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A review on mechanism of action, resistance, synergism, and clinical implications of mupirocin against *Staphylococcus aureus*

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ABSTRACT

Mupirocin (MUP), bactroban, or pseudomonic acid is a natural crotonic acid derivative drug extracted from *Pseudomonas fluorescens* which is produced by modular polyketide synthases.

This antibiotic has a unique chemical structure and mechanism of action. It is a mixture of A–D pseudomonic acids and inhibits protein synthesis through binding to bacterial isoleucyl-tRNA synthetase.

MUP is often prescribed to prevent skin and soft tissue infections caused by *S. aureus* isolates and where the MRSA isolates are epidemic, MUP may be used as a choice drug for nasal decolonization. It is also used for prevention of recurring infections and control the outbreaks.

The emergence of MUP resistance has been increasing particularly among methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in many parts of the world and such resistance is often related with MUP widespread uses. Although both low-level and high-level MUP resistance were reported among MRSA isolates, the rate of resistance is different in various geographic areas.

In this review, we will report the global prevalence of MUP resistance, discuss synergism and mechanism of action of MUP, and provide new insights into the clinical use of this antibiotic.

1. Introduction

In 1976, Sutherland et al. introduced mupirocin (MUP) as a promising drug against gram-positive bacteria [1].

MUP, bactroban, or pseudomonic acid is a crotonic acid derivative drug initially extracted from *Pseudomonas fluorescens* in 1971. It is a secondary metabolite produced in the bacterial stationary phase which inhibits protein synthesis through binding to bacterial isoleucyl-tRNA synthetase [2].

MUP has a wide spectrum of activities against Gram-positive bacteria, including staphylococci and streptococci, and is rarely active against Gram-negatives [3]. The nosocomial infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) isolates has increased during recent years and has associated with hospital outbreaks leading to considerable morbidity and mortality. Therefore, as a part of comprehensive program to control the spread of methicillin-resistant *Staphylococcus aureus* (MRSA), MUP can decolonize the anterior nares [4].

Furthermore, this drug is useful for the treatment of both primary and secondary superficial skin infections caused by *S. aureus* isolates (such as impetigo), usually with 80% improvment in infected patients and 90% eradication in the *S. aureus* isolates [5].

The long term use of MUP and its multiple courses have led to MUP resistance among *S. aureus* isolates. Nowadays this resistance is reported all over the world, although not all of these reports exactly differentiate high-level from low-level MUP resistance [2].

The current study was done to review mechanism of action of MUP, narrate the global epidemiology of MUP resistance, discuss synergism of MUP with other anti-bacterial agents, and describe new insights into the clinical implications of this drug.

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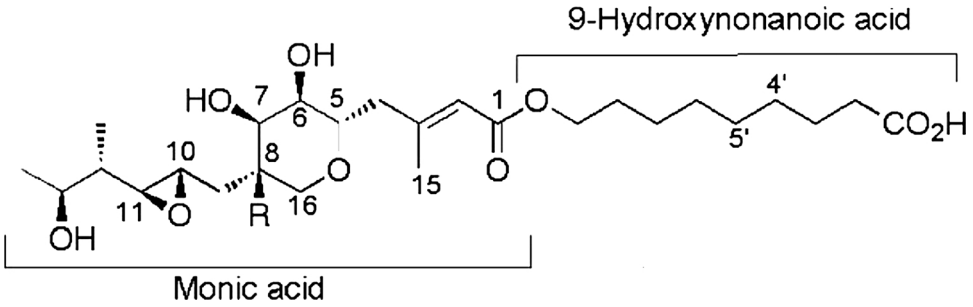

Fig. 1. Structure of mupirocin (9-hydroxy nonanoic acid and monic acid). (The figure was adopted and reproduced from Gao et al. with permission from the publisher) [7].

2. Antimicrobial properties

2.1. Structure of drug

MUP is identified as one of the first of an extensive family of drugs produced by the modular polyketide synthases. MUP contains of 9-hydroxy nonanoic acid (a short fatty acid side-chain) and monic acid (a C polyketide-derived substructure), which have linked by an unsaturated ester linkage (Fig. 1) [6,7].

MUP has a unique chemical structure which is a mixture of several pseudomonic acids, with pseudomonic acid A constituting the major component of the mixture (more than 90%). Pseudomonic acid A is the product of an esterification between the 17C polyketide monic acid and the 9C fatty acid 9-hydroxy-nonanoic acid. The possibility that the entire molecule is assembled as a single polyketide with a Baeyer-Villiger oxidation inserting an oxygen into the carbon backbone has been ruled out because C1 of monic acid and C9 of 9-hydroxy-nonanoic acid are both derived from C1 of acetate (Figs. 1 and 2) [8].

The pseudomonic acid B, which has an additional hydroxyl group at C8, and pseudomonic acid C, which has a double bond at C10 − C11, instead of the epoxide of pseudomonic acid A, are two other major components. The pseudomonic acid D with a double bond at C4 and C5 in the 9-hydroxy-nonanoic acid portion of MUP has also been reported as a very minor component (Fig. 2) [7].

2.2. Mechanism of action

MUP inhibits protein synthesis through binding to its target enzyme, the bacterial isoleucyl-tRNA synthetase, but not their mammalian orthologs (blocking the formation of bacterial isoleucyl-tRNA) (Fig. 3) [9]. *P. fluorescens* has a 74-kb gene cluster encoding MUP which includes *ileRS1* and *ileRS2* genes. Since *IleRS2* gene has no sensitivity to MUP and exhibits eukaryotic features, suggests that this gene protects the bacteria from MUP attack [10,11].

