Review

New Is Old, and Old Is New: Recent Advances in Antibiotic-Based, Antibiotic-Free and Ethnomedical Treatments against Methicillin-Resistant Staphylococcus aureus Wound Infections

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Abstract: Staphylococcus aureus is the most common pathogen of wound infections. Thus far, methicillin-resistant S. aureus (MRSA) has become the major causative agent in wound infections, especially for nosocomial infections. MRSA infections are seldom eradicated by routine antimicrobial therapies. More concerning, some strains have become resistant to the newest antibiotics of last resort. Furthermore, horizontal transfer of a polymyxin resistance gene, mcr-1, has been identified in Enterobacteriaceae, by which resistance to the last group of antibiotics will likely spread rapidly. The worst-case scenario, “a return to the pre-antibiotic era”, is likely in sight. A perpetual goal for antibiotic research is the discovery of an antibiotic that lacks resistance potential, such as the recent discovery of teixobactin. However, when considering the issue from an ecological and evolutionary standpoint, it is evident that it is insufficient to solve the antibiotic dilemma through the use of antibiotics themselves. In this review, we summarized recent advances in antibiotic-based, antibiotic-free and ethnomedical treatments against MRSA wound infections to identify new clues to solve the antibiotic dilemma. One potential solution is to use ethnomedical drugs topically. Some ethnomedical drugs have been demonstrated to be effective antimicrobials against MRSA. A decline in antibiotic resistance can therefore be expected, as has been demonstrated when antibiotic-free treatments were used to limit the use of antibiotics. It is also anticipated that these drugs will have low resistance potential, although there is only minimal evidence to support this claim to date. More clinical trials and animal tests should be conducted on this topic.

Keywords: methicillin-resistant Staphylococcus aureus (MRSA); wound infection; biofilm; antibiotics; ethnomedicine

1. Introduction

Staphylococcus aureus is the most common pathogen involved in skin and soft tissue infections and is the principal cause of surgical site infections (SSI) [1,2]. Wound infections often have negative impacts on patient outcomes, most commonly including a delay or deterioration of wound healing and potentially leading to sepsis. Furthermore, colonized staphylococcal cells are potential sources for cross-contamination, whereby S. aureus becomes a major nosocomial pathogen. Nosocomial infection is a major cause of surgical morbidity and mortality [3,4], and SSIs have a reported incidence rate of 2%–20% [5,6]. Evidence supports the use of S. aureus decolonization in surgical patients to prevent S. aureus infection, and this intervention has been associated with low rates
of postoperative *S. aureus* infection. The staphylococcal carriage is most commonly eradicated by intranasal application of mupirocin either alone or in combination with antiseptic soaps or systemic antimicrobial agents [7]. However, the major cause of nosocomial infection is methicillin-resistant *S. aureus* (MRSA) [8–10], which is hard to eradicate [7] despite reports of some cases treated by warming therapy [4]. Furthermore, the efficacy of eradication in patients with community-associated MRSA has not been established, and the necessity of routine decolonization is not supported by data [7]. MRSA outbreaks have created a significant challenge for surgery and clinical practice in recent decades; the failure of traditional antimicrobial treatments has gradually become a worldwide problem [11–13], especially in the developing world [14]. Thus, effective therapeutic options to combat *S. aureus* infection, with an emphasis on MRSA, are urgently needed.

2. Antibiotics Developed to Combat MRSA

There are several therapeutic strategies, including clinical strategies and some still under development, to combat drug-resistant *S. aureus*: antibiotic-based treatments, alternative treatments, antibiotic-free treatments, immunotherapy, therapeutic vaccines and possible combinations of these options [15–17]. Among these strategies, the use of antibiotics is effective and the most historically important. However, an unsettling trend has been witnessed in recent decades: increased antibiotic resistance and decreased antibiotic research and development [18–20]. From 1968 to 2003, only two novel classes of systemic antibiotics were developed: linezolid (2000) and daptomycin (2003) [19]. There are two primary contributors to this situation. Commercial interests with low profit motivations have failed to garner enthusiasm for antibiotic development because of their short-term use [13]. Second, the high level of difficulty in conducting clinical trials against drug-resistant strains dampens the hope of many candidates for final approval [18]. However, a new trend has emerged after the U.S. FDA (Food and Drug Administration)'s reboot of antibiotic development [20] involving an acceleration of drug approvals and documented antibiotic development. Some newly approved antibiotics (Table 1) are effective in preventing and controlling MRSA wound infections.

**Table 1.** Some U.S. Food and Drug Administration (FDA) approved antibiotics to combat methicillin-resistant *Staphylococcus aureus* (MRSA) infection [21].

| Antibiotics | Indications | Therapeutic Relevance | Resistant Strains Reported | Month/Year Approved |
|-------------|-------------|-----------------------|----------------------------|---------------------|
|             |             | For MRSA Infections   | For Wound Infections       | Resistant Strains   |
| Oritavancin | For the treatment of acute bacterial skin and skin structure infections | [22,23] | [22,23] | Low potential [24] | August 2014 |
| Sivextro | For the treatment of acute bacterial skin and skin structure infections | [25,26] | [27–29] | Low potential [25,30] | June 2014 |
| Dalvance | For the treatment of acute bacterial skin and skin structure infections | [31,32] | [31,32] | VanA vancomycin-resistant enterococci [33] | May 2014 |
| Teflaro | For the treatment of bacterial skin infections and bacterial pneumonia | [34–36] | [34,35,37] | *A. S. aureus* [38] | October 2010 |
| Telavancin | For the treatment of complicated skin and skin structure infections | [39–41] | [40,42] | VanA vancomycin-resistant enterococci [33] | September 2009; June 2013 |
| Tigecycline | For the treatment of complicated skin and skin structure and intra-abdominal infections and bacterial pneumonia | [39,43–46] | [45,47–49] | *Staphylococcus* spp. [50], an MRSA [51], an *S. pneumoniae* [52] | June 2005 |
Table 1. Cont.

| Antibiotics | Indications | Therapeutic Relevance | Resistant Strains Reported | Month/Year Approved |
|-------------|-------------|-----------------------|----------------------------|---------------------|
| Daptomycin  | For the treatment of complicated skin and skin structure infections | For MRSA Infections: [39,43,45,53–55], For Wound Infections: [45,53] | Dermabacter hominis [56], Staphylococcus spp. [45], a daptomycin non-susceptible S. aureus [57] | September 2003 |
| Linezolid   | For the treatment of infections, including pneumonia, infections of the skin and infections caused by a resistant bacterium (Enterococcus faecium) | For MRSA: [62–64] | Vancomycin-resistant Enterococcus faecium: [61]; MRSA: [62–64] | April 2000 |

Antibiotic development is new, hard and time-consuming. However, a cost-effective and evidence-based strategy should be implemented to identify new therapeutic indications of clinically used drugs, i.e., drug repurposing, rescue and repositioning [65]. This approach, although old, is both easy and time-saving. Ebselen is an organoselenium compound [66], and celecoxib is a marketed inhibitor of cyclooxygenase-2 [67]. Both exhibit demonstrated antimicrobial activity, especially for MRSA and vancomycin-resistant S. aureus (VRSA). Furthermore, ebselen has been shown to be remarkably active, to significantly reduce established staphylococcal biofilms and to act synergistically with traditional antimicrobials [66]. Simvastatin has been predicted to exhibit activity as a topical antimicrobial against skin bacterial infection due to its broad-spectrum (including MRSA) antibacterial, anti-staphylococcal biofilm, anti-inflammatory and wound healing activities [68]; furthermore, simvastatin can also synergistically act with traditional antimicrobials. Recently, tamoxifen, a selective estrogen receptor modulator widely used for the treatment of breast cancer, has been repositioned to enhance MRSA clearance by boosting neutrophil bactericidal capacity [69].

However, there is an intrinsic obstacle to antibiotic development: antibiotics are the only drugs for which widespread use decreases their utility, i.e., “fighting back by microbes” [70]. There is almost no exception among the novel antibiotics (Table 1). A dilemma of antibiotics thus arises: antibiotics themselves are the cause of many healthcare-acquired infections (HCAI), further leading to “a return to the pre-antibiotic era”, as the World Health Organization has warned [71]. If this situation were to come to pass, once-curable infections would become fatal. Frighteningly, [72] horizontal transfer of a polymyxin resistance gene, mcr-1, has been identified in Enterobacteriaceae, and it is believed that this marks the beginning of the spread of resistance to the last group of antibiotics, leading to increased numbers of pan-drug-resistant strains. However, there is some hope. Teixobactin [73], discovered in a screen of uncultured bacteria, is a novel antibiotic that may not trigger the development of resistance. The biosynthetic gene cluster has been identified for future synthetic approaches. No resistant mutants of S. aureus were obtained by either serial passage at sub-MIC (minimum inhibitory concentration) levels of teixobactin or after culture on media with four-fold MIC of teixobactin. However, these results merely imply the rare occurrence of chromosomal mutation; as noted [72], a plasmid-mediated transfer mechanism contributes significantly to multi- and even pan-drug resistance. Furthermore, before it is introduced to clinical practice, drug resistance should be considered from an ecological and evolutionary view [74]. For example, a biofilm is a complex community with spatial and physiological heterogeneity in which the evolution of an exploitative interaction occurs [75,76]. Such evolution provokes marked changes in the symbiotic nature of heterogeneous strains/species and affects community function [75], e.g., antibiotic resistance. A previous study [77] revealed that clinically relevant resistance to the last class of antibiotics can be derived from competitive interactions between bacterial cells in a staphylococcal biofilm. Taken together, these data indicate that the concern of “a return to the pre-antibiotic era” has not been lifted. Alternative antibiotic-free treatments are therefore urgently required.
3. Topical Antibiotic-Free Treatments against MRSA

Although their single use rarely eradicates MRSA infections, topical antibiotic-free treatments can alter microbial burden, inhibit biofilm formation and disrupt formed biofilms. Because biofilm formation confers antibiotic resistance to bacteria [78], these treatments also play crucial roles in combating drug-resistant microbes through the inhibition and disruption of biofilms. Furthermore, these treatments improve wound healing through the removal of necrotic tissue, the alteration of the microbial burden, the reduction of local edema, and tissue repair and regeneration through wound contraction and remodeling, increasing angiogenesis and blood flow [79–83]. Among these effects, debridement is essential for successful wound care. Debridement has been shown [82] to effectively reduce the microbial burden in MRSA wound infections in several modalities, including traditional sharp debridement, hydrosurgery and plasma-mediated bipolar radiofrequency ablation (PBRA). Combinations of these antibiotic-free treatments are believed to be a promising approach to cure drug-resistant S. aureus wound infections. For example, debridement can improve the topical efficacy of species-specific bacteriophages against S. aureus biofilm-infected wounds by disrupting the matrix mass to aid the penetration of these bacteriophages [83].

