European Review for Medical and Pharmacological Sciences 2022; 26: 5553-5561

Antimicrobial mechanisms of traditional Chinese medicine and reversal of drug resistance: a narrative review

B.-G. LIU[1], M. XIE[2], Y. DONG[1], H. WU[3], D.-D. HE[3], G.-Z. HU[3], E.-P. XU[1]

[1]Academy of Chinese Medical Sciences, [2]College of Traditional Chinese Medicine, Henan University of Chinese Medicine, Zhengzhou, China
[3]College of Veterinary Medicine, Henan Agricultural University, Zhengzhou, China

B.-G. Liu and M. Xie contributed equally to this work

Abstract. – OBJECTIVE: In recent years, the extensive use of antibiotics worldwide has led to an increase in the number of drug-resistant bacterial strains, thus resulting in an increasingly severe degree of bacterial resistance. For thousands of years, traditional Chinese medicine (TCM) has provided natural and unique advantages in the treatment of infectious diseases. Therefore, it is important to develop further and use TCM to treat clinical infections caused by drug-resistant bacteria.

MATERIALS AND METHODS: A literature search was performed using PubMed, Web of Science, Google Scholar, and the China National Knowledge Infrastructure databases. The articles were analyzed to extract information on the antimicrobial effects of Chinese herbal medicines, compounded Chinese medicines, monomeric compounds of herbal origin, and the combined use of Chinese medicine and antimicrobial drugs and to determine the synergistic effect of the combination of Chinese medicine and antibiotics, as well as investigate the possibility of restoring the antibiotic sensitivity of drug-resistant strains.

RESULTS: The mechanisms underlying the antibacterial properties of TCM involve altering membrane permeability, inhibiting protein and nucleic acid synthesis, inhibiting enzyme activity *in vivo*, and controlling the ability of pathogenic bacteria. In addition, the mechanism underlying TCM-induced reversal of bacterial drug resistance is discussed, particularly in terms of the elimination of resistant (R) plasmids and the inhibition of extended-spectrum β-lactamases, bacterial biofilm formation, and bacterial efflux pump activity.

CONCLUSIONS: This paper reviewed the recent relevant literature on antimicrobial action and its mechanisms, as well as the mechanisms of drug resistance reversal by TCM to provide a reference for clinical drug use, prevention and control of bacterial infection, and research and development of new drugs.

Key Words:
Traditional chinese medicine, Antibacterial, Bacterial resistance, Extended-spectrum β-lactamases, Drug-resistant bacterial infection.

Introduction

Due to the excess use of antibiotics in clinical practice, the emergence of drug-resistant bacteria has accelerated. The World Health Organization (WHO) has listed bacterial drug resistance as a major public health problem and called for joint actions to contain it[1]. Bacterial drug resistance refers to the decrease in the susceptibility of bacteria to drugs after repeated contact with the drug, such as the drug efficacy to combat bacterial infections is reduced or even nullified. Bacteria can rapidly mutate to survive under the indirect induction of antibiotic use, consequently, the continuous emergence of newly mutated pathogens and the spread of this resistance to different species pose a great threat to human health. With the unreasonable use of antibiotics, multidrug resistant (MDR) bacteria, including "superbacteria", developed gradually and their number increased[2-4]. Therefore, it is necessary to find effective and easy methods to counteract drug resistance. However, developing new anti-infective drugs is difficult, it is a great investment, and can be time consuming. If the alarming development

Corresponding Authors: Bao-Guang Liu, Ph.D, e-mail: liubaoguang83@sina.com
Er-Ping Xu, Ph.D, e-mail: xuerping0371@163.com

of bacterial resistance is not effectively controlled, infectious diseases that could be easily treated will threaten the human population again in the future. Therefore, finding effective drugs or alternative methods to treat drug-resistant bacterial infections is urgently required[5,6].

In recent years, many researchers[7-9] have faced severe challenges associated with drug-resistant bacteria in clinical treatments; therefore, they have turned their attention to TCM, hoping to find alternative treatments to address the issue of bacterial resistance. For thousands of years, TCM has been used for disease control and prevention. TCM is characterized by many components and multiple targets, and it has the advantages of sources, fewer side effects, and shows good prospects in antibacterial effect. For these reasons, TCM is believed to be an important source for the screening and development of new anti-infective drugs in the future[7,8]. TCM and its compounds can inhibit drug-resistant bacteria, improve bacterial resistance, moreover, it can improve the human body's resistance to disease. TCM plays an important role in the treatment of drug-resistant bacterial infections through its multitarget and multiroute properties[9]. During the research and development of new drugs, some TCM monomers, or compounds were found to be quite efficient in alleviating and treating infectious diseases, and some TCM have become an important material in the research and development of novel drugs[10,11].

In this context, this paper reviewed the mechanisms underlying the antimicrobial action of and reversal of drug resistance by TCM to obtain a theoretical reference for the clinical prevention and control of infection and the development of new drugs.

Materials and Methods

A literature search was performed using PubMed, Web of Science, Google Scholar, and the China National Knowledge Infrastructure databases. The articles were analyzed to extract information on the antimicrobial effects of Chinese herbal medicines, compounded Chinese medicines, monomeric compounds of herbal origin, and the combined use of Chinese medicine and antimicrobial drugs and to determine the synergistic effect of the combination of Chinese medicine and antibiotics as well as investigate the possibility of restoring the antibiotic sensitivity of drug-resistant strains.