The epoxide side chain of MUP is structurally similar to that of

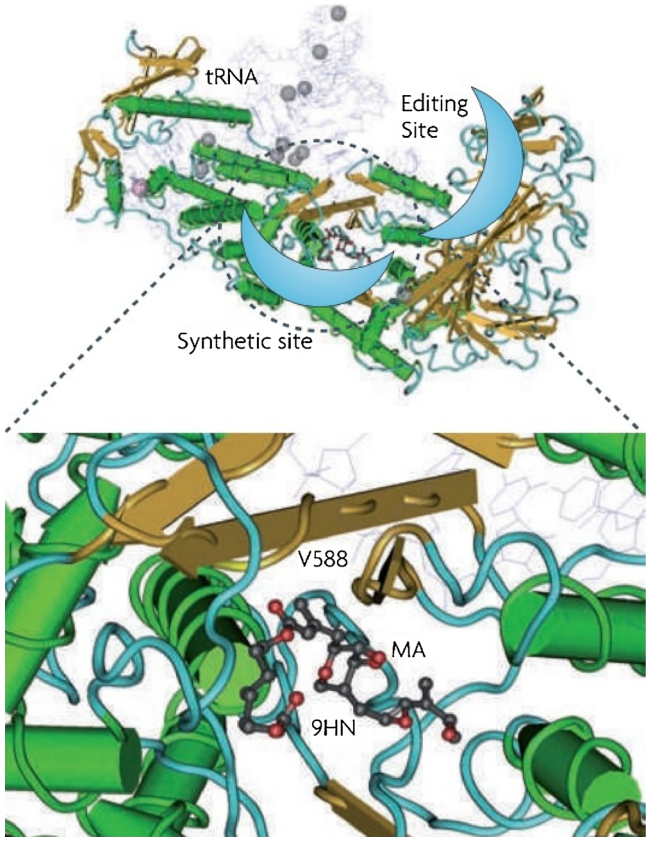

Fig. 3. Binding of mupirocin to its target enzyme, isoleucyl-trNA synthetase, from *Staphylococcus aureus*. (The figure was adopted and reproduced from Thomas et al. with permission from the publisher) [9].

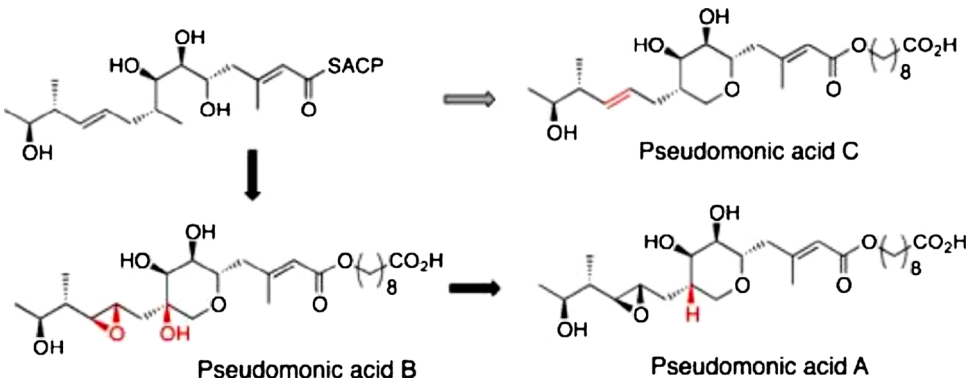

Fig. 2. Structure of mupirocin and major pseudomonic acids. (The figure was adopted and reproduced from Gao et al. with permission from the publisher) [7].

isoleucine and can bind to the isoleucine-specific binding pocket of isoleucyl-tRNA synthetase [12]. Because of the formation of the isoleucyl-tRNA synthetase is blocked, the cellular levels of the isoleucine-charged transfer RNA are depleted, leading to cessation of protein and RNA synthesis in bacteria. Due to the very low affinity of MUP for mammalian isoleucyl-transfer-RNA synthetase, it is not associated with substantial toxicity in humans. At the concentrations near the minimum inhibitory concentration (MIC) for *Staphylococcus aureus* the sodium salt of MUP is bacteriostatic. However, the antibiotic is bactericidal at higher concentrations including those applied to the skin with the 2% formulation, and after 1 day of exposure [13].

2.3. Activity in Biofilms

The increasing evidence has implicated biofilms in approximately 70% of chronic infections in humans during the last 15 years. Since the biofilms contribute to the development of antibiotic resistance, they can also complicate infection management. Because of this spreading of antibacterial resistance the insufficient number of antibiotics in development by the pharmaceutical industry, biofilm eradication strategies are increasingly important [14].

Ha et al performed a study on drug susceptible isolates of S. aureus and allowed them to form biofilms in vitro. They found that topical MUP concentrations of 125 μg/mL could reduce S. aureus biofilm mass by more than 90% [15].

In a investigation conducted by Bakkiyaraj et al., the anti-biofilm properties of a MUP spray against clinical isolates of *Escherichia coli* were evaluated. They have formulated the MUP spray with Eudragit E100 and tested its anti-biofilm effects and showed significant anti-biofilm activities at the commercial ointment concentration [16].

Ishikawa et al. investigated the effect of MUP on biofilm formation and demonstrated that MUP can reduce biofilm formation in vitro among *P. aeruginosa* isolates. In this study MUP decreased biofilm formation and glycocalyx production for 10 days, although biofilm formation with glycocalyx was observed on day 6–10 without MUP [17].

In addition, in the study of TB et al. using a standardized biofilm sheep model, regular treatment with MUP flushes over a 5 day period showed an almost complete eradication of biofilms as assessed by mucosal surface coverage, with sustained effects over the 8 day period of follow-up [18].