The most common topical treatment in wound care is the use of a dressing. The wound dressing improves wound healing and tissue restoration; furthermore, modern wound dressings often exhibit excellent antimicrobial activity conferred by either non-antibiotics or antibiotics or a combination of the two [84]. Recently, an electrochemical scaffold (“e-scaffold”) made of conductive carbon fabric was proposed as an alternative antibiotic-free wound dressing to eliminate difficult-to-treat biofilms [85]. Low and constant concentrations of H$_2$O$_2$ are generated by the dressing to destroy biofilms through the electrochemical conversion of oxygen by applying an electric potential to the “e-scaffold”. Although the test strain was multidrug-resistant Acinetobacter baumannii, the dressing is expected to be used as a treatment against MRSA and MRSA-formed biofilms. Another antibiotic-free dressing is used to deliver human β-defensin 3 (hBD-3) by a bioengineered skin tissue; the dressing contains NIKS$^{hBD-3}$ stably expressing hBD-3 after a NIKS human keratinocyte cell line was transfected ex vivo with a construct containing an epidermis-specific promoter driving hBD-3. Use of the dressing has been shown to result in a therapeutically relevant reduction in growth of an MRSA mutant (also a resistant to daptomycin and vancomycin) in an animal model of infected third-degree burn wounds [86].

Negative pressure wound therapy (NPWT) and NPWTi (NPWT with instillation) are complicated dressings to manage large complex injuries to soft tissue and have been shown to effectively reduce the infection rate of both chronic non-healing and acute contaminated open wounds [79–81]. Despite the lack of definitive conclusions concerning their use, partially due to the lack of large randomized controlled trials (RCTs), evidence from a small number of retrospective comparative cohorts demonstrates an association between the use of NPWT and a reduction in SSI [87]. Furthermore, clinical practices indicate their relevance in the prevention and control of MRSA infections [79,88,89]. Combined with antibiotics, NPWT successfully treated a pump pocket MRSA infection after a left ventricular assist device implantation [88] and a peri-prosthetic MRSA infection after incisional herniorrhaphy [89]. However, the results of a previous study demonstrate that NPWT reduces the effectiveness of local antibiotic depots, which is an adjunctive therapy for open wounds [79]. Large prospective RCTs of NPWT are therefore needed to support the current evidence that it is effective in treating MRSA with the adjunction of antibiotic therapy.

A previous case report indicated that acupuncture and moxibustion improved staphylococcal wound healing and resulted in full recovery with a partial withdrawal of antibiotics in a patient with a poor response to antibiotics, suggesting their complementary role in staphylococcal wound care [90]. Interestingly, larval therapy has been used as an alternative treatment for hard-to-heal chronic and infected wounds [91]. Some anti-MRSA factors have been identified in larval excretions/secretions [92]. Furthermore, larval therapy can eliminate S. aureus biofilms with the adjunction of antibiotic treatments [93]. These treatments provide clues to combat MRSA infection using natural means, on which ethnomedicine depends, for the long term.
4. Ethnomedical Treatments against MRSA

Antibiotics are gradually losing the war against microbes worldwide [11–13,70–72], and greater suffering can be observed in the developing world [14]. The desperate situation urges people to revisit the “old-fashioned” but still in use ethnomedicine, which roots from practical, empirical and “almost forgotten” knowledge about naturally derived materials. The resources are primarily based on botanical materials (herbs) but may include animal and mineral materials. Many active compounds have been identified from these materials; furthermore, some of them can be engineered and synthesized. In fact, natural products contribute significantly to modern healthcare. However, most ethnomedical treatments and remedies are yet to be verified, and more evidence is required to support their modern use. For example, acupuncture and moxibustion represent evidence-based complementary therapies for some diseases [94–96]. Although they have been reported to successfully treat MRSA infections [90], no evidence-based recommendations have been reported, nor are there ongoing clinical trials in PubMed, Cochrane Library and CenterWatch.

The unsuitability of natural product-centered paradigms in ethnomedical study is perhaps a responsible factor for the slow translation of ethnomedicine to evidence-based medicine. Ethnomedicinal materials may contain complex active compounds that result in a broad but vague spectrum of their ethnomedical indications due to pleiotropic effects. Additionally, the prescribed formulas may have different recipes to improve their therapeutic efficacy through altering the proportions of ingredients (in Chinese Traditional Medicine, the so-called “pattern differentiation and treatment determination, Bianzheng lunzhi”) [97]. “Treat as a whole” is the superior approach in the pharmacological study of those materials.

In accordance with the historical context and philosophy of their ethnomedical treatment, people in the developing world continue to use some naturally derived materials as topical wound healing agents, following the “treat it as a whole” approach. To facilitate audience reading, we have summarized in Table 2 some agents (either single or formula) that exhibit anti-staphylococcal activities. These agents exhibit complex activities on either planktonic microbes or biofilms or both. Their bactericidal effects are mediated by the inhibition of essential survival factors [98] or the microbial enzymatic activities [99,100] of the pathogens, by the antiseptics (e.g., H₂O₂ and methylglyoxal) that they contain [101], produce [102–104] and stabilize [105], and by harnessing physiological factors through active compounds, such as antimicrobial peptides [106] and alkaloids [107]. At the biofilm level, these agents target all formation stages, including the planktonic stage, initial adhesion to surfaces and sessile micro-colony formation. The agents inhibit the expression of key genes involved in biofilm formation [108], act as quorum sensing (QS) inhibitors [109,110], inhibit microbial adhesion by either impairing adherence ability of those biofilm-forming microbes [111] or by covering microbes and/or surfaces [78] and decreasing the produced biomass [112], thereby inhibiting formation and improving the eradication of biofilms.

| Table 2. Some ethnomedicinal materials with ethnomedical purposes for wound healing. |
|---|---|---|---|---|
| Regions | Resources of Materials | Effects | Note | References |
| | | Anti-Biofilm | Anti-MRSA | |
| Bangladesh | *Bacopa monnieri* Linn. (Plantaginaceae) | Unknown | + | *In vitro* assays | [99] |
| Malaysia | *Cinnamomum* spp. | +[113] | +[71] | 1. Better effects against MRSA than MSSA [71] | [71,113] |
| | Leguminosae family | Unknown | +[114] | 1. Anti-non-S.A. biofilm [115,116] | [114–116] |

| Regions      | Resources of Materials                  | Effects Anti-Biofilm | Anti-MRSA Note                                                                 | References |
|-------------|----------------------------------------|----------------------|--------------------------------------------------------------------------------|------------|
| China       | Fructus Euodiae                         | Unknown              | 1. Active compounds: quinolone alkaloids                                         | [107]      |
|             |                                        | +                    | 2. *In vitro* assays                                                             |            |
|             | Sanguisorba officinalis L.              | +                    | 1. *In vitro* assays                                                             | [108]      |
|             |                                        | +                    | 2. Inhibiting MRSA biofilm formation in an ica-dependent manner                  |            |
|             | Toona sinensis (A. Juss.) Roem. (TSL)   | Unknown              | 1. Active compounds: sesquiterpenes                                              | [117]      |
|             |                                        | +                    | 2. *In vitro* assays                                                             |            |
| Thailand    | Rhodomyrtus tomentosa (Aiton) Hassk.    | +[111] +[118–122]    | 1. Active compound: rhodomyrtone                                                  | [111,118–122] |
|             |                                        |                      | 2. Inhibiting microbial adherence ability to sustain surfaces                    |            |
|             | Herbal formulas                         | +[123] +[124,125]    | 1. *In vitro* assays                                                             | [123–126]  |
|             |                                        |                      | 2. Ethnomedical purposes can be clues for their medical applications             |            |
|             |                                        |                      | 3. Antagonistic interactions in combination with topical antiseptics            |            |
| Italy       | Some medicinal plants                   | +                    | Ethnomedical purposes can be clues for their medical applications                | [127]      |
| Iran        | Malva sylvestris L., Solanum nigrum L. and Rosa damascene Mill. | +[127] +[127] | *In vitro* assays                                                              | [127,128] |
| African     | Ficus sansibarica Warb. Subsp. Sansibarica (Moraceae) | +    | *In vitro* assays                                                              | [129]      |
| Ethiopia    | Guizotia schimperi Sch. Bip. ex Walp.   | Unknown              | *In vitro* assays                                                              | [130]      |
| Togo        | Balanites aegyptica (L.) Delile (Balanitaceae) | Unknown              | *In vitro* assays                                                              | [131]      |
| African     | Aspilia africana C. D Adams (Compositae) | Unknown              | *In vitro* assays                                                              | [133]      |
| Australia   | Eremophila longifolia (R. Br.) F. Muell | Unknown              | 1. The first known Western scientific justification for the smoking ceremonies involving leaves of Eremophila longifolia | [135]      |
| Mediterranean | Quercus cerris L., Fagaceae            | +                    | *In vitro* assays                                                              | [136]      |
| Chilean     | Some medicinal plants                   | Unknown              | *In vitro* assays                                                              | [137]      |
| Extensive   | Tea tree                                | Unknown              | 1. Clinical trial [138]                                                         | [138,139]  |
|             |                                        | +                    | 2. Case study [139]                                                            |            |
| North American | Lichens                          | Unknown              | *In vitro* assays                                                              | [140]      |
| Worldwide   | Garlic                                  | +[141] +[142]        | *In vitro* assays                                                              |            |

MSSA: Methicillin-sensitive Staphylococcus aureus.