Antibacterial Effect of TCM

Antibacterial Action of Chinese Herbal Medicines

There are 879 types of Chinese herbal medicines that show certain antibacterial effects *in vivo* or *in vitro* tests. *Coptis chinensis*, *Scutellaria baicalensis* and *honeysuckle* are the first three kinds of antibacterial activity[12]. Previous studies[13-15] found that TCM showed a certain antibacterial effect in clinical tests for intestinal pathogenic bacteria. For example, *Coptis chinensis*, *phellodendri*, *Scutellaria baicalensis*, *forsythia*, *pomegranate peel*, *purslane*, *Schisandra chinensis*, *honeysuckle*, *radix paeoniae paeoniae*, *Qinpi*, and others, have good antibacterial properties against *Escherichia. coli*, *Shigella*, and *Salmonella*. Moreover, the water and alcohol extracts of *Coptis chinensis* showed a strong antibacterial effect against *Staphylococcus aureus* at a concentration of 0.5 mg/mL[16]. *In vitro* screening of the antibacterial activity of several Chinese medicines revealed that 15 samples, including *Subtilis sativus*, showed good antibacterial activity against the clinically common *S. aureus*, *Bacillus* spp., *Candida albicans,* and *Pseudomonas aeruginosa*[17]. TCM can also be potentially applied in agriculture, for example, *Cnidium cnidii* and *Forsythia* spp. can inhibit the growth rate of pathogenic bacteria mycelium in diseased kiwifruit by up to 70%, which is of great significance during the storage and transportation of agricultural products[18]. At the same time, it impedes the development of drug resistance, therefore, TCM has a good application prospect in the resistance to multiple sources of pathogens[19-23].

Generally, the strong antimicrobial effect of TCM, such as *radix scutellariae*, rhizoma coptidis, radix et rhizoma rhei. With the expansion of research on TCM in recent years, some of TCM also have certain antibacterial function, such as *astragalus membranaceus*, *salvia miltiorrhiza*, and radix paeoniae alba. These drugs provide a guarantee for the clinical treatment of infectious diseases.

Antibacterial Effect of Compounded Chinese Medicines

The compatibility of different TCM treatments with antibacterial effects can enhance these effects. Previous studies[24] have revealed that the antibacterial activity of *Scutellaria baicalensis* and *dandelion* combined with *Artemisia argyi* leaves is better than the antibacterial effect against

hemolytic Streptococcus when used alone. The combined application of *Coptis chinensis, Scutellaria baicalensis*, and *phellodendri* not only has a strong inhibitory effect on *P. aeruginosa* and MDR *E. coli*, but it can also downregulate the levels of inflammatory factors in the serum of rats and improve immunity[25,26]. Compounded Chinese medicines DC shows good inhibitory effect on standard *E. coli* and ESBLs producing *E. coli in vitro* and *in vivo*, and it also has anti-inflammatory effect on infected mice[27]. They are characterized by multiple components, targets, and pathways and their antibacterial effect is not only represented by the direct inhibition of bacteria but also associated with the inhibition of inflammatory response and regulation of immune response.

Antibacterial Effect of Monomeric Compounds of Herbal Origin

Recently, various technologies, such as supercritical fluid extraction, and enzymatic hydrolysis, have been applied to extract different monomeric compounds of herbal origin[28]. A large number of studies have indicated that the effective components responsible for TCM's antibacterial activity mainly include flavonoids, alkaloids, terpenes, coumarins, and polysaccharides. Berberine has a certain inhibitory effect on various microorganisms, such as *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*. Studies[29] have shown that the inhibitory effect of berberine varies in different bacteria, particularly, the effect is stronger on gram-positive bacteria than on gram-negative bacteria *in vitro*.

The results of studies on the *in vitro* antifungal properties of various Chinese medicine monomers against *Sporotrichia globosa*, revealed that this fungus is highly sensitive to allicin, a lesser degree, to paeonol, matrine, and osthol[30]. It has been found[31] that naringin can be used as a food preservative as it inhibits biofilm formation, especially those formed by the food-borne *Pseudomonas* spp., suggesting that TCM has a broad application in the treatment of biofilm-associated infections.

Antibacterial Effect of Chinese Medicine Combined with Antibacterial Drugs

TCM and TCM compounds in combination with antibacterial drugs can not only inhibit the growth of microorganisms but also reverse the resistance of some drug-resistant strains. The combination of eugenol and colistin was used to conduct antibacterial tests on clinically isolated *E. coli*, and this combination showed synergistic antibacterial activity, suggesting that eugenol can aid in the prevention and control of colistin-resistant *E. coli*[32]. Furthermore, scholars[33] have found that the combination of TCM and antibiotics showed good infection control in patients suffering from severe burns, reducing the probability of drug-resistant strains. We examined the berberine, quercetin, baicalin monomers and antimicrobial drug combination of drug resistance of *Acinetobacter* and the results revealed that the three TCM monomers were combined with imipenem, meropenem, and tigecycline, the MIC values of each monomer and antibacterial drugs were decreased, and the biofilm formation of the drug-resistant *Acinetobacter* were inhibited. Experimental results also showed that the combination of TCM and antibiotics, could restore the sensitivity of drug-resistant bacteria to antibiotics, which is of great significance for guiding clinical drug use[34].