In the other study done by Gunther et al., MUP showed detectable efficacy in inhibiting metabolic effect in methicillin-resistant *S. aureus* (MRSA) biofilms after short exposure times. Even after 3.5 h of exposure to MUP, the level of metabolic inhibition of the bacteria in the MRSA biofilms did not exceed 20%. In this study, 2% MUP showed between 1 and 20% inhibition of the metabolic activity of MRSA biofilms after exposure times of up to 3.5 h [19].

3. Mupirocin resistance

MUP resistance was identified immediately after its introduction. Mup-resistant *S. aureus* was first reported in 1987 at St Thomas' Hospital [20].

The frequency of MUP resistance is different among clinical strains of MRSA (from 0% to 65%) which is correlated with increased use in hospitals. However, this prevalence is unknown in pediatric patients due to the few studies that have been done [21].

The decreasing MUP using has been led to the decreasing of the prevalence of MRSA infection over recent decades in many areas worldwide. MUP decolonization is most common MRSA-specific control strategy which in combination with chlorhexidine can successfully decrease the MRSA bloodstream infections [22–24].

The lower resistance breakpoint value (MIC, mg/L) for MUP has been recommended 4 mg/l according to guidelines. However, several factors are related with this breakpoint in the outcome of therapy including the concentrations of the *S.aureus* isolates in the layers of skin and nose, the existence of reservoirs of *S.aureus* and ineffective actions [25,26].

3.1. Mechanisms of resistance

According to antibiotic susceptibility testing, there are three groups of MUP susceptibility for *S. aureus* isolates. At a MIC of ≤ 4 μg/ml these isolates are susceptible to MUP, at MICs of 8–64 μg/ml they are low-level resistance, and MIC of ≥ 512 μg/ml refers to high-level MUP resistance. Due to the MIC of 128–256 μg/ml is uncommon among *S. aureus* isolates, it is not mentioned in the above classification (Although it is usually considered as low-level resistance) [27,28].

Low-level MUP resistance (chromosome-encoded MUP resistance) is because of the point mutations in the *ileS* gene (isoleucyl-tRNA synthetase gene), leading to a Val-to-Phe change in the MUP-binding site. These point mutations in the *ileS* gene arises from combinations of $V_{588}F$, $V_{631}F$, $G_{593}V$, $R_{816}C$, $H_{67}Q$, and $F_{563}L$ mutations in isoleucyl-tRNA synthetase [29].

There are two mechanisms of high-level MUP resistance (plasmid-encoded MUP resistance). The first mechanism is mediated by acquisition of a plasmid-mediated *mupA* or *ileS2* gene (an alternate isoleucyl-tRNA synthetase). The second mechanism is due to the mupB gene which has 65% similar sequence with mupA) (Fig. 4) [9,30].

High-level MUP resistance can be acquired by MRSA isolates with low-level MUP resistance through the acquisition of the pSK41-like plasmid. This plasmid is a family of staphylococcal multi-resistant conjugative plasmids which confers high-level MUP resistance [31,32]. Pérez-Roth et al. showed the relationship between traK gene of pSK41-like plasmid and ileS2 gene. They used the *traK* gene as a marker for plasmids carrying related transfer systems and this was found for all the plasmids with ileS2 implying that all these plasmids are related to a common ancestor [33].

In addition, IS 256 and IS 257 elements which may be present in both chromosome and plasmids, can affect on the expression of MUP resistance (*mupA* gene) among *S. aureus* isolates, through the activation of the transcription of the resistance genes [34].

3.2. Epidemiology of resistance

Recently, the emergence of MUP resistance has been increasing among *Staphylococcus* species in many parts of the world and such resistance seems to be more among MRSA isolates due to the prior MUP uses. The available evidence from various studies was collected from PubMed and Web of Science databases during the period 1990–2017 to narrate the global epidemiology of MUP resistance (Table 1 and Fig. 5).

3.2.1. America

Alarming reports on the prevalence of MUP-resistant *S. aureus* isolates in american countries have been published. Simor et al. in their investigation done antimicrobial susceptibility tests of MRSA strains collected from 32 Canadian hospitals during 1995–2004 and detected approximately 4% (n = 198) high-level MUP resistance isolates. The prevalence rate of high-level MUP resistance MRSA strains increased from 1.6% (n = 46) in 1995–1999 to 7% in the second 5 years of surveillance (2000–2004). All MRSA strains with high-level MUP resistance had a Hind III-associated plasmid-encoding mupA gene [35].

In another study, 409 MRSA strains were isolated from Madigan Army Medical Center during 2006–2007 and E test was carried out for screening the MUP-resistant MRSA isolates. The results revealed that although 95.9% (n = 392) of MRSA isolates were found to be fully sensitive to MUP (MIC < 1 μg/mL), 1.7% (n = 7) of them had MIC values of > 1024 μg/mL, and 2.4% (n = 10) isolates had MIC values of 1–32 μg/mL [36].

