

Effect of medicinal plants on methicillin-resistant *Staphylococcus aureus* (MRSA) strains in Iran

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Abstract

Nowadays, about 44% of nosocomial infections worldwide are caused by MRSA ([Methicillin-resistant *Staphylococcus aureus*](#)). *Staphylococcus aureus* is one of the most common bacteria causing nosocomial infections in infectious diseases such as endocarditis, osteomyelitis and food poisoning. By using antibiotic resistance, antibiotics fight against pathogenic germs. They resist against these drugs by the mutation; new generations come to existence that cannot be fought. This study is a systematic review and requires the results of articles in the field under study, so all data used in this study are collected from valid scientific databases.

Keywords: Medicinal plants, *Staphylococcus aureus*, MRSA

INTRODUCTION

The emergence of MRSA has challenged public health programs and has led to major deaths and infections worldwide; so, infections caused by this pathogen and related problems require special attention [1, 2]. It is estimated that about 44% of nosocomial infections worldwide are caused by MRSA [3, 4]. The health care funding, including post-discharge treatment costs, and the costs of hospitalization and medication used to fight the pathogen, is high [5]. *Staphylococcus aureus* is one of the most common bacteria causing nosocomial infections in infectious diseases such as endocarditis, osteomyelitis and food poisoning. With the presence of beta-lactam-resistant *Staphylococcus aureus*, a new penicillin antibiotic called methicillin was prepared; unfortunately, the methicillin-resistant *Staphylococcus aureus* strains were isolated very early from patients [6, 7].

Staphylococcus aureus is resistant to methicillin. The existence of complicated and intelligent mechanisms that induce bacterial resistance has led to the problem of bacterial resistance to antibiotics, a problem that has challenged the treatment systems in recent decades. Therefore, finding new antimicrobial compounds with the least side effects is a subject that has always been of interest to researchers. Species of medicinal herbs that exist in different geographical areas and have medicinal effects on pathogens are of interest. Because of their inherent nature, plants need to have specific defense mechanisms and endogenous antimicrobial compounds, so they can be a great potential source of antimicrobial compounds. Accordingly, many studies have been conducted in our country on the effect of medicinal

plants on methicillin-resistant *Staphylococcus* strains, but no systematic and review study exist on this field. Regarding the importance of antibiotic resistance and very slow speed in discovering and introducing new antibiotics, we aimed in this study to investigate systematically the effects of medicinal plants against methicillin-resistant *Staphylococcus aureus*. We intend to introduce the most effective herbal remedies in the field for subsequent studies, studies of the mechanism of effect and other studies like clinical trials.

Therefore, the main purpose of this study was to investigate the effect of medicinal plants on methicillin-resistant *Staphylococcus aureus* (MRSA) strains in Iran.

In this study, we systematically review the studies done to answer the question of the effect of medicinal plants on

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methicillin-resistant *Staphylococcus aureus* (MRSA) strains. We used the articles whose full texts are published in reputable databases of medical articles such as pubmed, cochrane library, EMBASE, MEDLINE and Persian-language databases such as Iran Medex using keywords herbal medicine, *Staphylococcus*, Methicillin, Medicinal Plants and Resistance, *Staphylococcus* and medicinal plant. We attempted to refer to full-text articles or to mention to the effect of one or more medicinal plants on methicillin-resistant *Staphylococcus aureus*. We excluded the articles that were as case report studies or studies that were merely abstracts of the paper, or whose results were published in both Farsi and English, with the same results. The case studies include full text of all relevant articles in the field under study that are extracted from various sources based on appropriate keywords. Statistical and scientific analysis of all researches is done with SPSS software.