Mechanisms of TCM's Antimicrobial Action

Modification of Cell Membrane Permeability

Bacterial cell membrane integrity is important for the maintenance of the cell's normal life activities. For example, if the integrity of the cell membrane and cell wall is compromised, the growth, development, and reproduction of bacteria will be affected, leading to bacterial death. *Radix isatidis*, bergamot water decoctions, bergamot essential oil, and hesperidin were used to test MIC and minimum bactericidal concentration (MBC) for *E. coli*, *S. aureus*, *P. aeruginosa,* and *B. subtilis*. Moreover, the extracellular relative contents of soluble protein and nucleic acid were tested, and the results revealed that hesperidin active ingredients (bergamot) had the lowest MIC and MBC for *S. aureus*, and its growth was the slowest. Further, the extracellular soluble protein and nucleic acid levels increased, suggesting that hesperidin acts by changing the permeability of the bacterial cell membrane[35]. In addition, studies[36,37] have found that both carvacrol and cinnamaldehyde can destroy bacterial cell membranes and exudate bacterial cytoplasmic contents.

Inhibition of Protein and Nucleic Acid Synthesis

Proteins are the basic material of life and are largely responsible for life activities. Without

proteins, there would be no life. All the important components of bacteria have the participation of protein, and protein synthesis is regulated by nucleic acids. Blocking this process, or denaturating and inactivating proteins can destroy bacterial functions. According to relevant studies[38], the content of cellular soluble proteins in *Girardinia suborbiculata* ethanol extract (GSEE) treatment decreased markedly compared with that in the control group; in addition, GSEE had a significant inhibitory effect on the synthesis of cellular nucleic acid. It is speculated that its antibacterial mechanism may be achieved by inhibiting the expression of soluble protein and synthesis of nucleic acid of the bacteria[38].

Inhibition of Enzyme Activity

DNA topoisomerase is a key enzyme in the regulation of nucleic acid metabolism that can catalyze DNA strand expansions and breaks, and complete DNA replication, transcription, and other processes. On investigating the antibacterial mechanism of eugenol and thymol against *Candida*, it was found that these compounds could inhibit H^+-ATP and turn the intracellular environment acidic, thus causing cell death. The ATP molecule also represents a source of energy. The inhibition of ATP synthase affects bacterial metabolic processes and consequently bacterial growth[39]. A study[40] on the inhibitory activity of luteolin against *S. aureus*, and its mechanism revealed that when the concentration of luteolin was 1.6 mg/mL, the activities of topoisomerases I and II were completely inhibited, and when the concentration was >0.8 g/L, the bacteria DNA was directly broken, thus affecting the synthesis of nucleic acids.

Control of Bacterial Pathogenicity

The pathogenicity of bacteria depends on the pathogenic agents they secrete, which can cause direct damage to host tissues or assist in invading the body and evading the body's immune response[41]. The quorum sensing system (QS) property of bacteria is considered to be a hub within which the regulation of bacterial pathogenicity occurs through the control of the expression of pathogenic factors and of biofilm formation. Pathogenic factors can lead to a number of infection-related symptoms in the body, whereas the formation of biofilm strengthens the survival and transmission ability[42]. Relevant reports have revealed that, they established a screening system that can detect small molecular inhibitors of the QS through the amount of cell growth. By detecting the level of inhibition produced by three Chinese medicines on the QS of *P. aeruginosa*, the results showed that these medicines had different effects on different pathogenic genes regulated by the QS[43]. Another study[44] found that the Chinese herb *Scubbella* had a certain inhibitory effect on the expression of the QS system-related genes of *P. aeruginosa* and could also affect the movement of bacteria. In short, Chinese medicine can regulate the QS of bacteria and weaken their pathogenic ability.

Bacterial Resistance and Current Status

Bacterial resistance involves inherent and acquired resistance. When bacteria are exposed to an environment containing antibacterial drugs for a long time, sensitive bacteria are eliminated, whereas those with inherent or acquired resistance continue to survive and spread. At present, the emergence of drug-resistant strains and multi-resistant strains, and even the emergence of superbacteria, has resulted in antibacterial drugs losing their original antibacterial effects, which in turn affects clinical drug use[45,46]. It is clear that antimicrobial resistance is now a critical challenge for the treatment of microbial diseases[47]. In addition, antimicrobials are widely used in animal husbandry, and high doses or irrational use leads to the rapid spread of antibiotic-resistant genes and resistant bacteria in various environmental microbial communities[48].

In 2013, the WHO published a global antimicrobial resistance monitoring report, including information on multiple drug-resistant bacteria in Europe and the United States (mainly including *E. coli*, *S. aureus*, *K. pneumoniae*, *Enterococcus*, *S. pneumoniae*, and *P. aeruginosa*) that cause infection and lead to high death tolls[49]. However, CHINET bacterial resistance monitoring results in China showed that the rate of drug resistance of clinical isolates to commonly used antibacterial drugs is increasing and, in particular, the resistance of gram-negative bacteria is more serious. Infections by drug-resistant bacteria have become a major threat to human health and negatively impact disease prevention and treatment[50].