In the study performed by Ramsey et al. in the United States, the characteristics of MUP-resistant S. aureus isolates (18 S. aureus strains with high-level resistance and 19 S. aureus strains with low-level

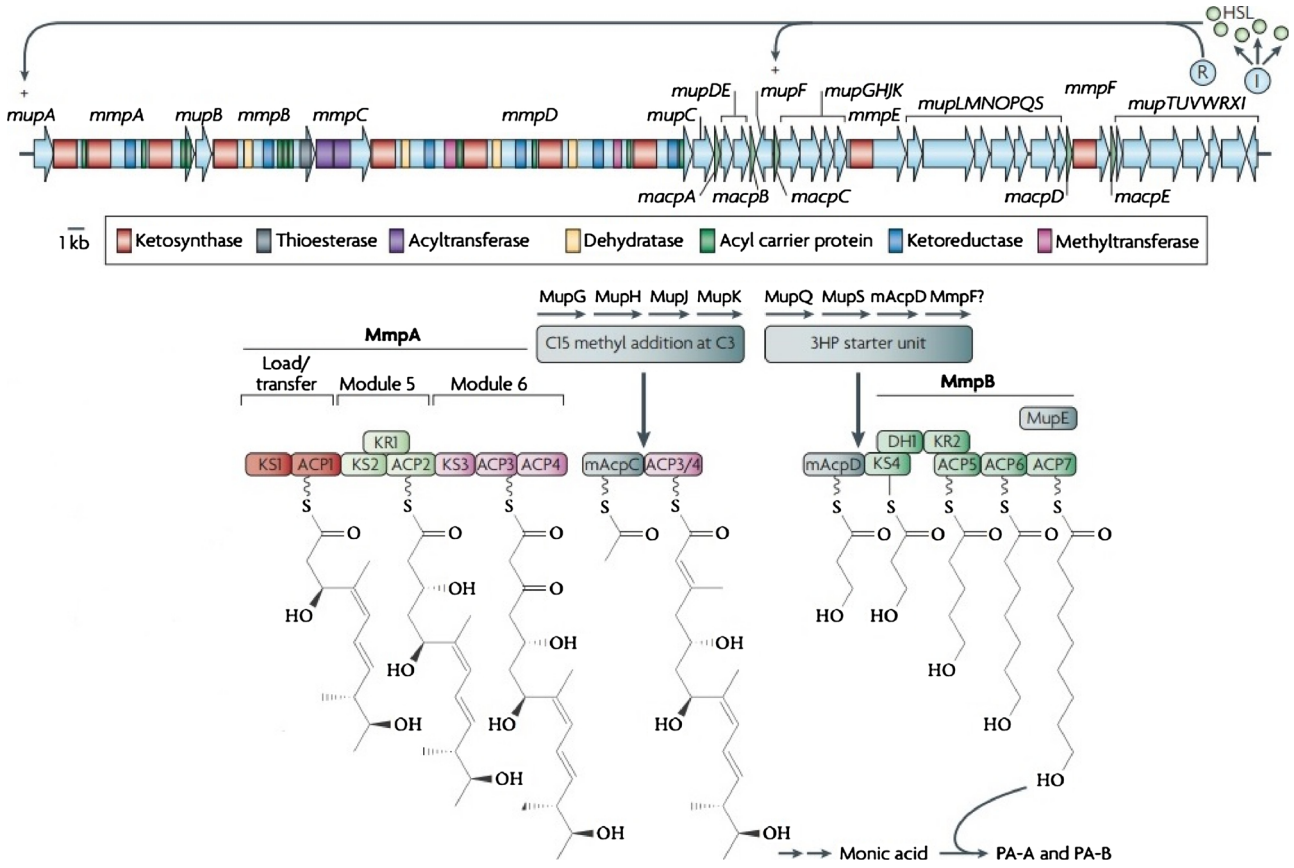

Fig. 4. The mupirocin biosynthesis genes and the proposed pathway of mupirocin production. (The figure was adopted and reproduced from Thomas et al. with permission from the publisher) [9].

resistance) were defined. The results demonstrated that in some of the isolates low-level MUP resistance was related to *mupA* gene. In addition, both mechanisms of MUP resistance were shown from several various clones in different geographic regions US [37].

Antonov et al. performed a study on 358 *S. aureus* strains isolated from 249 outpatient children in New York City. They demonstrated that in the beginning of the study, approximately 19% (n = 68) of children were infected with MUP-resistant *S. aureus*. As well as, approximately 31% (n = 110) of *S. aureus* strains isolated during the period of investigation were MUP-resistant, mostly due to widespread MUP uses [38].

3.2.2. Asia

In Asia, both low-level and high-level MUP resistance were reported among *Staphylococcus* isolates. However, the rate of resistance is different in various geographic areas (Table 1).

In South Korea, MUP utilization has began since 1994 and the first case of resistance was reported in 2003. Yoo et al. in their study detected 6.14% (n = 25) high-level and 2.89% (n = 21) low-level MUP-resistant S. aureus isolates, of which 21 high-level MUP-resistant isolates had the most predominant mupA restriction fragment length polymorphism type [39].

In another study, Youn et al. performed a 10-year (2003–2013) follow-up study on MUP prescription in a Korean hospital. They demonstrated that during these 10 years (from the beginning of the study to the end of it), the annual MUP utilization almost doubled. In this period, the prevalence of high-level and low-level MUP-resistant MRSA isolates doubled and tripled, respectively [40].

Fujimura et al. carried out a study on 1368 MRSA strains isolated from 15 general Japanese hospitals during 1997–2001 to determine the prevalence of MUP resistance. Although the rate of low-level MUP-resistant MRSA strains was increased from 0.8% (n = 2261) in 1997 to 2.4% (n = 6254) in 2001, high-level MUP-resistant MRSA strains were not isolated [41].

Rudresh et al. conducted an investigation in India on 98 S. aureus strains isolated from skin and soft-tissue to document the rate of MUP resistance. The prevalence of high-level MUP-resistant S. aureus strains was 8.2% (n = 8) and the prevalence of low-level MUP-resistant S. aureus strains was 17% (n = 17) [42].

Liu et al. reported the rate of MRSA isolates with high-level MUP resistance in China. From the 803 MRSA isolates studied, 6.6% (n = 53) were high-level MUP-resistant isolates, while the low-level MUP-resistant MRSA isolates were not detected [43].