Ethnomedical drugs may combat drug-resistant strains through their anti-biofilm activities because biofilm formation confers antibiotic resistance to bacteria [78]. For example, the medicinal plant *Duabanga grandiflora* has been demonstrated to inhibit MRSA biofilm formation through the
reduction of cell-surface attachment and the attenuation of the level of penicillin-binding protein 2a (PBP2a) [143]. PBP2a, encoded by mecA, is a protein that confers β-lactam antibiotic resistance to S. aureus, thereby promoting the emergence of MRSA [144]. Furthermore, naturally derived materials may contain some inhibitors of multidrug efflux pumps [145], which are used to detoxify antibiotics by multi- and pan-resistant S. aureus [146]. Together, naturally derived materials can be used to reverse microbial antibiotic resistance and therefore aid in limiting the overuse of antibiotics. However, whether they themselves have a low resistance potential remains unclear. Indeed, “MRSA” is a medical term but not an ethnomedical one. The use of ethnomedicine remains insufficiently supported by evidence: ethnomedical drugs effectively treat MRSA infections with a low resistance potential.

5. A Feasible and Cost-Effective but Challenging Way: To Use Ethnomedical Drugs Topically

The topical use of ethnomedical drugs is not only an ethnomedical practice but a paradigm for ethnomedicine study. The complexity of their effects may decrease to a large extent while in topical use. A reverse proof is deduced from the selection between systemic and topical antibiotics for wound infection. Systemic antibiotics are often the putative preferred choice, perhaps because the antibiotic bioavailability is more stable than that of topical treatments when loci ischemia occurs [147]. Using ethnomedical drugs topically in wound dressings is therefore feasible and, given the ease of obtaining these drugs, cost-effective.

Based on naturally derived materials or natural products, several new wound dressings have been under development through either combination with other antimicrobial agents or when used alone [112]. For example, aloe vera inner gel has been demonstrated to exhibit antimicrobial activities against some Gram-negative (G−) bacteria and fungi [112]. Silver [148,149] and honey [101], both well-known, naturally derived antimicrobials, have also been used in the development of new wound dressings. Polymer films containing silver nanoparticles can confer an anti-MSSA (methicillin-sensitive strains of Staphylococcus aureus) effect on biological dressings [150]. Manuka honey synergistically enhanced the effectiveness of several antibiotics against MRSA and Pseudomonas aeruginosa [103] and can also exert positive effects on wound dressings when combined with silver, thereby lowering antimicrobial resistance and limiting the overuse of antibiotics [151]. Moreover, several herbs have been demonstrated to enhance silver nanoparticles (AgNPs) [152,153], and some of these herbs can also act as stabilizers of AgNPs [152]. Indeed, silver is generally accepted as an evidence-based topical wound antimicrobial that is used as a preparation of either a solution or nanoparticles in wound dressings [148,149]; however, silver is suggested to treat G− bacteria more effectively, whereas mupirocin is the recommendation for MRSA wound infection [154].

A prerequisite of using ethnomedical drugs to combat MRSA infections more robustly than antibiotics is to make fewer mistakes in their use than were made in antibiotic use. A mistake that is still made is to make poor choices between systemic and topical administrations for wound infection. Systemic antibiotics are ideally never applied in topical use due to the risks of promoting both resistance and allergy [155], whereas topical antibiotics are not recommended for systemic use due to serious adverse effects [156]. Few topical antibiotics have been proven to be effective in clinical trials [156,157], although topical treatment with retapamulin and mupirocin is significantly more effective than systemic treatment with linezolid and vancomycin in eradicating MRSA in a murine superficial skin wound infection model [158]. Moreover, the topical use of antibiotics may result in systemic toxicity, allergy, wound healing delay and normal flora dysfunction [157,159]. Hence, it is crucial in wound care to rationally use systemic and topical antibiotics. Otherwise, overuse and misuse of antibiotics will drastically promote antibiotic resistance. One evidence-based suggestion is that topical antibiotic therapy might be an effective alternative to oral antibiotic therapy in treating diabetic patients with a mildly infected foot ulcer and might reduce the risk of selecting antimicrobial-resistant bacteria [159]. The overuse and misuse of topical antibiotics is perhaps due to an optimism bias that topical use rarely enhances the risk of antibiotic resistance. However, irrespective of whether the antibiotics are systemic or topical, widespread use is associated with the emergence of resistant bacterial
strains [147]. In fact, topical antibiotics have long been known to promote the antibiotic resistance of S. aureus [155]. Clearly, the appropriate use of these agents remains a great challenge for antibiotic therapies for MRSA wound infections but a greater one for ethnomedical treatments. Nonetheless, there is still no clear definition of “systemic/topical” and “sensitive/resistant” in ethnomedicine.

To prevent the reoccurrence of a similar dilemma, the development and application of ethomedical drugs should avoid mistakes once made with antibiotics. Ethnomedical drugs should be divided into systemic and topical categories through evaluating their potential systemic adverse effects, allergies and toxicity, as well as local hypersensitivity and bio-absorbance, thereby avoiding misuse. To a large extent, the avoidance of antimicrobial misuse will result in a low resistance potential. However, the emergence of resistant mutants is the essential factor responsible for drug resistance. Thus, drug resistance should be monitored from the beginning of and throughout the development and application of ethnomedical drugs. Additionally, well-designed clinical trials and high-quality animal tests should be conducted because most of the ethnomedical studies on MRSA infection are conducted at the levels of case studies and in vitro assays (Table 2). The lack of evidence dampens the translation of ethnomedicine into evidence-based therapies.

6. Conclusions

Some newly developed antibiotics exhibit high effectiveness in combating MRSA infection, as do candidates under development. With a combination of debridement and modern wound dressings, these agents can successfully treat MRSA wound infections on the basis of limiting their usage. However, antibiotic resistance rapidly spreads, resulting in increasing numbers of multidrug- and even pan-drug-resistant strains. In addition to the development of novel antimicrobials and antibiotic-free treatments, the verification and validation of ethnomedical drugs is a feasible and cost-effective approach to address this issue. The topical use of ethnomedical drugs represents both the development of new wound dressings as well as a platform to study ethnomedical drugs in a “treat it as a whole” approach, which improves the translation of ethnomedicine into evidence-based practice. Naturally derived materials can therefore act as evidence-based drugs for modern medicine. The medical use of honey and silver is a successful paradigm. Despite the limited efficacy of their single use, their combined use in modern wound dressings contributes significantly to combating MRSA infections. Significantly, some naturally derived materials used in ethnomedicine may reverse the antibiotic resistance of MRSA through the attenuation of their PBP2a levels and the inhibition of their multidrug efflux pumps. The medicinal plant Duabanga grandiflora is therefore worthy of significant study. However, most ethnomedical materials are not well-studied, although they exhibit some relevance in combating MRSA infections based on in vitro assays. Furthermore, the tested strains were MSSA in some studies. Well-designed clinical trials and high-quality animal tests are therefore required in the future. Additionally, to avoid creating a similar crisis point in the future, the development and the application of ethnomedical drugs should learn the lessons of previous antibiotic treatment use.

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References

1. Chahoud, J.; Kanafani, Z.; Kanj, S.S. Surgical site infections following spine surgery: Eliminating the controversies in the diagnosis. Front. Med. 2014, 1. [CrossRef]
2. Munoz, P.; Hortal, J.; Giannella, M.; Barrio, J.M.; Rodriguez-Creixems, M.; Perez, M.J.; Rincon, C.; Bouza, E. Nasal carriage of S. aureus increases the risk of surgical site infection after major heart surgery. J. Hosp. Infect. 2008, 68, 25–31. [CrossRef] [PubMed]
3. Lee, C.Y.; Chen, P.Y.; Huang, F.L.; Lin, C.F. Microbiologic spectrum and susceptibility pattern of clinical isolates from the pediatric intensive care unit—a single medical center—6 years’ experience. J. Microbiol. Immunol. Infect. 2009, 42, 160–165. [PubMed]

4. Ellis, S.L.; Finn, P.; Noone, M.; Leaper, D.J. Eradication of methicillin-resistant Staphylococcus aureus from pressure sores using warming therapy. Surg. Infect. 2003, 4, 53–55. [CrossRef] [PubMed]

5. Negi, V.; Pal, S.; Juyal, D.; Sharma, M.K.; Sharma, N. Bacteriological profile of surgical site infections and their antibiogram: A study from resource constrained rural setting of Uttarakhad State, India. J. Clin. Diagn. Res. JCDR 2015, 9, DC17–DC20. [CrossRef] [PubMed]