Staphylococcus aureus has acquired multiple resistance to a wide range of antibiotics including beta-lactam, aminoglycosides, tetracyclines, fluoroquinolones and macrolides. Therefore, a limited number of antibiotics are currently available as anti-staphylococcal drugs such as vancomycin, ticoplanin and linsolide. Observations of methicillin-resistant *Staphylococcus aureus* strains during a year after introducing methicillin introduction in 1961 were reported from among the clinical samples of European hospitals. Now these resistant strains are spread all over the world. According to existing reports, the frequency of methicillin-resistant *Staphylococcus aureus* strains in East Asian countries such as China, Korea, and Taiwan is more than 70%, in North America more than 50%, in Europe 20% and in Iran approximately 50% [8].

The minimum inhibitory concentration that inhibits the growth of microorganisms is MIC (Minimum Inhibitory Concentration) and the minimum bactericidal concentration that can kill microorganisms is called MBC (Minimum Bactericidal Concentration). Many studies have investigated the minimum inhibitory and bactericidal concentrations of MRSA strains.

There are also various questions about the frequency distribution of the studied plants on methicillin-resistant *Staphylococcus aureus*, the antibiotic resistance of *Staphylococcus aureus* isolates, the frequency distribution of methicillin-resistant *Staphylococcus aureus* isolates determining MIC of medicinal plants affecting methicillin-resistant *Staphylococcus aureus* and MBC of medicinal plants affecting methicillin-resistant *Staphylococcus aureus*; various researches have answered these.

Motevasel et al. conducted a study in 2013 in Shiraz, aimed at investigating the effect of *Zataria multiflora* on methicillin-resistant *Staphylococcus aureus* (MRSA). They showed that in 75 methicillin-resistant isolates of this bacterium, the minimum inhibitory concentration (MIC) of the extract,

which inhibited the growth of MRSA strains, varied from 2 to 39 $\mu\text{g} / \text{ml}$. The extract was able to inhibit the growth of *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* and methicillin-sensitive *Staphylococcus aureus* at concentrations of 8 to 16 $\mu\text{g} / \text{ml}$. The extract was also able to kill 62.6% of the tested MRSA isolates at a concentration of 512 $\mu\text{g} / \text{ml}$ (MBC). The extract of thyme can inhibit the growth of the aforementioned bacteria, and the bactericidal effect of thyme extract is less than its inhibitory effect on MRSA bacteria [9].

In a 2014 study done by Motamedi et al. in Kermanshah in 2014, with the aim of investigating the effect of *Teucrium polium* extract as a native antibacterial plant against 50 MRSA strains, they found that *Teucrium polium* extract has significant inhibitory effect against MRSA isolates even at the lowest concentration. *MecA* and *pvl* negative strains were more sensitive to methanol extract but the presence of *mecA* had no significant effect on their resistance. Based on these results and the increasing trend of hospital-acquired *Staphylococcus aureus* infections, we can state that *Teucrium polium* is an effective medicinal plant for the treatment of infections caused by this bacterium and can be used as a natural source of new antibiotic production [10].

Dadgar et al. (2007) in Gorgan studied the effects of 20 medicinal plants on methicillin-resistant and susceptible *Staphylococcus aureus*. Among the 20 plants under study, ethanolic extract of 8 plants of *Eucalyptus*, *Peganum harmala*, *Artemisia*, *Nigella Sativa*, *Barberry*, *Hypericum perforatum*, *Pomegranate* and *tamarisk* in disk-diffusion method showed the best anti-staphylococcal effect with respect to the inhibition zone, so that their maximum mean inhibition zone was 22.4 mm. The lowest MIC of these plants was 1% mg / ml for pomegranate. Also, in most cases, the inhibition zone of the plants under study was more in methicillin-resistant strains than sensitive ones. This study showed that *Artemisia*, *Barberry*, *Eucalyptus*, *Peganum harmala*, *Artemisia*, *Nigella Sativa*, *Pomegranate* and *tamarisk* have the most antibacterial effects of MRSA and MSSA strains [11].