3.2.3. Europe

In european countries, different reports about the status of current patterns of MUP resistance in *S. aureus* were enclosed (Table 1). In Europe, high-level MUP resistance among *S. aureus* isolates was first reported in the UK in 1961. Nowadays, the data shows that low-level MUP-resistant MRSA isolates were increased [44].

Schmitz et al. have investigated the prevalence of low-level and high-level MUP resistance among 699 *S. aureus* strains isolated from 19 European hospitals. MUP susceptibility tests demonstrated that high-level and low-level MUP resistance were detected among 1.6% (n = 11) and 2.3% (n = 2.3) of *S. aureus* isolates, respectively [45].

In the study performed by Lee et al. in a Swiss tertiary care hospital, the trends in MUP-resistant MRSA isolates were shown. They demonstrated that low-level MUP resistance surprisingly increased among clinical isolates of MRSA during 1999–2008 years [from 0% (n = 17) to 79% (n = 19)] [46].

In another study carried out by Moorhouse et al. in Ireland, the MUP susceptibility tests were done for 1152 *S. aureus* isolates. Overall, of this

Table 1
Prevalence of mupirocin resistance worldwide.

Location /reference	Publication date	Bacteria	No. of resistant bacteria	MIC (μg/ml)	Resistance mechanism	Resistance rate
United Kingdom [82]	1992	*S.aureus*	9 (I) 6 (H)	8-256 (I) ≥ 2048 (H)	–	42.8% (I) 28.5% (H)
United Kingdom [83]	1993	*S. aureus*	4 (I) 4 (H)	8- 256 (I) ≥512 (H)	–	–
Poland(84)	1999	*S.aureus* *S. epidermidis S. haemolyticus S. xylosus*	7 (L) 46 (H)	32-128 (L) ≥1024 (H)	*mupA* gene	2.5% (L) 17% (H)
Malaysia [85]	2001	*MRSA*	4 (H) 1 (L)	8–256 (L) ⩾512 (H)	–	0.25% (L) 1% (H)
South Korea(86)	2003	*S. aureus* *CoNS*	S. aureus: 0 (L), 16 (H) CoNS: 21 (L), 34 (H)	–	*mupA* gene *ileS2* gene	*S. aureus*: 0% (L), 5% (H) CoNS: 10.3% (L), 16.7% (H)
India [87]	2006	*S. aureus*	2 (L) 10 (H)	5-200	–	1% (L) 5% (H)
South Africa [88]	2006	MRSA MSSA	–	5-200	–	–
Spain [33]	2006	*MRSA*	48	–	*ileS2* gene	12.8%
Canada [35]	2007	*MRSA*	396 (L) 198 (H)	–	*mupA* gene	8% (L) 4% (H)
USA [89]	2007	*MRSA*	14 (L) 26 (H)	8–256 (L) ⩾512 (H)	–	4.6% (L) 8.6% (H)
Belgium [90]	2008	*MRSA*	39 (L) 32 (H)	8–32 (L) ⩾512 (H)	–	31.2% (L) 25.6% (H)
Brazil [91]	2008	*S. haemolyticus*	5 (H, L) 1 (I)	–	–	8% (H, L) 2% (I)
Turkey([92]	2008	*MRSA* *CoNS*	75	5	*ileS2* gene	45%
Ireland(93)	2009	*MSSA* *MRSA* *S. epidermidis* *S. xylosus*	CoNS: 10 (L) 22 (H)	8–32 (L) ⩾1024 (H)	–	MRSA: 0% (L), 3% (H) MSSA: 0% (L), 1% (H) CoNS: 10% (L), 22% (H)
Nigeria(94)	2009	*S. aureus*	14 (L) 3 (H)	8–24 (L) ⩾1024 (H)	–	17.6% (L) 82.2% (H)
USA [95]	2009	*MRSA*	17 (L) 3 (H)	8–256 (L) ⩾512 (H)	–	2.9% (L) 0.5% (H)
Brazil [96]	2010	*MSSA*	5	256 (H)	–	1.1%
China(43)	2010	*MRSA*	53 (H)	8–256	*mupA* gene	6.6% (H)
Pakistan [97]	2011	*MRSA*	2 (L) 0 (H)	5-200	*mupA* gene	1%
Singapore [98]	2011	*CoNS* *MRSA* *MSSA*	MRSA: 0 (L), 6 (H) MSSA: 0 (L), 1 (H) CoNS: 11 (L), 77 (H)	8–256 (L) ⩾512 (H)	*ileS2* gene	–
USA [99]	2011	*MRSA*	13	–	*mupA* gene	6.8%
USA [100]	2011	*MRSA* *MSSA*	MRSA: 3 (L), 11 (H) MSSA: 1 (L), 5 (H)	–	*mupA* gene	MRSA: 2.7% (L), 10.1% (H) MSSA: 3.5% (L), 17.8% (H)
Iran [101]	2012	MRSA MSSA	–	20 μg	–	68%
South Korea [102]	2012	*MRSA*	16 (L) 11 (H)	8–256 (L) > 256 (H)	–	8.4% (L) 5.7% (H)
Australia [103]	2013	MRSA MSSA	9(H) 26(H)	–	–	1.3% (H) 1.6% (H)
India [104]	2013	*S. aureus* CoNS	2 (L) 3 (H)	5-200	–	3.3%
Iran [105]	2013	*MRSA* MSSA	–	5	–	11%
France [48]	2013	*MRSA* *CoNS*	MRSA: 3 (L), 3 (H) CoNS: 33 (L), 40 (H)	–	*mupA* gene	MRSA: 1.4% (L), 0.8% (H) CoNS: 4.7% (L), 5.6% (H)
India [106]	2014	*MRSA*	7 (L) 8 (H)	8–256 (L) ⩾512 (H)	–	46.7 % (L) 53.3 % (H)
India [42]	2014	*S. aureus* *CoNS*	21 (L) 15 (H)	8–256 (L) ⩾512 (H)	–	*S. aureus*: 17% (L), 8.2% (H) CoNS: 8.9% (L), 15.6% (H)