Mechanisms Through which Chinese Medicine Reverses Drug Resistance

Elimination of Resistance Plasmids

Drug-resistant plasmids, also known as plasmids, are present in drug-resistant strains and

can lead to the development of drug resistance. These plasmids can be transmitted to the progeny through replication, they can also be passed between strains through horizontal transfer[51]. Studies have found that the sensitivity of drug-resistant bacteria to antibiotics can be restored to a certain extent through the action of TCM. Compound preparations of dandelion, diplod, and honeysuckle can restore the sensitivity of *S. aureus* to penicillin, ampicillin, and amoxicillin, and eliminate drug-resistant plasmids[52]. Another study[53] found that the drug-resistant plasmid of *E. coli* could be eliminated at a rate of nearly 70% by ethanol extract derived from *Artemisia argyi* leaves. In addition, *rhubarb*, *Scutellaria baicalensis*, *Coptis chinensis*, and other TCM compounds have been reported to be effective, to a certain degree, in eliminating drug-resistant plasmids[54,55]. Compared with the results of previous experiments, different Chinese medicines were found to have different effects in terms of eliminating bacterial resistance. Moreover, the plasmid elimination rate of the same Chinese medicines for the same drug-resistant bacteria was not completely identical, which may be because of the difference between the bacterial strains or the different mechanisms of drug resistance. Although several studies have confirmed that TCM can eliminate drug-resistant plasmids, its underlying mechanism of action remains unclear and needs further investigation.

Inhibition of Extended-Spectrum β-lactamases

Bacterial production of β-lactamases is the main cause of bacterial resistance to β-lactamide antibiotics[56]. Currently, the use of novel β-lactamase inhibitors can restore the sensitivity of some β-lactamase-producing resistant strains to β-lactamase antibiotics[57], and research is being conducted to identify these molecules. It has been found that Shuanghuanglian and Qingkailing, two antipyretic and detoxifying TCM compounds, can eliminate the drug-resistant plasmid of extended-spectrum β-lactamases (ESBLs) and inhibit the activity of β-lactamase[58]. Decontions of HuanglianJiedu decoction, Sanhuang decoction, and Wuwei disinfection decoction can inhibit the activity of ESBLs, which is an important mechanism for reducing bacterial resistance[59]. Therefore, in light of the current challenge posed by the increasingly severe bacterial drug resistance, TCM can be considered for the treatment of ESBL-producing bacterial infections.

Inhibition of Bacterial Biofilm Formation

The formation of bacterial biofilm is a major reason why antimicrobial treatments for bacterial infection fail[60,61]. Bacterial biofilm formation is complex and dynamic and includes the following main phases: initial bacterial adhesion, formation of microcolonies, continuous aggregation of microcolonies, maturation of biofilm, and release of biofilm bacteri[62]. The biofilm resistance mechanism is complex and may be associated with the osmotic barrier, nutrient restriction, expression of specific resistance genes, QS, and immune escape[63-65]. A large number of studies[66,67] have shown that monomers, such as berberine, allicin, TCM extracts such as that of *Euphorbia* burnet, Tanreqing compound[68], and HuanglianJiedu decoction[69] can interfere with the formation of bacterial biofilm, and ultimately reverse drug resistance.

Bacterial Inhibition Via Active Efflux Pump

The efflux pump system of bacteria is an important mechanism for the emergence of drug resistance. Efflux pumps, a type of protein in the cell membrane, can discharge the antibiotic drugs entering bacteria, thus causing them to develop drug resistance[70]. According to relevant studies[71], the Chinese medicine compounds Tanreqing and meropem, cefoperazone, and ceftazidime have a synergistic antibacterial effect with other antibiotics. In inhibiting the expression levels of bacterial efflux pump genes, the three drugs were compared by the effect: cefoperazone>tanreqing>ceftazidime. Tanreqing, ceftazidime, and cefoperazone can reduce the drug resistance of bacteria by down-regulating the expressions of bacterial efflux pump genes, and reducing the clinical dose of antibiotics, and thus, play a bacteriostatic effect[71].

Conclusions and Future Prospects of Chinese Medicine

At present, due to the irrational use, and even abuse of antibiotics, bacterial drug resistance is becoming increasingly severe, seriously threatening the health of human beings, livestock, and poultry. To better prevent and control various infections caused by bacteria, achieve synergistic effects, and improve curative effects, the combined use of antibiotics in clinical settings should be strengthened. In China, TCM represents a millenary tradition

and is widely used to prevent and treat various infectious diseases. TCM show good antibacterial effects as it can inhibit or kill bacteria, regulate the body's immunity, reduce bacterial resistance, delay or even reverse bacterial resistance, a number of TCM and its compound have a good anti-infection effect. However, due to its relatively slow antibacterial effect and large dosage, TCM should be used in combination with antibiotics. Alternatively, its active components should be extracted, and its chemical structure should be modified to enhance the antibacterial effects[72].