6. Hohmann, C.; Eickhoff, C.; Radzwiwill, R.; Schulz, M. Adherence to guidelines for antibiotic prophylaxis in surgery patients in German hospitals: A multicentre evaluation involving pharmacy interns. Infection 2012, 40, 131–137. [CrossRef] [PubMed]

7. Simor, A.E. Staphylococcal decolonisation: An effective strategy for prevention of infection? Lancet Infect. Dis. 2011, 11, 952–962. [CrossRef]

8. Tong, S.Y.; Holden, M.T.; Nickerson, E.K.; Cooper, B.S.; Koser, C.U.; Cori, A.; Jombart, T.; Cauchemez, S.; Fraser, C.; Wuthiekanun, V.; et al. Genome sequencing defines phylogeny and spread of methicillin-resistant Staphylococcus aureus in a high transmission setting. Genome Res. 2015, 25, 111–118. [CrossRef] [PubMed]

9. Falagas, M.E.; Karageorgopoulos, D.E.; Leptidis, J.; Korbila, I.P. MRSA in Africa: Filling the global map of antimicrobial resistance. PLoS ONE 2013, 8, e68024. [CrossRef] [PubMed]

10. Fry, D.E. The continued challenge of Staphylococcus aureus in the surgical patient. Am. Surg. 2013, 79, 1–10. [PubMed]

11. Bahemia, I.A.; Muganza, A.; Moore, R.; Sahid, F.; Menezes, C.N. Microbiology and antibiotic resistance in severe burns patients: A 5 year review in an adult burns unit. Burns J. Int. Soc. Burn Inf. 2015, 41, 1536–1542. [CrossRef] [PubMed]

12. Arias, C.A.; Murray, B.E. Antibiotic-resistant bugs in the 21st century—A clinical super-challenge. N. Engl. J. Med. 2009, 360, 439–443. [CrossRef] [PubMed]

13. Reardon, S. Antibiotic resistance sweeping developing world. Nature 2014, 509, 141–142. [CrossRef] [PubMed]

14. McKenna, M. Vaccine development: Man vs. MRSA. Nature 2012, 482, 23–25. [CrossRef] [PubMed]

15. Zhao, Z.; Sun, H.Q.; Wei, S.S.; Li, B.; Feng, Q.; Zhu, J.; Zeng, H.; Zou, Q.M.; Wu, C. Multiple B-cell epitope vaccine induces a Staphylococcus enterotoxin B-specific IgG1 protective response against MRSA infection. Sci. Rep. 2015, 5, 12371. [CrossRef] [PubMed]

16. Bal, A.M.; Gould, I.M. Antibiotic resistance in Staphylococcus aureus and its relevance in therapy. Expert Opin. Pharmacother. 2005, 6, 2257–2269. [CrossRef] [PubMed]

17. Boucher, H.W.; Talbot, G.H.; Bradley, J.S.; Edwards, J.E.; Gilbert, D.; Rice, L.B.; Scheld, M.; Spellberg, B.; Bartlett, J. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. Clin. Infect. Dis. 2009, 48, 1–12. [CrossRef] [PubMed]

18. Spellberg, B.; Powers, J.H.; Brass, E.P.; Miller, L.G.; Edwards, J.E., Jr. Trends in antimicrobial drug development: Implications for the future. Clin. Infect. Dis. 2004, 38, 1279–1286. [CrossRef] [PubMed]

19. Shlaes, D.M.; Sahm, D.; Opiela, C.; Spellberg, B. The FDA reboot of antibiotic development. Antimicrob. Agents Chemother. 2013, 57, 4605–4607. [CrossRef] [PubMed]

20. U.S. Food and Drug Administration. FDA Approved Drugs for Infections and Infectious Diseases. Available online: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed on 20 December 2015).

21. Corey, G.R.; Kabler, H.; Mehra, P.; Gupta, S.; Overcash, J.S.; Porwal, A.; Giordano, P.; Lucasti, C.; Perez, A.; Good, S.; et al. Single-dose oritavancin front-loaded dosing regimens to daily dosing: An analysis of the SIMPLIFI trial. Antimicrob. Agents Chemother. 2011, 55, 3476–3484. [CrossRef] [PubMed]
24. Mlynarczyk, A.; Mlynarczyk, B.; Kmera-Muszyńska, M.; Majewski, S.; Mlynarczyk, G. Mechanisms of the resistance and tolerance to β-lactam and glycopeptide antibiotics in pathogenic Gram-positive cocci. *Mini Rev. Med. Chem.* 2009, 9, 1527–1537. [CrossRef] [PubMed]

25. Zhanel, G.G.; Love, R.; Adam, H.; Golden, A.; Zelenitsky, S.; Schweizer, F.; Gorityala, B.; Lagace-Wiens, P.R.; Rubinstein, E.; Walkty, A.; et al. Tedizolid: A novel oxazolidinone with potent activity against multidrug-resistant Gram-positive pathogens. *Drugs* 2015, 75, 253–270. [CrossRef] [PubMed]

26. Thomson, K.S.; Goering, R.V. Activity of tedizolid (TR-700) against well-characterized methicillin-resistant *Staphylococcus aureus* strains of diverse epidemiological origins. *Antimicrob.Agents Chemother.* 2013, 57, 2892–2895. [CrossRef] [PubMed]

27. Prokocimer, P.; de Anda, C.; Fang, E.; Mehra, P.; Das, A. Tedizolid phosphate vs. linezolid for treatment of acute bacterial skin and skin structure infections: The ESTABLISH-1 randomized trial. *JAMA* 2013, 309, 559–569. [CrossRef] [PubMed]

28. Prokocimer, P.; Bien, P.; Surber, J.; Mehra, P.; DeAnda, C.; Bulitta, J.B.; Corey, G.R. Phase 2, randomized, double-blind, dose-ranging study evaluating the safety, tolerability, population pharmacokinetics, and efficacy of oral torezolid phosphate in patients with complicated skin and skin structure infections. *Antimicrob. Agents Chemother.* 2011, 55, 583–592. [CrossRef] [PubMed]

29. Moran, G.J.; Fang, E.; Corey, G.R.; Das, A.F.; de Anda, C.; Prokocimer, P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): A randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect. Dis.* 2014, 14, 696–705. [CrossRef]

30. Sahm, D.F.; Deane, J.; Bien, P.A.; Locke, J.B.; Zuill, D.E.; Shaw, K.J.; Bartizal, K.F. Results of the surveillance of Tedizolid activity and resistance program: *In vitro* susceptibility of Gram-positive pathogens collected in 2011 and 2012 from the United States and Europe. *Diagn. Microbiol. Infect. Dis.* 2015, 81, 112–118. [CrossRef] [PubMed]

31. Barnea, Y.; Lerner, A.; Aizic, A.; Navon-Venezia, S.; Rachi, E.; Dunne, M.W.; Puttagunta, S.; Carmeli, Y. Efficacy of dalbavancin in the treatment of MRSA rat sternal osteomyelitis with mediastinitis. *J. Antimicrob. Chemother.* 2015, 71, 460–463. [CrossRef] [PubMed]

32. Esposito, S.; Noviello, S.; Leone, S. Dalbavancin in the treatment of MRSA rat sternal osteomyelitis with mediastinitis. *J. Antimicrob. Chemother.* 2015, 71, 617–625. [CrossRef] [PubMed]

33. Zhanel, G.G.; Calic, D.; Schweizer, F.; Zelenitsky, S.; Adam, H.; Lagace-Wiens, P.R.; Rubinstein, E.; Gin, A.S.; Hoban, D.J.; Karlowsky, J.A. New lipoglycopeptides: A comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010, 70, 859–886. [CrossRef] [PubMed]

34. Goldstein, E.J.; Citron, D.M.; Merriam, C.V.; Tyrrell, K.L. Cefaroline versus isolates from animal bite wounds: Comparative *in vitro* activities against 243 isolates, including 156 Pasteurella species isolates. *Antimicrob. Agents Chemother.* 2012, 56, 6319–6323. [CrossRef] [PubMed]

35. Friedland, H.D.; O’Neal, T.; Biek, D.; Eckburg, P.B.; Rank, D.R.; Llorens, L.; Smith, A.; Withereill, G.W.; Laudano, J.B.; Thyre, D. CANVAS 1 and 2: Analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. *Antimicrob. Agents Chemother.* 2012, 56, 2231–2236. [CrossRef] [PubMed]

36. Biedenbach, D.J.; Alm, R.A.; Lahiri, S.D.; Reiszner, E.; Hoban, D.J.; Sahm, D.F.; Bouchillon, S.K.; Ambler, J.E. *In vitro* activity of ceftaroline against *Staphylococcus aureus* isolated in 2012 from Asia-Pacific countries: AWARE surveillance program. *Antimicrob. Agents Chemother.* 2015, 60, 343–347. [CrossRef] [PubMed]

37. Yanik, K.; Guluzade, E.; Bilgin, K.; Karadag, A.; Eroğlu, C.; Birinci, A.; Gunaydin, M. Cefaroline activity on certain respiratory tract and wound infection agents at the minimum inhibitory concentration level. *J. Infect. Dev. Ctries.* 2015, 9, 1086–1090. [CrossRef] [PubMed]

38. Lahiri, S.D.; Alm, R.A. Potential of *Staphylococcus aureus* isolates carrying different PBP2a alleles to develop resistance to ceftaroline. *J. Antimicrob. Chemother.* 2016, 71, 34–40. [CrossRef] [PubMed]