(*continued on next page*)

Table 1 (*continued*)

Location /reference	Publication date	Bacteria	No. of resistant bacteria	MIC (μg/ml)	Resistance mechanism	Resistance rate
USA [107]	2014	*S.aureus*	–	8-256	*mupA* gene	9.8%
Belgian [108]	2015	*MRSA* *MSSA*	MRSA: 26 (L), 39 (H) MSSA: 1 (L), 4 (H)	2-128 (L) ⩾256 (H)	–	MRSA: 2.1% (L), 3.1% (H) MSSA: 0.1% (L), 0.6% (H)
India [109]	2015	*MRSA*	1 (L) 3 (H)	8–256 (L) ⩾512 (H)	–	25 % (L) 75% (H)
Iran [110]	2015	MRSA MSSA	–	5	*mupA* gene	1.85%
USA [111]	2015	*S. aureus*	16 (L) 96 (H)	8–64 (L) ⩾1024 (H)	–	14.3 % (L) 85.7% (H)
China [112]	2016	*S. lugdunensis*	3 (L) 10 (H)	32 (L) ≥1024 (H)	Mutation V588F within the chromosomal ileS gene (L) *ileS2* gene (H)	2.2%(L) 7.3%(H)
Egypt [113]	2016	S. aureus	5 (L) 8 (H)	8–256 (L) ⩾512 (H)	*mupA* gene	38.5 % (L) 61% (H)
India [114]	2016	*MRCoNS*	4 (L) 22 (H)	5-200	*mupA* gene	4.8 % (L) 26.5 % (H)
Iran [115]	2016	*MRSA*	12 (H)	⩾512 (H)	–	41.4% (H)
Iran [116]	2016	*S. aureus*	2	–	–	3.8%
USA [117]	2016	MRSA	35	–	*mupA* gene	6.9%
Greece [118]	2017	*MRSA*	100 (H)	⩾512 (H)	*mupA* gene	98% (H)
Nepal [119]	2017	MRSA MSSA	50 (H)	⩾1024 (H)	–	51% (H)

Abbreviations: L Low level-resistant; I Intermediate level-resistant; H High level-resistant; CoNS coagulase-negative staphylococci; MRSA methicillin-resistant *staphylococcus aureus*.

isolates, 2% (n = 23) were MUP-resistant [47].

Desroches et al. conducted a study on epidemiology of the MUP-resistant MRSA isolates in France and detected a MUP-resistant MRSA clone carring *mupA* gene. They showed that of 367 MRSA clinical isolates, 2.2%(n = 8) were resistant to MUP, of which 0.8% (n = 3) had high-level resistance and 1.4% (n = 5) low-level resistance and in this survey the *mupB* gene was not detected [48].