The present study confirmed[9,10] that Chinese herbal medicines, compounded Chinese medicines, and monomeric compounds of herbal origin possess certain antibacterial properties, and that TCM can inhibit pathogenic gene expression and reduce the secretion of pathogenic factors. These characteristics indicate that TCM has certain unique advantages in inhibiting bacterial resistance. Research is now focused on the development of a new generation of TCM antibiotics, for example, from plants[73]. In addition, nanoliposomes have been shown to deliver drug formulations to target bacteria *in vivo* and *in vitro*, and silver nanoparticles can also be synthesized from TCM[74,75]. Based on the clinical applications and existing antibiotics for the treatment of drug-resistant bacteria, the research and development of new antimicrobial agents is time consuming and involves several difficulties. Understanding the effect of traditional medicine on drug-resistant bacteria and evaluating its underlying mechanism can reduce the clinical usage of antibiotics to a certain extent. This approach can reduce the generation of drug-resistant strains by reducing bacterial antibiotic resistance. Therefore, it is necessary to continue with the isolation and detection of resistance of bacteria to understand its pathogenic mechanisms and genetic background and thus lay a theoretical foundation for further research.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Acknowledgements
We thank Xiaoshen Li (South Agricultury University, China) for reading this manuscript and providing helpful feedback.

Funding
This work was supported by grants from the Natural Science Foundation of Henan Province (Grant No. 222300420481), the Henan Post-doctoral Research Project Start-up Funding (Grant No. 19030075), the Henan of Chinese Medicine Special Research Project (Grant No. 2019ZY1019, 2021ZY2144), and the Henan University of Chinese Medicine Research Start-up Funding (Grant No. RSBSJJ2018-11, RSBSJJ2018-32).

Consent for Publication
Not applicable.

Authors' Contribution
BGL and EPX participated in study conception, design, and prepared the manuscript. MX, YD, BGL, WH, DDH, and GZH reviewed the manuscript. BGL and EPX revised the manuscript and coordinated the whole project. All authors read and reviewed the final manuscript.

Ethics Approval and Consent to Participate
Not applicable.

Data Availability Statement
The data supporting the findings of this study are included within the manuscript and its supporting information.

References

1) Klein EY, Boeckel TV, Martinez EM, Pant S, Gandra S, Levin SA. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Nati Acad Sci USA 2018; 115: 3463-3470.
2) Liu BG, Wu H, Zhai YJ, He ZP, Sun HR, Cai T, He DD, Liu JH, Wang SM, Pan YS, Yuan L, Hu GZ. Prevalence and molecular characterization of oqxAB in clinical Escherichia coli isolates from companion animals and humans in Henan Province, China. Antimicrob Resist Infect Control 2018; 7: 18.
3) Deng Y, Liu J, Peters BM, Chen L, Miao J, Li B, Li L, Chen D, Yu G, Xu Z, Shirtliff ME. Antimicrobial resistance investigation on Staphylococcus strains in a local hospital in Guangzhou, china, 2001-2010. Microb Drug Resist 2015; 21: 102-104.
4) Licker M, Anghel A, Moldovan R, Hogea E, Muntean D, Horhat F, Seclaman E, Tamas L, Anghel M, Baditoiu L. Genotype-phenotype correlation in multiresistant Escherichia coli and Klebsiella pneumoniae strains isolated in Western Romania. Eur Rev Med Pharmaco Sci 2015; 19: 1888-1894.