39. Zhanel, G.G.; Adam, H.J.; Baxter, M.R.; Fuller, J.; Nichol, K.A.; Denisiuik, A.J.; Lagace-Wiens, P.R.; Walkty, A.; Karlowsky, J.A.; Schweizer, F.; et al. Antimicrobial susceptibility of 22746 pathogens from Canadian hospitals: Results of the CANWARD 2007–11 study. *J. Antimicrob. Chemother.* 2013, 68 (Suppl. 1), i7–i22. [CrossRef] [PubMed]

40. Stryjewski, M.E.; Barriere, S.L.; O’Riordan, W.; Dunbar, L.M.; Hopkins, A.; Genter, F.C.; Corey, G.R. Efficacy of telavancin in patients with specific types of complicated skin and skin structure infections. *J. Antimicrob. Chemother.* 2012, 67, 1496–1502. [CrossRef] [PubMed]
41. Pfaffer, M.A.; Mendes, R.E.; Sader, H.S.; Jones, R.N. Telavancin activity against Gram-positive bacteria isolated from respiratory tract specimens of patients with nosocomial pneumonia. J. Antimicrob. Chemother. 2010, 65, 2396–2404. [CrossRef] [PubMed]

42. Brinkman, M.B.; Fan, K.; Shiveley, R.L.; van Anglen, L.J. Successful treatment of polymicrobial calcaneal osteomyelitis with telavancin, rifampin, and meropenem. Ann. Pharmacother. 2012, 46, e15. [CrossRef] [PubMed]

43. Souli, M.; Karaiskos, I.; Galani, L.; Maraki, S.; Perivolioti, E.; Argypoulou, A.; Charissiadou, A.; Zachariadou, L.; Tsipakou, S.; Papaioannou, V.; et al. Nationwide surveillance of resistance rates of Staphylococcus aureus clinical isolates from Greek hospitals, 2012–2013. Infect. Dis. 2016, 48, 287–292. [CrossRef] [PubMed]

44. Eckmann, C.; Heizmann, W.; Bodmann, K.F.; von Eiff, C.; Petrik, C.; Loeschmann, P.A. Tigecycline in the treatment of patients with necrotizing skin and soft tissue infections due to multiresistant bacteria. Surg. Infect. 2015, 16, 618–625. [CrossRef] [PubMed]

45. Wong, S.Y.; Manikam, R.; Muniandy, S. Prevalence and antibiotic susceptibility of bacteria from acute and chronic wounds in Malaysian subjects. J. Infect. Dev. Ctries. 2015, 9, 936–944. [CrossRef] [PubMed]

46. Romanowski, E.G.; Kowalski, T.A.; O’Connor, K.E.; Yates, K.A.; Mah, F.S.; Shanks, R.M.; Kowalski, R.P. The in vitro evaluation of tigecycline and the in vivo evaluation of RPX-978 (0.5% Tigecycline) as an ocular antibiotic. J. Ocul. Pharmacol. Ther. 2016, 32, 119–126. [CrossRef] [PubMed]

47. Ramirez, M.S.; Traglia, G.M.; Perez, J.F.; Muller, G.L.; Martinez, M.F.; Golic, A.E.; Mussi, M.A. White and blue light induce reduction in susceptibility to minocycline and tigecycline in Acinetobacter spp. and other bacteria of clinical importance. J. Med. Microbiol. 2015, 64(Pt 5), 525–537. [CrossRef] [PubMed]

48. Heidari, H.; Emameini, M.; Dabiri, H.; Jabalameli, F. Virulence factors, antimicrobial resistance pattern and molecular analysis of Enterococcus strains isolated from burn patients. Microb. Pathog. 2016, 90, 93–97. [CrossRef] [PubMed]

49. O’Riordan, W.; Mehra, P.; Manos, P.; Kingsley, J.; Lawrence, L.; Cammarata, S. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. Int. J. Infect. Dis. IJID 2015, 30, 67–73. [CrossRef] [PubMed]

50. Pinheiro, L.; Brito, C.I.; Pereira, V.C.; Oliveira, A.; Bartolomeu, A.R.; Camargo, C.H.; Cunha, M.L. Susceptibility profile of Staphylococcus epidermidis and Staphylococcus haemolyticus isolated from blood cultures to vancomycin and novel antimicrobial drugs over a period of 12 years. Microb. Drug Resist. 2015. [CrossRef] [PubMed]

51. Niveditha, N.; Sujatha, S. Worrisome trends in rising minimum inhibitory concentration values of antibiotics against methicillin resistant Staphylococcus aureus—Insights from a tertiary care center, South India. Braz. J. Infect. Dis. 2015, 19, 585–589. [CrossRef] [PubMed]

52. Lupien, A.; Gingras, H.; Leprohon, P.; Ouellette, M. Induced tigecycline resistance in Staphylococcus aureus—Insights from a tertiary care center, South India. J. Infect. Dev. Ctries. 2015, 9, 936–944. [CrossRef] [PubMed]

53. Cogo, A.; Gonzalez-Ruiz, A.; Pathan, R.; Hamed, K. Real-world treatment of complicated skin and soft tissue infections with daptomycin: Results from a large European Registry (EU-CORE). Infect. Dis. Ther. 2015, 4, 273–282. [CrossRef] [PubMed]

54. Dhand, A.; Bayer, A.S.; Pogliano, J.; Yang, S.J.; Bolaris, M.; Nizet, V.; Wang, G.; Sakoulas, G. Use of anti-staphylococcal β-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant Staphylococcus aureus: Role of enhanced daptomycin binding. Clin. Infect. Dis. 2011, 53, 158–163. [CrossRef] [PubMed]

55. Stone, P.A.; AbuRahma, A.F.; Campbell, J.R.; Hass, S.M.; Mousa, A.Y.; Nanjundappa, A.; Srivastava, M.; Modak, A.; Emmett, M. Prospective randomized double-blinded trial comparing 2 anti-MRSA agents with supplemental coverage of cefazolin before lower extremity revascularization. Ann. Surg. 2015, 262, 495–501. [CrossRef] [PubMed]

56. Fernandez-Natal, I.; Saez-Nieto, J.A.; Medina-Pascual, M.J.; Albersmeier, A.; Valdezate, S.; Guerra-Laso, J.M.; Rodriguez, H.; Marrodan, T.; Parras, T.; Tauch, A.; et al. Dermabacter hominis: A usually daptomycin-resistant Gram-positive organism infrequently isolated from human clinical samples. New Microbes New Infect. 2013, 1, 35–40. [CrossRef] [PubMed]
57. Saravolatz, L.D.; Pawlak, J.; Johnson, L.B. 

In vitro activity of oritavancin against community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA), vancomycin-intermediate S. aureus (VISA), vancomycin-resistant S. aureus (VRSA) and daptomycin-non-susceptible S. aureus (DNSSA). 

Int. J. Antimicrob. Agents 2010, 36, 69–72. [CrossRef] [PubMed]

58. Wunderink, R.G.; Niedermaier, M.S.; Kollef, M.H.; Shorr, A.F.; Kunkel, M.J.; Baruch, A.; McGee, W.T.; Reisman, A.; Chastre, J. 

Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: A randomized, controlled study. 

Clin. Infect. Dis. 2012, 54, 621–629. [CrossRef] [PubMed]

59. Yayan, J.; Ghebremedhin, B.; Rasche, K. 

No outbreak of Vancomycin and linezolid resistance in Staphylococcal pneumonia over a 10-year period. 

PLoS ONE 2015, 10, e0138895. [CrossRef] [PubMed]

60. Akhi, M.T.; Ghotaslou, R.; Beheshtirouy, S.; Asgharzadeh, M.; Pirzadeh, T.; Asghari, B.; Alizadeh, N.; Ostadgavahi, A.T.; Somesaraei, V.S.; Memar, M.Y. 

Antibiotic susceptibility pattern of aerobic and anaerobic bacteria isolated from surgical site infection of hospitalized patients. 

Jundishapur J. Microbiol. 2015, 8, e20309. [CrossRef] [PubMed]

61. Herrero, I.A.; Issa, N.C.; Patel, R. 

Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. 

N. Engl. J. Med. 2002, 346, 867–869. [CrossRef] [PubMed]

62. Cidral, T.A.; Carvalho, M.C.; Figueiredo, A.M.; de Melo, M.C. 

Emergence of methicillin-resistant coagulase-negative staphylococci resistant to linezolid with rRNA gene C2190T and G2603T mutations. 

APMIS 2015, 123, 867–871. [CrossRef] [PubMed]

63. Caballero, J.D.; Pastor, M.D.; Vindel, A.; Maiz, L.; Yague, G.; Salvador, C.; Cobo, M.; Morosini, M.I.; del Campo, R.; Canton, R.; et al. 

Emergence of cfr-mediated linezolid resistance in a methicillin-resistant Staphylococcus aureus epidemic clone isolated from patients with cystic fibrosis. 

Antimicrob. Agents Chemother. 2015. [CrossRef]

64. Cafini, F.; Nguyen, L.T.; Higashide, M.; Roman, F.; Prieto, J.; Morikawa, K. 

Horizontal gene transmission of the cfr gene to MRSA and Enterococcus: Role of Staphylococcus epidermidis as a reservoir and alternative pathway for the spread of linezolid resistance. 

J. Antimicrob. Chemother. 2015. [CrossRef]

65. Savoia, D. 

New antimicrobial approaches: Reuse of old drugs. 

Curr. Drug Targets 2016, 17, 731–738. [CrossRef] [PubMed]

66. Thangamani, S.; Younis, W.; Seleem, M.N. 

Repurposing ebselen for treatment of multidrug-resistant staphylococcal infections. 