3.2.4. Africa

A few studies have been done to report the prevalence of high-level

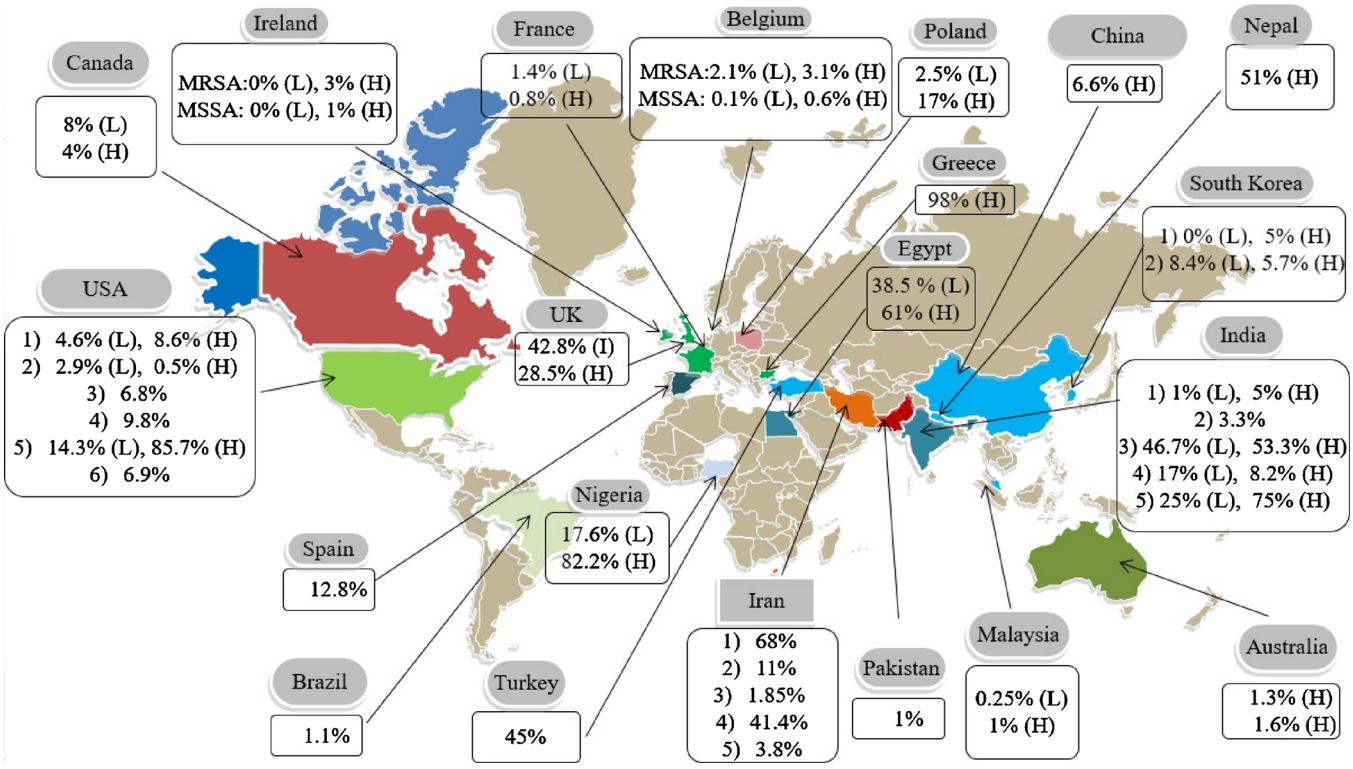

Fig. 5. Global epidemiology of mupirocin resistance against *Staphylococcus aureus*.

and low-level MUP-resistant S. aureus isolates in Africa and current MUP resistance patterns is unclear in sub-Saharan Africa (Table 1).

In the study performed by Fritz et al., 1089 patients infected with skin and soft tissue infections were followed for up to one year to identify MUP-resistant *S. aureus* isolates. They reported that 2.1% (n = 23) of patients were infected with *S. aureus* isolates which were high-level resistant to MUP [49].

Nicholson and colleagues have reported the prevalence of low-level and high-level resistance to MUP among MRSA isolates. They showed that 30% of MRSA isolates were low-level and 24% high-level resistant to MUP [50].

Moyo et al. have conducted a study on 89 patients infected with *S. aureus* isolates. They reported that 25% (n = 22) of the isolates were MRSA, of which 1.1% (n = 1) were MUP-resistant [51].

In another study done by Orrett, 188 MRSA isolates mostly collected from bloodstream and surgical site infections were tested for MUP resistance. He showed that 26% (n = 49) of MRSA isolates were high-level and 44% (n = 83) low-level resistant to MUP [52].

Monecke et al. have conducted a study on 294 *S. aureus* strains isolated during 2012–2013 years. They reported that 15.3% (n = 45) of these strains were MRSA, of which 5.8% (n = 17) were mupA-positive isolates [53].

4. Synergism

Synergy is the cooperation of two or more agents to produce a combined effect greater than the sum of their separate effects and drug synergism is an interaction between two or more drugs that causes the total effect of the drugs to be greater than the sum of the individual effects of each drug. A synergistic effect can be beneficial or harmful.

The studies on synergism against *staphylococcus* species are very limited and few researchs have been reported. In current study, the synergism of MUP with amoxicillin-clavulanate, monoterpenes, HT61, and propolis against MRSA was reported.

4.1. Synergism of mupirocin with amoxicillin-clavulanate against MRSA

In order to fight against MRSA isolates, combinations of MUP and amoxicillin-clavulanate have been studied and confirmed that this synergy had a therapeutic benefit in the prevention of *staphylococcal* infections [54,55].

Alou et al. have demonstrated that combinations of MUP as an inhibitor of protein synthesis and amoxicillin-clavulanate as an inhibitor of cell wall synthesis can show synergistic activity against MRSA and MSSA isolates in vitro. They have reported synergy for 15% (n = 2) of MSSA isolates and 20% (n = 2) of MRSA isolates [54].

In another study performed by Ghiselli et al., it was used a rat model to study the effect of MUP in the prophylaxis against *S. aureus* vascular graft infection. They shown that the MUP–amoxicillin-clavulanate combination can completely inhibit the MSSA and MRSA growth in vivo. [55].

4.2. Synergism of Mupirocin with monoterpenes against MRSA

The monoterpenes are essential oils which have antibacterial properties specially against *S. aureus* isolates due to their derivatives (terpenoids) (56, 57).

For example, Trombetta et *al.* in their study showed the antibacterial effect of three types of monoterpenes including linalyl acetate, menthol, and thymol against S. aureus strains [56].

As well as Hosseinkhani and colleagues have demonstrated that the monoterpenes including thymol, paracymene, and gamma-terpinene can inhibit the growth of S. aureus isolates with an inhibitory zone diameter between 30–60 mm and MIC < 0.02 μL/mL [57].

Kifer et al. performed a study to show the antibacterial effect of three monoterpenes including thymol, menthol and 1,8-cineole combined with MUP against MRSA isolates in their planktonic and biofilm phases. The results showed that the MICs of MUP were 3-fold lower than the MICs of monoterpenes. Although the single substance of MUP was failed to eliminate the biofilm, MUP combined with 1,8 cineole destroy the MRSA isolates grown in biofilm. MUP combined with menthol showed antagonism effect and MUP combined with thymol had inconclusive effect [58].

4.3. Synergism of Mupirocin with HT61 against MRSA

HT61 is a quinoline-derived cationic bactericidal agent against both MRSA and MSSA isolates which has a synergism efficacy with MUP against *S. aureus* isolates [59].

In the study conducted by Hubbard et al., the mechanism of action of HT61 on bacterial membranes was studied. Their study demonstrated that, HT61 can depolarize the membrane to release the intercellular constituents at concentrations above and below the drug's MIC [60].

In another study performed by Hu et al. [61]., the effect of combination of HT61 and MUP against of MSSA and MRSA clinical isolates was investigated. In their study, no interaction was reported between HT61 and MUP using the fractional inhibitory concentration index. They reported that HT61-MUP combination showed a potency with significant killing of MSSA and MRSA isolates in vivo (mouse model).