5) Chellat MF, Raguz L, Riedl R. Targeting antibiotic resistance. Angew Chem Int Ed Engl 2016; 55: 6600-6626.
6) Bonomo RA. β-lactamases: A Focus on Current Challenges. Cold Spring Harb Perspect Med 2017; 7: a025239.
7) Stavri M, Piddock LJ, Gibbons S. Bacterial efflux pump inhibitors from natural sources. J Antimicrob Chemother 2007; 59: 1247-1260.
8) Huang M, Tan YQ, Luo J, Shen JY. Antimicrobial Resistance of Chinese Herbal Medicine. Chin J Exper Tradi Form 2018; 24: 218-224.
9) Jia LY, Deng D, Sun LH, Bu JH, Chen ZY, Ye MQ, Zhang W, Fang BJ. Mechanism of traditional Chinese medicine in treating drug-resistant bacterial infection. Chin J Exper Tradi Form 2020; 26: 228-234.
10) Chang CH, Huang WY, Lai CH, Hsu YM, Yao YH, Chen TY, Wu JY, Peng SF, Lin YH. Development of novel nanoparticles shelled with heparin for berberine delivery to treat Helicobacter pylori. Acta Biomater 2011; 7: 593-603.
11) Hsu SC, Chung JG. Anticancer potential of emodin. Biomedicine 2012; 2: 108-116.
12) Wang MY, Shao XX, Li JT, Han W, Ren X, Fu XJ. Study on the distribution law and influence factors of antibacterial activity of Chinese medicine. Nat Prod Res Dev 2020; 32: 2031-2039.
13) Chan BCL, Han XQ, Lui SL, Wong CW, Wang TBY, Cheung DWS, Cheng SW, Ip M, Han SQB, Yang XS, Jolivalt C, Lau CBS, Leung PC, Fung KP. Combating against methicillin-resistant Staphylococcus aureus-two fatty acids from purslane (Portulaca oleraceaL.) exhibit synergistic effects with erythromycin. J Pharm Pharmacol 2015; 67: 107-116.
14) Gu X, Zhou J, Zhou Y, Wang H, Zhao H. Huanglian jiedu decoction remodels the periphery microenvironment to inhibit Alzheimer's disease progression based on the "brain-gut" axis through multiple integrated omics. Alzheimers Res Ther 2021; 13: 1-18.
15) Shi Z, Liu Z, Liu C, Wu M, Su H, Ma X, Zang Y, Wang J, Zhao Y, Xiao X. Spectrum-effect relationships Between chemical fingerprints and antibacterial effects of Lonicerae japonicae Flos and Lonicerae Flos base on UPLC and microcalorimetry. Front Pharmacol 2016; 7: 12.
16) Wang YS, Zhao YN, Zhai YY, Zhang TH, Jiang SN, Yang Y, Wang H. Six kinds of traditional Chinese medicine alcohol extract and water extract on Staphylococcus aureus and Escherichia coli antibacterial effect evaluation. Chin J Vet Med 2020; 56: 62-65.
17) Hu H, Zuo GY, Zhang YP. Screening of antimicrobial activities of 36 Chinese herbal medicines in vitro. Guihaia 2018; 38: 428-440.
18) Lv RH, Lin C, Bai CX, Fang YN, Feng Z, Shi LN, Lv RH, Zhang XR. Isolation, identification of common fungi during kiwifruit storage and screening of antifungal Chinese medicine. J Henan Agric Sci 2020; 49: 78-84.
19) Parameswari P, Devika R, Vijayaraghavan P. In vitro anti-inflammatory and antimicrobial potential of leaf extract from Artemisia nilagirica (Clarke) pamp. Saudi J Biol Sci 2019; 26: 460-463.
20) Zhang F, Ramachandran G, Mothana RA, Noman OM, Alobaid WA, Rajivgandhi G, Manoharan N. Anti-bacterial activity of chitosan loaded plant essential oil against multi drug resistant K. pneumoniae. Saudi J Biol Sci 2020; 27: 3449-3455.
21) Sun MY. Effect of 5 kinds of Chinese Traditional Medicine such as Honeysuckle on antibacterial activity of Pig-derived E. coli. Chin J Vet Drug 2020; 54: 66-70.
22) Hemeg HA, Moussa IM, Ibrahim S, Dawoud TM, Alhaji JH, Mubarak AS, Kabli SA, Alsubki RA, Tawfik AM, Marouf SA. Antimicrobial effect of different herbal plant extracts against different microbial population. Saudi J Biol Sci 2020; 27: 3221-3227.
23) Syed A, Benit N, Alyousef AA, Alqasim A, Arshad M. In-vitro antibacterial, antioxidant potentials and cytotoxic activity of the leaves of Tridax procumbens. Saudi J Biol Sci 2020; 27: 757-761.
24) Li F, Luo KJ, Tang M, He FF, Wang W, Du ZY. Study on the antibacterial effects of Chinese Herbs Medicine in vitro. J Commun Med 2016; 14: 16-17.
25) Yin XL, Bai YC, Li ZP, Zhang LY, Zhao WZ. Biochemical and immune influences of modified three yellow soups on mice inoculated drug-resistant E. coli. J Hebei North Univ (Natural Science Edition) 2016; 32: 12-15.
26) Zhang T, Wu JF, Xiao XY, Deng JY, Li SD, Liu JQ, Cai R. Study on inhibitory effects of multidrug resistant Pseudomonas aeruginosa by Sanhuang Diyu Powder. J Hunan Univ Chin Med 2017; 37: 823-826.
27) Dong BL, Cai YQ, Zhu ZD, Zhu SS, Zhu YJ. Antibacterial effects of Chinese herbal compound DC on standard E. coli and ESBLs producing E. coli in vitro and in vivo. J Guangdong Pharm Univ 2020; 36: 809-814.
28) Ye CL, He S, Cao WL, Zhang ZY. Research progress in new technologies for extraction and separation of Chinese materia medica. Chin Trad Herb Drugs 2015; 46: 457-464.
29) Cernakova M, Kostalova D. Antimicrobial activity of berberine-a constituent of Mahonia aquifolium. Folia Microbiol 2002; 47: 375-378.
30) Qu XY, Li SS, Qu Y, Abdulhakim SN, Song Y, Cui Y. In vitro antifungal susceptibility of 10 Chinese herbal monomers against Sporothrix globosa. Chin J Mycol 2020; 15: 145-149.
31) Husain FM, Perveen K, Qais FA, Ahmad I, El-Sheikh MA. Naringin inhibits the biofilms of metallo-β-lactamases (mβls) producing pseudomonas species isolated from camel meat. Saudi J Biol Sci 2020; 28: 333-341.
32) Wang YM, Kong LC, Liu J, Ma HX. Synergistic effect of eugenol with colistin against clinical isolat-

ed colistin-resistant Escherichia coli strains. Antimicrob Resist Infect Control 2018; 7: 17.

33) Lin M, Lv DK, Zhang JL, Chen FJ. Clinical study on effect of Chinese herbal medicine on severe burn infection and application of antimicrobial agents. New Chin Med 2020; 52: 109-112.

34) Peng Q, Ling BD, Lin F, Yuan HY, Wang QH, Meng QL, Chen H. Research on the effects of traditional Chinese medicine monomer combined with antibacterial drugs Against extensively drug resistant Acinetobacter baumannii. Pharmacol Clin Chin Mater Med 2020; 36: 140-145.

