids, beta-sitosterol, daucoesterol, chebupentol, arjungenin, terminoic acid and arjunolic acid	Aqil F, 2005 ^[41]
<i>Terminalia bellerica</i> (fruits)	Throughout temperate broad-leaf deciduous forests of India	Bahera	Beta-sitosterol, gallic and ellagic acids, ethyl gallate, galloyl glucose, chebulagic acid	Aqil F, 2005 ^[41]
<i>Emblica officinalis</i> (fruits)	Throughout India	Amla	Zeatin, zeatinriboside and zeatin nucleotide	Mehrotra S, 2010 ^[40]
<i>Azadirachta indica</i> (leaves)	All over India	Neem	Tetranortriterpenoids	Mehrotra S, 2010 ^[40] Sarmiento WC, 2011 ^[43] Hena JV, 2011 ^[42]

MRSA=Methicillin resistant staphylococcus aureus

components, eupomatenoid-5 only had antibacterial properties and was responsible for anti-MRSA activity of *P. regnellii*.

Future prospects

The lack of newer antibiotics under development, emergence of drug resistance among several pathogenic bacterial species and their world wide spread along with limited therapeutic options with antibiotics attributed to their higher toxicity and comorbidities in patients have heralded the futility of antibiotics in near future. Although natural herbal products are in use for centuries for treatment of infective ailments, not much is known about their active principles, scientific basis of use, pharmacological and safety profiles. A vast area of traditional medicine has remained undiscovered. Hence, phytochemistry became more relevant in treatment of MDR pathogens like MRSA. However, some aspect needs to be addressed. Difference in extraction method, instruments and raw materials (plants grown on different regions) may lead to wide variation in results and needs standardization.^[43] Most studies utilize diffusion methods for determining antibacterial activity and interpret the results in terms of size of zone of inhibition (ZOI). Unlike antibiotics phytochemicals do not have universally accepted guidelines on ZOI cut offs for diffusion method and also ZOI cannot reflect the concentration of phytochemicals in infected tissues required to inhibit bacterial growth. Hence, it may be more

appropriate to determine the MIC and MBC. Since plant extract may contain numerous substances and one or more components may contribute to antibacterial activity, the identification of the active phytoconstituent from a plethora of alkaloids or glycosides of the extract often become challenging. Finally, the *in vitro* antibacterial action needs further support by animal studies and human clinical trials to determine the safety profile, therapeutic window and optimum dosage schedule in addition to its therapeutic efficacy before considering for routine use.

CONCLUSION

The threat of MRSA in developing as well as in developed countries is on the rise. Plants used in traditional medicine the rich source of bioactive phytoconstituents. Evidence suggests that several medicinal plants have demonstrable anti-MRSA activity and have a prospect of being considered as a potential treatment option for MRSA infections.

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