Sci. Rep. 2015, 5, 11596. [CrossRef] [PubMed]

67. Thangamani, S.; Younis, W.; Seleem, M.N. 

Repurposing celecoxib as a topical antimicrobial agent. 

Front. Microbiol. 2015, 6. [CrossRef] [PubMed]

68. Thangamani, S.; Mohammad, H.; Abushabha, M.F.; Hamed, M.I.; Sobreira, T.J.; Hedrick, V.E.; Paul, L.N.; Seleem, M.N. 

Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. 

Sci. Rep. 2015, 5, 16407. [CrossRef] [PubMed]

69. Corriden, R.; Hollands, A.; Olson, J.; Derieux, J.; Lopez, J.; Chang, J.T.; Gonzalez, D.J.; Nizet, V. 

Tamoxifen augments the innate immune function of neutrophils through modulation of intracellular ceramide. 

Nat. Commun. 2015, 6, 8369. [CrossRef] [PubMed]

70. Taubes, G. 

The bacteria fight back. 

Science 2008, 321, 356–361. [CrossRef] [PubMed]

71. Buru, A.S.; Pichika, M.R.; Neela, V.; Mohandas, K. 

In vitro antibacterial effects of Cinnamomum extracts on common bacteria found in wound infections with emphasis on methicillin-resistant Staphylococcus aureus. 

J. Ethnopharmacol. 2014, 153, 587–595. [CrossRef] [PubMed]

72. Liu, Y.Y.; Wang, Y.; Walsh, T.R.; Yi, L.X.; Zhang, R.; Spencer, J.; Doi, Y.; Tian, G.; Dong, B.; Huang, X.; et al. 

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. 

Lancet Infect. Dis. 2015, 15, 161–168. [CrossRef]

73. Ling, L.L.; Schneider, T.; Peoples, A.J.; Spoering, A.L.; Engels, I.; Conlon, B.P.; Mueller, A.; Schaberle, T.F.; Hughes, D.E.; Epstein, S.; et al. 

A new antibiotic kills pathogens without detectable resistance. 

Nature 2015, 517, 455–459. [CrossRef] [PubMed]

74. Stewart, P.S.; Costerton, J.W. 

Antibiotic resistance of bacteria in biofilms. 

Lancet 2001, 358, 135–138. [CrossRef]

75. Hansen, S.K.; Rainey, P.B.; Haagensen, J.A.; Molin, S. 

Evolution of species interactions in a biofilm community. 

Nature 2007, 445, 533–536. [CrossRef] [PubMed]

76. Wimpenney, J.; Manz, W.; Szewczyk, U. 

Heterogeneity in biofilms. 

FEMS Microbiol. Rev. 2000, 24, 661–671. [CrossRef] [PubMed]
77. Koch, G.; Yepes, A.; Forstner, K.U.; Wermser, C.; Stengel, S.T.; Modamio, J.; Ohlsen, K.; Foster, K.R.; Lopez, D. Evolution of resistance to a last-resort antibiotic in Staphylococcus aureus via bacterial competition. *Cell* 2014, 158, 1060–1071. [CrossRef] [PubMed]

78. Segev-Zarko, L.; Saar-Dover, R.; Brumfeld, V.; Mangoni, M.L.; Shai, Y. Mechanisms of biofilm inhibition and degradation by antimicrobial peptides. *Biochem. J.* 2015, 468, 259–270. [CrossRef] [PubMed]

79. Stinner, D.J.; Hsu, J.R.; Wenke, J.C. Negative pressure wound therapy reduces the effectiveness of traditional local antibiotic depot in a large complex musculoskeletal wound animal model. *J. Orthop. Trauma* 2012, 26, 512–518. [CrossRef] [PubMed]

80. Hasan, M.Y.; Teo, R.; Nather, A. Negative-pressure wound therapy for management of diabetic foot wounds: A review of the mechanism of action, clinical applications, and recent developments. *Diabet. Foot Ankle* 2015, 6, 27618. [CrossRef] [PubMed]

81. Kim, P.J.; Attinger, C.E.; Oliver, N.; Garwood, C.; Evans, K.K.; Steinberg, J.S.; Lavery, L.A. Comparison of outcomes for normal saline and an antiseptic solution for negative-pressure wound therapy with instillation. *Plast. Reconstr. Surg.* 2015, 136, 657e–664e. [CrossRef] [PubMed]

82. Nusbaum, A.G.; Gil, J.; Rippy, M.K.; Warne, B.; Valdes, J.; Claro, A.; Davis, S.C. Effective method to remove wound bacteria: Comparison of various debridement modalities in an in vivo porcine model. *J. Surg. Res.* 2012, 176, 701–707. [CrossRef] [PubMed]

83. Seth, A.K.; Geringer, M.R.; Nguyen, K.T.; Agnew, S.P.; Dumanian, Z.; Galiano, R.D.; Leung, K.P.; Mustoe, T.A.; Hong, S.J. Bacteriophage therapy for Staphylococcus aureus biofilm-infected wounds: A new approach to chronic wound care. *Plast. Reconstr. Surg.* 2013, 131, 225–234. [CrossRef] [PubMed]

84. Jin, S.G.; Yousaf, A.M.; Jang, S.W.; Son, M.W.; Kim, K.S.; Kim, D.W.; Li, D.X.; Kim, J.O.; Yong, C.S.; Choi, H.G. In vivo wound-healing effects of novel benzalkonium chloride-loaded hydrocolloid wound dressing. *Drug Des. Res.* 2015, 76, 157–165. [CrossRef] [PubMed]

85. Sultana, S.T.; Atci, E.; Babauta, J.T.; Mohamed Falghoush, A.; Snekvik, K.R.; Call, D.R.; Beyenal, H. Electrochemical scaffold generates localized, low concentration of hydrogen peroxide that inhibits bacterial pathogens and biofilms. *Sci. Rep.* 2015, 5, 14908. [CrossRef] [PubMed]

86. Gibson, A.L.; Thomas-Virnig, C.L.; Centanni, J.M.; Schlosser, S.J.; Johnston, C.E.; van Winkle, K.F.; Szilagyi, A.; He, L.K.; Shankar, R.; Allen-Hoffmann, B.L. Nonviral human β defensin-3 expression in a bioengineered human skin tissue: A therapeutic alternative for infected wounds. *Wound Repair Regen.* 2012, 20, 414–424. [CrossRef] [PubMed]

87. Sandy-Hodgetts, K.; Watts, R. Effectiveness of negative pressure wound therapy/closed incision management in the prevention of post-surgical wound complications: A systematic review and meta-analysis. *BJ BI Database Syst. Rev. Implement. Rep.* 2015, 13, 253–303.

88. Kimura, M.; Nishimura, T.; Kinoshita, O.; Okada, S.; Inafuku, H.; Kyo, S.; Ono, M. Successful treatment of pump pocket infection after left ventricular assist device implantation by negative pressure wound therapy and omental transposition. *Ann. Thorac. Cardiovasc. Surg.* 2014, 20, 842–845. [CrossRef] [PubMed]

89. Steenvoorde, P.; de Roo, R.A.; Oskam, J.; Neijenhuis, P. Negative pressure wound therapy to treat peri-prosthetic methicillin-resistant Staphylococcus aureus infection after incisional herniorrhaphty. A case study and literature review. *Ostomy Wound Manag.* 2006, 52, 52–54.

90. Diogenes, M.S.; Carvalho, A.C.; Tabosa, A.M. Acupuncture and moxibustion as fundamental therapeutic complements for full recovery of staphylococcal skin infection after a poor 50-day treatment response to antibiotics. *J. Altern. Complement. Med.* 2008, 14, 757–761. [CrossRef] [PubMed]

91. Diaz-Roa, A.; Gaona, M.A.; Segura, N.A.; Ramirez-Hernandez, A.; Cortes-Vecino, J.A.; Patarroyo, M.A.; Bello, F. Evaluating Sarcoesiopsis magellanica blowfly-derived larval therapy and comparing it to Lucilia sericata-derived therapy in an animal model. *Acta Trop.* 2015, 154, 34–41. [CrossRef] [PubMed]

92. Bexfield, A.; Nigam, Y.; Thomas, S.; Ratcliffe, N.A. Detection and partial characterisation of two antibacterial factors from the excretions/secretions of the medicinal maggot Lucilia sericata and their activity against methicillin-resistant Staphylococcus aureus (MRSA). *Microbes Infect.* *Inst. Pasteur* 2004, 6, 1297–1304. [CrossRef] [PubMed]