4.4. Synergism of Mupirocin with Propolis against MRSA

The studies on natural herbal products have become more valuable than synthetic products, due to the increasing prevalence of bacterial resistance to chemical drugs and also lower cytotoxicity of the herbals [62,63]. Although many studies performed on the effects of natural herbal products in the world, nowadays there are few available herbal medicines for treatment of bacterial infections compared with antibiotics [64,65].

Propolis, a natural resinous substance collected by honeybees from several plants, is a complex mixture of compounds such as botanical balsams and resin with bees's digestive enzymes. Propolis has antibacterial properties including both bacteriostatic and bactericidal activities which is mostly because of the phenolic acid fraction [8,66].

In a study performed by Darwish and colleagues, they reported antibacterial effect of propolis against MRSA isolates. The results of broth microdilution method demonstrated that propolis type I with MIC 4.69 μg/ml and type II with MIC 18.75 μg/ml had antibacterial activity against MRSA isolates. As well as, The antimicrobial susceptibility testing showed that the propolis type I produced the highest antibacterial activity with inhibition zone of 17.00 mm than other fractions against the MRSA isolates [67].

Onlen et al. in their study evaluated the antibacterial activity of propolis and its synergism with MUP against MRSA isolates in nasal carriage. They have investigated the treatment and control groups in vivo (rabbit model). The treatment groups treated with MUP and the control groups were received phosphate-buffered solution without MUP. The propolis combined with MUP resulted in a significant decrease in the count of neutrophils in the mucous membranes of rabbits compared with the control group. In this study, the propolis-MUP combination showed significant decrease in bacterial cell count and inflammatory response [68].

5. Clinical treatment

5.1. Use for nasal decolonisation

Due to the lack of FDA breakpoints for MUP, along with limited availability of commercial tests, there is not specific recommendation on MUP susceptibility testing and specific program for screening the MRSA isolates them from the nose [69].

Oral MUP is not routinely suggested for decolonization and it should only be considered in patients who continue to have infections [69]. When the MRSA isolates are epidemic, MUP may be used as a choice drug for nasal decolonisation [70]. In these patients, MUP can be used to reduce infection despite increasing the MUP resistance [71].

In a study performed by Dupeyron et al., they have used MUP in the prevention of MRSA infections for 2242 patients hospitalized in a gastroenterology unit during a period of 52 months. Overall, it was shown that after MUP using, this drug significantly reduced nasal MRSA colonization [72].

In a prospective cohort study done by Doebbeling et al., the effect of intranasal MUP ointment against *S.* aureus carriage in healthy hospital staff was investigated. The results of this study showed that six months after treatment, the nasal colonization was 48% versus 72% in placebo group; while one year after treatment, the nasal colonization was 53% versus 76% in placebo group [73].

MUP-based nasal decolonization in hemodialysis patients can reduce the prevalence of *S. aureus* bacteremia. Although due to the threat of MUP resistance, it is often not routinely used in this population [74].

Boelaert et al. in their study demonstrated that nasal calcium MUP decreased the rate of *S. aureus* bacteremia among patients hospitalized in the hemodialysis unit. MUP-based nasal decolonization led to eradication of 96% nasal colonization of *S. aureus* and decrease from 0.097 to 0.024 in the incidence of *S. aureus* bacteraemia (per patient-year) [75].

5.2. Use for controlling outbreaks

The infection control programmes can limit the endemic infection or colonization with drug-resistant bacteria such as MRSA isolates [76].

In a randomized controlled research trial Ellis and colleagues targeted intranasal MUP for preventing the colonization and infection by isolates of CA-MRSA among soldiers (a highly endemic population). The military trainees nasally colonized with MRSA isolates were treated with intranasal MUP and after a 16 weeks followeing up no MUP resistance was detecteds [77].

Irish et al. carried out a study on an outbreak of an epidemic HA-MRSA and according to UK guidelines used nasal MUP for eradication of the MRSA isolates. During this work a MUP-resistant MRSA emerged in 12 patients and 11 staff. This outbreak control had significant medical, social and financial implications [78].

5.3. Use to prevent recurring infection

Approximately 70% of patients infected with CA-MRSA skin and soft tissue infections will experience recurrent infections over one year, even after the best initial therapy. MUP-based decolonization of *S. aureus* isolates is one of the main approaches for patients colonized with subsequent skin and soft tissue infections [79].

Mascitti et al. have done an investigation on preferred treatment and prevention strategies for recurrent CA-MRSA skin and soft-tissue infections. In this study, approximately 40% (n = 77) of volunteers used MUP with antiseptic body wash. MUP-based decolonization was effective in more than half of the patients at preventing subsequent CA-MRSA skin and soft tissue infections [80].

In a placebo-controlled study performed by Raz et al., MUP was used to prevent the recurrent *staphylococcal* nasal colonization and skin infection in 17 patients and was not used in the placebo group (17 MUP-untreated patients). The results of this study showed that the number of skin infections was 26 in MUP-treated patients and 62 in MUP-untreated patients. As well as, the number of nasal colonization was 22 in MUP-treated patients and 83 MUP-untreated patients [81].

6. Conclusion

MUP is predominantly used for nasal decolonization and it can be considered as a topical drug useful against superficial skin infections such as impetigo or folliculitis caused by *S. aureus* isolates. The patients infected with MRSA isolates has increased the morbidity and mortality rates in recent years. An effective global MRSA control will require the use of combined drugs which the total effects of them are greater than the sum of their separate effects. MUP combined with amoxicillin-clavulanate, monoterpenes, HT61, or propolis has a promising synergistic effect against MRSA isolates and decreases the duration of MUP treatment. This drug also used for prevention of recurring infections and control the outbreaks. MUP also used for prevention of recurring infections and control the outbreaks. However, the data shows that the emergence of MUP resistance following its widespread use is increasing among MRSA isolates worldwide.

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