35) Wang XH, Guo R, Nei XB, Chen HM, Zhi WW, Tian ML, Liu F. Antibacterial activity of Citri Sarcodactylis Fructus and its antibacterial mechanism against Staphylococcus aureus. Chin J Antibiot 2021; 46: 437-441.

36) Shen S, Zhang T, Yuan Y, Lin S, Xu J, Ye H. Effects of cinnamaldehyde on Escherichia coli and Staphylococcus aureus membrane. Food Control 2015; 47: 196-202.

37) Mittal RP, Rana A, Jaitak V. Essential oils: an impending substitute of synthetic antimicrobial agents to overcome antimicrobial resistance. Curr Drug Targets 2019; 20: 605-624.

38) Jiang ZX, Peng X, Zhang XL, Zhu L, Li HX, Chen ZB. Studies on antibacterial mechanism of ethanol extract from Girardinia suborbiculata C.J. Chen on Staphylococcus aureus. J Southwest Univ (Natural Science Edition) 2011; 33: 184-188.

39) Ahmad A, Khan A, Yousuf S, Khan LA, Manzoor N. Proton translocating atpase mediated fungicidal activity of eugenol and thymol. Fitoterapia 2010; 81: 1157-1162.

40) Wang Q, Xie MJ. Antibacterial activity and mechanism of luteolin on Staphylococcus aureus. Acta Microbiol 2010; 50: 1180-1184.

41) Yang S, Guo Q, Duan K.M. Perspectives on antibacterial activities of traditional Chinese medicine and its potential mechanisms. Chin J Biochem Pharm 2016; 36: 15-19.

42) Nain Z, Mansur FJ, Syed SB, Islam MA, Karim MM. Inhibition of biofilm formation, quorum sensing and other virulence factors in Pseudomonas aeruginosa by polyphenols of Gynura procumbens leaves. J Biomol Struct Dyn 2021; 39: 1-8.

43) Sun WJ, Wang Y, Shen LX, Duan KM. A novel screening system for Pseudomonas aeruginosa quorum sensing inhibitors. Chin J Biotech 2009; 25: 1173-1179.

44) Xiao J, Shen LX, Zhao L, Wu YT, Duan KM, Guo Q. Inhibition of the quorum sensing system in Pseudomonas aeruginosa PAO1 by Sculellaria barbata. Chin J Antibiot 2014; 39: 885-890.

45) Li XF, Shi HQ, Liang Y, Li J, Jiang B, Song GB. Interaction of biofilm and efflux pump in clinical isolates of carbapenem resistant P. aeruginosa. Eur Rev Med Pharmaco Sci 2022; 26: 1729-1737.

46) Liu BG, Yuan XL, He DD, Hu GZ, Miao MS, Xu EP. Research progress on the oxazolidinone drug linezolid resistance. Eur Rev Med Pharmaco Sci 2020; 24: 9274-9281.

47) Chen L, Wang X. Molecular mechanism of bacterial drug resistance based on embedded system and rapid detection method of drug resistance gene. Microprocess Microsy 2021; 82: 103912.

48) Sazykin IS, Khmelevtsova LE, Seliverstova EY, Sazykina MA. Effect of antibiotics used in animal husbandry on the distribution of bacterial drug resistance (Review). Appl Biochem Microbiol 2021; 57: 20-30.

49) Solomon SL, Oliver KB. Antibiotic resistance threats in the United States: stepping back from the brink. Am Fam Physician 2014; 89: 938-941.

50) Li J, Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, Pan F, Huang WX. Linezolid vs. vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis. Eur Rev Med Pharmaco Sci 2017; 21: 3974-3979.

51) Paul D, Chanda DD, Chakravarty A, Bhattacharjee A. An insight into analysis and elimination of plasmids encoding metallo-β-lactamases in Pseudomonas aeruginosa. J Glob Antimicrob Resist 2020; 21: 3-7.

52) Xiao X, Li YL, Yang R. Elimination test in vitro of complex prescription dandelion's injection on antibiotic-resistant plasmid of Staphylococcus aureus. Chin Vet Sci 2010; 40: 307-311.

53) Ju HT, Han WY, Wang SR, Liang HC, Wang XL, Jiang WZ, Lei LC. Location of resistance gene and elimination of antibiotic plasmids from Escherichia coli. Chin J Vet Sci 2000; 20: 561-564.

54) Shu G, Ma C, Huang C, Huang L, Zhong QQ, Lin JC. The R plasmid curing effects of four different traditional Chinese medical compounds to Escherichia coli and Salmonell. J Henan Agric Sci 2013; 42: 149-153.

55) Yang Q, Shu G, Ma C, Huang C, Zhong QQ, Lin JC. Study on elimination of R plasmids of three kinds of bacteria by single Chinese medicine. Heilongjiang Anim Sci Vet Med 2014; 19: 154-157.

56) Khalifa SM, Abd El-Aziz AMA, Hassan R, Abdelmegeed ES. β-lactam resistance associated with β-lactamase production and porin alteration in clinical isolates of E. coli and K. pneumoniae. Plos One 2021; 16: e0251594.