Zardoshti et al. in 2015 in Urmia carried out a research entitled evaluating the combined effect of phosphomycin antibiotic and thyme essence on methicillin resistant *Staphylococcus aureus* isolates. Out of 5 methicillin-resistant *Staphylococcus aureus* isolates, 15% of all studied concentrations of phosphomycin were sensitive and 2% were resistant; in total 43.5 isolates were resistant and 56.5% were sensitive to phosphomycin. The isolates were sensitive to different concentrations of thyme essence. In 97.4% of isolates, the synergistic effect was observed between the antibiotic phosphomycin and Thyme essence. Due to the synergistic effect of Thyme essence and the phosphomycin antibiotic on most resistant strains of *Staphylococcus aureus*, further studies may complement the use of these two compounds at least as antimicrobial agents in the formulation of topical compounds [12].

Yadegar et al. conducted a research to investigate and compare the antibacterial effects of ethanolic extract of leaf, flower and root of thyme on methicillin-resistant *Staphylococcus aureus*. They showed that concentrations of 3.31 and 6.62 mg / ml of alcoholic extract of leaves, concentrations of 5.687 and 11.375 mg / ml of ethanolic extract of flower and those of 5.437 and 10.875 mg / ml of alcoholic extract of Thyme root were able to inhibit and kill all three standard and clinical strains, respectively. We did not observe any difference between strains. Although the clinical

application of herbal extracts and essences seems to be valuable due to their less side effects compared to conventional therapeutic agents, we should conduct further researches into the mechanism of action of the effective compounds of this plant on the microbial agents for clinical application of alcoholic extracts of Thyme [13].

By reviewing the texts, we can conclude that the most important variables published in the articles are as follows:

Table 1: Variables used in the texts

Row	Variable	Scale	Role	Practical definition	Unit
1	Bacterial species	Nominal	Principal	A set of strains that share many traits	<i>Staphylococcus aureus</i>
2	Antibiogram	Nominal qualitative	Principal	Performing antibiogram and using CLSI tables	Sensitive, semi-sensitive and resistant
3	MRSA	Nominal qualitative	Principal	Based on oxacillin disk resistance test and PCR	Yes, No
4	Medicinal Plants	Nominal	Principal	A collection of different herbs that have medicinal effects on bacterial pathogens	Name of plant under study
5	Extraction method	Nominal qualitative	Principal	Different methods by which extracts of plants are extracted	Soaking, Percolation, Soxhlet, ...
6	MIC	Nominal qualitative	Principal	Minimum inhibitory concentration that can inhibit the growth of germs	Micrograms per milliliter
7	MBC	Nominal qualitative	Principal	Minimum lethal concentration that can kill germs	Micrograms per milliliter

CONCLUSION

The existence of complicated and intelligent mechanisms that induce bacterial resistance has led to the problem of bacterial resistance to antibiotics, a problem that has challenged the treatment systems in recent decades. Therefore, finding new antimicrobial compounds with the least side effects is a subject that has always been of interest to researchers. Because of their inherent nature, plants need to have specific defense mechanisms and endogenous antimicrobial compounds, so they can be a great potential source of antimicrobial compounds [14, 15]. Since Iran has unique resources in terms of vegetation and herbal diversity and Iranian traditional medicine is one of the richest and most prestigious traditional herbal medicine in the world, any study on the medicinal herbs and their therapeutic properties is one of the important things that can be done in this regard. Accordingly, many studies have been conducted in our country on the effect of medicinal plants on methicillin-resistant *Staphylococcus* strains, but no systematic and review study exist on this field. Regarding the importance of antibiotic resistance and very slow speed in discovering and introducing new antibiotics, we aimed in this study to investigate systematically the effects of medicinal plants against methicillin-resistant *Staphylococcus aureus*. We intend to introduce the most effective herbal remedies in the field for subsequent studies, studies of the mechanism of effect and other studies like clinical trials.

The results of this research could provide other researchers with comprehensive information on the effects of various herbal remedies on methicillin-resistant *Staphylococcus aureus* (MRSA). This could help identify high-efficacy herbal remedies for this pathogen, as well as provide information to investigate the mechanism of their effect in clinical trials and so on.

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