93. Van der Plas, M.J.; Dambrot, C.; Dogterom-Ballering, H.C.; Kruithof, S.; van Dissel, J.T.; Nibbering, P.H. Combinations of maggot excretions/secretions and antibiotics are effective against Staphylococcus aureus biofilms and the bacteria derived therefrom. *J. Antimicrob. Chemother.* 2010, 65, 917–923. [CrossRef] [PubMed]
94. Deare, J.C.; Zheng, Z.; Xue, C.C.; Liu, J.P.; Shang, J.; Scott, S.W.; Littlejohn, G. Acupuncture for treating fibromyalgia. In *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2013.
95. Manheimer, E.; Cheng, K.; Wieland, L.S.; Min, L.S.; Shen, X.; Berman, B.M.; Lao, L. Acupuncture for treatment of irritable bowel syndrome. In *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2012.
96. Linde, K.; Allais, G.; Brinkhaus, B.; Manheimer, E.; Vickers, A.; White, A.R. Acupuncture for tension-type headache. In *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2009.
97. Temrangsee, P.; Kondo, S.; Itharat, A. Antibacterial activity of extracts from five medicinal plants.
98. Zhang, S.; Wang, J.; Xu, W.; Liu, Y.; Wang, W.; Wu, K.; Wang, Z.; Zhang, X. Antibacterial effects of Traditional Chinese Medicine monomers against *Streptococcus pneumoniae* via inhibiting pneumococcal histidine kinase (VicK). *Front. Microbiol.* 2015, 6. [CrossRef] [PubMed]
99. Emran, T.B.; Rahman, M.A.; Uddin, M.M.; Dash, R.; Hossen, M.F.; Mohiuddin, M.; Alam, M.R. Molecular docking and inhibition studies on the interactions of *Bacopa monnieri*’s potent phytochemicals against pathogenic *Staphylococcus aureus*. *Daru* 2015, 23. [CrossRef] [PubMed]
100. Duan, F.; Li, X.; Cai, S.; Xin, G.; Wang, Y.; Du, D.; He, S.; Huang, B.; Guo, X.; Zhao, H.; et al. Haloemodin as novel antibacterial agent inhibiting DNA gyrase and bacterial topoisomerase I. *J. Med. Chem.* 2014, 57, 3707–3714. [CrossRef] [PubMed]
101. Molan, P.; Rhodes, T. Honey: A Biologic Wound Dressing. *Wounds* 2015, 27, 141–151. [PubMed]
102. Asadollahi, F.; Mehrzad, J.; Chaichi, M.J.; Taghavi Razavizadeh, A. Photoimmunological properties of borage leaf extract. *Arch. Oral Biol.* 2015, 60, 468–473. [CrossRef] [PubMed]
103. Jenkins, R.; Cooper, R. Improving antibiotic activity against wound pathogens with manuka honey in vitro. *PLoS ONE* 2012, 7, e45600. [CrossRef] [PubMed]
104. Pan, X.; Bligh, S.W.; Smith, E. Quinolone alkaloids from *Fructus Euodiae* show activity against methicillin-resistant *Staphylococcus aureus*. *Phytother. Res.* PTR 2014, 28, 305–307. [CrossRef] [PubMed]
105. Chen, X.; Shang, F.; Meng, Y.; Li, L.; Cui, Y.; Zhang, M.; Qi, K.; Xue, T. Ethanol extract of *Li, W.Z.; Tan, L.L.; Li, Q.J.; Zhou, B.J.; Gao, Y.X.; Ding, W.J. Stabilizing the bactericidal activity of hydrogen peroxide: A brand new function of certain Chinese herbs. *Chin. J. Integr. Med. Med.* 2014, 20, 468–473. [CrossRef] [PubMed]
106. Lee, J.; Han, S.Y.; Ji, A.R.; Park, J.K.; Hong, I.H.; Ki, M.R.; Lee, E.M.; Kim, A.Y.; Lee, E.J.; Hwang, J.S.; et al. Antimicrobial effects of coprisin on wounds infected with *Staphylococcus aureus* in rats. *Wound Repair Regen.* 2013, 21, 876–882. [CrossRef] [PubMed]
107. Pan, X.; Limsuwan, S.; Homlaead, S.; Watcharakul, S.; Chusri, S.; Moosigapong, K.; Saisongkram, K.; Voravuthikunchai, S.P. Inhibition of microbial adhesion to plastic surface and human buccal epithelial cells by *Rhodomyrtus tomentosa* leaf extract. *Arch. Oral Biol.* 2014, 59, 1256–1265. [CrossRef] [PubMed]
108. Cataldi, V.; di Bartolomeo, S.; di Campli, E.; Nostro, A.; Cellini, L.; di Giulio, M. In vitro activity of *Aloe vera* inner gel against microorganisms grown in planktonic and sessile phases. *Int. J. Immunopathol. Pharmacol.* 2015, 28, 595–602. [CrossRef] [PubMed]
109. Budri, P.E.; Silva, N.C.; Bonsaglia, E.C.; Fernandes, A.J.; Araujo, J.P.J.; Doyama, J.T.; Goncalves, J.L.; Santos, M.V.; Fitzgerald-Hughes, D.; Rall, V.L. Effect of essential oils of *Syzygium aromaticum* and *Cinnamomum zeylanicum* and their major components on biofilm production in *Staphylococcus aureus* strains isolated from milk of cows with mastitis. *J. Dairy Sci.* 2015, 98, 5899–5904. [CrossRef] [PubMed]
114. Chew, Y.L.; Chan, E.W.; Tan, P.L.; Lim, Y.Y.; Stanslas, J.; Goh, J.K. Assessment of phytochemical content, polyphenolic composition, antioxidant and antibacterial activities of LeguminoSae medicinal plants in Peninsular Malaysia. BMC Complement. Altern. Med. 2011, 11. [CrossRef] [PubMed]

115. Husain, F.M.; Ahmad, I.; Khan, M.S.; Al-Shabib, N.A. Trigonella foenum-graceum (seed) extract interferes with quorum sensing regulated traits and biofilm formation in the strains of Pseudomonas aeruginosa and Aeromonas hydrophila. Evid. Based Complement. Altern. Med. 2015, 2015, 879540. [CrossRef] [PubMed]

116. Teixeira, E.H.; Napimoga, M.H.; Carneiro, V.A.; de Oliveira, T.M.; Cunha, R.M.; Havit, A.; Martins, J.L.; Pinto, V.P.; Goncalves, R.B.; Cavada, B.S. In vitro inhibition of Streptococci binding to enamel acquired pellicle by plant lectins. J. Appl. Microbiol. 2006, 101, 111–116. [CrossRef] [PubMed]

117. Wu, J.G.; Peng, W.; Yi, J.; Wu, Y.B.; Chen, T.Q.; Wong, K.H.; Wu, J.Z. Chemical composition, antimicrobial activity of flavonoids and triterpenes isolated from the extracts of Ficus sansibarica (seed) extract interferes with quorum sensing regulated traits and biofilm formation in the strains of Pseudomonas aeruginosa and Aeromonas hydrophila. Evid. Based Complement. Altern. Med. 2015, 2015, 879540. [CrossRef] [PubMed]

118. Sianglum, W.; Srimanote, P.; Taylor, P.W.; Rosado, H.; Voravuthikunchai, S.P. Transcriptome analysis of responses to rhodomyrtone in methicillin-resistant Staphylococcus aureus. PLoS ONE 2012, 7, e45744. [CrossRef] [PubMed]

119. Srisuwan, S.; Tongtawe, P.; Srimanote, P.; Voravuthikunchai, S.P. Rhodomyrtone modulates innate immune responses of THP-1 monocytes to assist in clearing methicillin-resistant Staphylococcus aureus. PLoS ONE 2014, 9, e110321. [CrossRef] [PubMed]

120. Visutthi, M.; Srimanote, P.; Voravuthikunchai, S.P. Responses in the expression of extracellular proteins of methicillin-resistant Staphylococcus epidermidis treated with rhodomyrtone. J. Microbiol. 2011, 49, 956–964. [CrossRef] [PubMed]

121. Sianglum, W.; Srimanote, P.; Wonglumsom, W.; Kittinyom, K.; Voravuthikunchai, S.P. Proteome analyses of cellular proteins in methicillin-resistant Staphylococcus aureus treated with rhodomyrtone, a novel antibiotic candidate. PLoS ONE 2011, 6, e16628. [CrossRef] [PubMed]

122. Limsuwan, S.; Trip, E.N.; Kouwen, T.R.; Piersma, S.; Hiranrat, A.; Mahabusarakam, W.; Voravuthikunchai, S.P.; van Dijl, J.M.; Kayser, O. Rhodomyrtone: A new candidate as natural antibacterial drug from Rhodomyrtus tomentosa. Phytomedicine 2009, 16, 645–651. [CrossRef] [PubMed]

123. Chusri, S.; Settharaksa, S.; Chokpaisarn, J.; Limsuwan, S.; Voravuthikunchai, S.P. Thai herbal formulas used for wound treatment: A study of their antibacterial potency, anti-inflammatory, antioxidant, and cytotoxicity effects. J. Altern. Complement. Med. 2013, 19, 671–676. [CrossRef] [PubMed]

124. Chusri, S.; Sompetch, K.; Mukdee, S.; Jansrisewangwong, S.; Srichai, T.; Maneenoon, K.; Limsuwan, S.; Voravuthikunchai, S.P. Inhibition of Staphylococcus epidermidis biofilm formation by traditional Thai herbal recipes used for wound treatment. Evid. Based Complement. Altern. Med. 2012, 2012, 159797. [CrossRef] [PubMed]

125. Sasitorn Chusri, N.C. Wanvalit Thongza-ard, Surasak Limsuwan and Supayan Piyawan Voravuthikunchai, in vitro antibacterial activity of ethanol extracts of nine herbal formulas and its plant components used for skin infections in Southern Thailand. J. Med. Plant Res. 2015, 6, 5616–5623.