57) Harakeh S, Azhar EI, Almasaudi S, Kissoyan KB, Fadlallah SM, Tanelian A, Matar GM. Effects of a specific nutrient combination on ESBL resistance. Saudi J Biol Sci 2019; 26: 1576-1580.

58) He M, Wu ZR, Li Y, Cao Y, Tao QC, Zhang RS, Hao SY, Guan S. Influences of Shuanghuanglian Injectable Powder and Qingkailing Injection on R plasmids and β-lactamase of drug-resistant Escherichia coli. J Beijing Univ Trad Chin Med 2012; 35: 105-108.

59) Lu YJ, Cheng N. The enzyme inhibitory effect of traditional Chinese medicine on extended-spectrum lactamases (ESBLs). Chin Hosp. Pharm J 2010; 30: 1097-1100.

60) Alghofaili F. Use of bacterial culture supernatants as anti-biofilm agents against Pseudomonas aeruginosa and Klebsiella pneumoniae. Eur Rev Med Pharmaco Sci 2022; 26: 1388-1397.

61) Lebeaux D, Ghigo JM, Beloin C. Biofilm-related infections: bridging the gap between clinical management and fundamental aspects of recalcitrance toward antibiotics. Microbiol Mol Biol Rev 2014; 78: 510-543.

62) Wang TH, Ling BD. Research progress of traditional Chinese medicine against bacterial biofilm infection. Pharmacol Clin Chin Mater Med 2021; 37: 260-264.

63) Nguyen D, Joshi-Datar A, Lepine F, Bauerle E, Olakanmi O, Beer K, McKay G, Siehnel R, Schafhauser J, Wang Y, Britigan BE, Singh PK. Active starvation responses mediate antibiotic tolerance in biofilms and nutrient-limited bacteria. Science 2011; 334, 982-986.

64) Liao J, Sauer K. The MerR-like transcriptional regulator BrlR contributes to Pseudomonas aeruginosa biofilm tolerance. J Bacteriol 2012; 194: 4823-4836.

65) Djeribi R, Boucherit Z, Bouchloukh W, Zouaoui W, Latrache H, Hamadi F, Menaa B. A study of pH effects on the bacterial surface physicochemical properties of Acinetobacter baumannii. Colloids Surf B Biointerfaces 2013; 102: 540-545.

66) Chen XL, Shang F, Meng YM, Li L, Cui YM, Zhang M, Qi KZ, Xue T. Ethanol extract of Sanguisorba officinalis L. inhibits biofilm formation of methicillin-resistant Staphylococcus aureus in an ica-dependent manner. J Dairy Sci 2015; 98: 8486-8491.

67) Shi C, Li M, Muhammad I, Ma X, Chang Y, Li R, Li CW, He JS, Liu FP. Combination of berberine and ciprofloxacin reduces multi-resistant Salmonella strain biofilm formation by depressing mRNA expressions of luxS, rpoE, and ompR. J Vet Sci 2018; 19: 808-816.

68) Yang WF, Liu JL, Blazekovic B, Sun YN, Ma SH, Ren CY, Vladimir-Knezevic S, Li CH, Xing YJ, Tian GJ, Wang Y. In vitro antibacterial effects of Tanreqing injection combined with vancomycin or linezolid against methicillin-resistant Staphylococcus aureus. BMC Complement Altern Med 2018; 18: 169.

69) Xia F, Zhang YF, Hu GX, Du M, Liao YL, Zhang MW. Inhibitory effects of Huanglian jiedu decoction on Pseudomonas aeruginosa Quorum Sensing System Regulating Virulence Factors and Biofilm. Chin Pharm 2020; 23: 1307-1311.

70) Gbian DL, Omri A. The impact of an efflux pump inhibitor on the activity of free and liposomal antibiotics against Pseudomonas aeruginosa. Pharmaceutics 2021; 13: 577.

71) Li YY, Li XY, Yang WF, Wang Y, He ZM. Effect of Tanreqing injection and antibiotics on multi-drug resistant Pseudomonas aeruginosa efflux pump. Chin J Exp Trad Med Formulae 2020; 26: 92-98.

72) Tegos G, Stermitz FR, Lomovskaya O, Lewis K. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. Antimicrob Agents Chemother 2002; 46: 3133-3141.

73) Siebra ALA, Oliveira LR, Martins AOBPB, Siebra DC, Albuquerque RS, Lemos ICS, Delmondes GA, Tintino SR, Figueredo FG, da Costa JGM, Coutinho HDM, Menezes IRA, Felipe CFB, Kerntopf MR. Potentiation of antibiotic activity by Passiflora cincinnata mast. front of strains Staphylococcus aureus and Escherichia coli. Saudi J Biol Sci 2018; 25: 37-43.

74) Mozafari MR, Torkaman S, Karamouzian FM, Rasti B, Baral B. Antimicrobial applications of nanoliposome encapsulated silver nanoparticles: A potential strategy to overcome bacterial resistance. Curr Nanosci 2021; 17: 26-40.

75) Veeraraghavan VP, Periadurai ND, Karunakaran T, Hussain S, Surapaneni KM, Jiao XS. Green synthesis of silver nanoparticles from aqueous extract of Scutellaria barbata and coating on the cotton fabric for antimicrobial applications and would healing activity in fibroblast cells (L929). Saudi J Biol Sci 2021; 28: 3633-3640.