126. Chusri, S.; Tongrod, S.; Chokpaisarn, J.; Limsuwan, S.; Voravuthikunchai, S.P. Antagonistic interactions of “Ya-Sa-Marn-Phlae” ethanol extract in combination with topical antiseptics against clinical isolates of Staphylococcus aureus. BioMed Res. Int. 2014, 2014, 867603. [CrossRef] [PubMed]

127. Quave, C.L.; Plano, L.R.; Pantuso, T.; Bennett, B.C. Effects of extracts from Italian medicinal plants on planktonic growth, biofilm formation and adherence of methicillin-resistant Staphylococcus aureus. J. Ethnopharmacol. 2008, 118, 418–428. [CrossRef] [PubMed]

128. Fahimi, S.; Abdollahi, M.; Mortazavi, S.A.; Hajimehdipoor, H.; Abdolghaffari, A.H.; Rezvanfar, M.A. Wound healing activity of a traditionally used poly herbal product in a burn wound model in rats. Iran. Red Crescent Med. J. 2015, 17, e19960. [CrossRef] [PubMed]

129. Awolola, G.V.; Koorbanally, N.A.; Chenia, H.; Shode, F.O.; Bajnath, H. Antibacterial and anti-biofilm activity of flavonoids and triterpenes isolated from the extracts of Ficus sansibarica Warb. subsp. sansibarica (Moraceae) extracts. Afr. J. Tradit. Complement. Altern. Med. 2014, 11, 124–131. [CrossRef] [PubMed]

130. Teka, A.; Rondevaldova, J.; Asfaw, Z.; Demissew, S.; van Damme, P.; Kokoska, L.; Vanhove, W. In vitro antimicrobial activity of plants used in traditional medicine in Gurage and Silti Zones, south central Ethiopia. BMC Complement. Altern. Med. 2015, 15, 286. [CrossRef] [PubMed]
131. Anani, K.; Adjoin, Y.; Ameyah, Y.; Karou, S.D.; Agbonon, A.; de Souza, C.; Gbeassor, M. Effects of hydroethanolic extracts of *Balanites aegyptiaca* (L.) Delile (Balanitaceae) on some resistant pathogens bacteria isolated from wounds. *J. Ethnopharmacol.* 2015, 164, 16–21. [CrossRef] [PubMed]

132. Munyendo, W.L.L.; Orwa, J.A.; Rukunga, G.M.; Bi, C.C. Bacteriostatic and bactericidal activities of *Aspilia mossambicensis*, *Ocimum gratissimum* and *Toddalia asiatica* extracts on selected pathogenic bacteria. *Res. J. Med. Plant* 2011, 5, 717–727. [CrossRef]

133. Okoli, C.O.; Akah, P.A.; Okoli, A.S. Potentials of leaves of *Aspilia africana* (Compositae) in wound care: An experimental evaluation. *BMC Complement. Altern. Med.* 2007, 7, 24. [CrossRef] [PubMed]

134. Palombo, E.A.; Semple, S.J. Antibacterial activity of Australian plant extracts against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). *J. Basic Microbiol.* 2002, 42, 444–448. [CrossRef]

135. Sadgrove, N.J.; Jones, G.L. A possible role of partially pyrolysed essential oils in Australian Aboriginal traditional ceremonial and medicinal smoking applications of *Eremophila longifolia* (R. Br.) F. Muell (*Scrophulariaceae*). *J. Ethnopharmacol.* 2013, 147, 638–644. [CrossRef] [PubMed]

136. Hobby, G.H.; Quave, C.L.; Nelson, K.; Compadre, C.M.; Beenken, K.E.; Smeltzer, M.S. *Quercus cerris* extracts limit *Staphylococcus aureus* biofilm formation. *J. Ethnopharmacol.* 2012, 144, 812–815. [CrossRef] [PubMed]

137. Holler, J.G.; Sondergaard, K.; Slotved, H.C.; Guzman, A.; Molgaard, P. Evaluation of the antibacterial activity of Chinese plants traditionally used for wound healing therapy against multidrug-resistant *Staphylococcus aureus*. *Planta Med.* 2012, 78, 200–205. [CrossRef] [PubMed]

138. Edmondson, M.; Newall, N.; Carvile, K.; Smith, J.; Riley, T.V.; Carson, C.F. Uncontrolled, open-label, pilot study of tea tree (*Melaleuca alternifolia*) oil solution in the decolonisation of methicillin-resistant *Staphylococcus aureus* positive wounds and its influence on wound healing. *Int. Wound J.* 2011, 8, 375–384. [CrossRef] [PubMed]

139. Sherry, E.; Boeck, H.; Warnke, P.H. Percutaneous treatment of chronic MRSA osteomyelitis with a novel plant-derived antiseptic. *BMC Surg.* 2001, 1, 1. [CrossRef] [PubMed]

140. Shrestha, G.; Raphael, J.; Leavitt, S.D.; St Clair, L.L. Evidence for a clonal origin of methicillin resistance in *Staphylococcus aureus* MRSA and vancomycin-resistant enterococci (VRE). *J. Basic Microbiol.* 2015, 56, 124–130. [CrossRef] [PubMed]

141. Wu, X.; Santos, R.R.; Fink-Gremmels, J. Analyzing the antibacterial effects of foods ingredients: Model experiments with allicin and garlic extracts on biofilm formation and viability of *Staphylococcus epidermidis*. *Food Sci. Nutr.* 2015, 3, 158–168. [CrossRef] [PubMed]

142. Viswanathan, V.; Phadatare, A.G.; Mukne, A. Antimycobacterial and antibacterial activity of *Allium Sativum* bulbs. *Indian J. Pharm. Sci.* 2014, 76, 256–261. [PubMed]

143. Santiago, C.; Lim, K.H.; Loh, H.S.; Ting, K.N. Inhibitory effect of *Duabanga grandiflora* oil solution in the decolonisation of methicillin-resistant *Staphylococcus aureus* positive wounds and its influence on wound healing. *Int. J. Mol. Sci.* 2016, 17, 617. [CrossRef]

144. Kreiswirth, B.; Kornblum, J.; Arbeit, R.D.; Eisner, W.; McGeer, A.; Low, D.E.; Novick, R.P. Evidence for a clonal origin of methicillin resistance in *Staphylococcus aureus*. *Science* 1993, 259, 227–230. [CrossRef] [PubMed]

145. Bharate, J.B.; Singh, S.; Wani, A.; Sharma, S.; Joshi, P.; Khan, I.A.; Kumar, A.; Vishwakarma, R.A.; Bharate, S.B. Discovery of 4-acetyl-3-(4-fluorophenyl)-1-(p-toly)-5-methylpyrrole as a dual inhibitor of human P-glycoprotein and *Nor A* efflux pump. *Org. Biomol. Chem.* 2015, 13, 5424–5431. [CrossRef] [PubMed]

146. Costa, S.S.; Viveiros, M.; Amaral, L.; Couto, I. Multidrug Eflux Pumps in *Staphylococcus aureus*: An Update. *Open Microbiol. J.* 2013, 7, 59–71. [CrossRef] [PubMed]

147. White, R.J.; Cutting, K.; Kingsley, A. Topical antimicrobials in the control of wound bioburden. *Ostomy Wound Manag.* 2006, 52, 26–58. [CrossRef]

148. Dai, T.; Huang, Y.Y.; Sharma, S.K.; Hashmi, J.T.; Kurup, D.B.; Hamblin, M.R. Topical antimicrobials for burn wound infections. *Recent Pat. Anti-Infect. Drug Discov.* 2010, 5, 124–151. [CrossRef] [PubMed]

149. Barajas-Nava, L.A.; Lopez-Alcalde, J.; Roque i Figuls, M.; Sola, I.; Bonfill Cosp, X. Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst. Rev.* 2013, 6, CD008738. [PubMed]

150. Guthrie, K.M.; Agarwal, A.; Tackes, D.S.; Johnson, K.W.; Abbott, N.L.; Murphy, C.J.; Czuprynski, C.J.; Kierski, P.R.; Schurr, M.J.; McAnulty, J.F. Antibacterial efficacy of silver-impregnated polyelectrolyte
multilayers immobilized on a biological dressing in a murine wound infection model. *Ann. Surg.* 2012, 256, 371–377. [CrossRef] [PubMed]

151. Wang, Y.L.; Yu, Q.H.; Chen, S.K.; Wang, Y.H. *In-vitro* activity of honey and topical silver in wound care management. *Drug Res.* 2015, 65, 592–596. [CrossRef] [PubMed]

152. Sun, W.; Qu, D.; Ma, Y.; Chen, Y.; Liu, C.; Zhou, J. Enhanced stability and antibacterial efficacy of a traditional Chinese medicine-mediated silver nanoparticle delivery system. *Int. J. Nanomed.* 2014, 9, 5491–5502.

153. Murugan, K.; Senthilkumar, B.; Senbagam, D.; Al-Sohaibani, S. Biosynthesis of silver nanoparticles using *Acacia* leucophloea extract and their antibacterial activity. *Int. J. Nanomed.* 2014, 9, 2431–2438.

154. Glasser, J.S.; Guymon, C.H.; Mende, K.; Wolf, S.E.; Hospenthal, D.R.; Murray, C.K. Activity of topical antimicrobial agents against multidrug-resistant bacteria recovered from burn patients. *Burns* 2010, 36, 1172–1184. [CrossRef] [PubMed]

155. Boot, J.R. Antibiotic resistance and topical treatment. *Br. Med. J.* 1978, 2, 649–650.

156. Heal, C.F.; van Driel, M.L.; Lepper, P.D.; Banks, J.L. Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. In *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2014.

157. Lipsky, B.A.; Hoey, C. Topical antimicrobial therapy for treating chronic wounds. *Clin. Infect. Dis.* 2009, 49, 1541–1549. [CrossRef] [PubMed]

158. Lundberg, C.V.; Frimodt-Moller, N. Efficacy of topical and systemic antibiotic treatment of meticillin-resistant *Staphylococcus aureus* in a murine superficial skin wound infection model. *Int. J. Antimicrob. Agents* 2013, 42, 272–275. [CrossRef] [PubMed]

159. Lipsky, B.A.; Holroyd, K.J.; Zasloff, M. Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: A randomized, controlled, double-blinded, multicenter trial of pexiganan cream. *Clin. Infect. Dis.* 2008, 47, 1537–1545. [CrossRef] [PubMed]