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*Review Article*

# Potential of Traditional Chinese Medicines to treat Drug-resistant Bacterial Infections: A Review

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## ABSTRACT

**Background:** Antibiotic drugs have been widely applied in the treatment of bacterial infections. However, with the overuse and unreasonable adoption of antibiotics, a variety of bacteria have developed resistance to commonly used antibiotics. Bacterial pathogens with multi-drug resistance mechanisms have made many infectious diseases more difficult to be treat and new therapies are urgently needed. **Methods:** An extensive review of ethno-botanical books, reviews and primary scientific studies was undertaken to identify TCMs used to treat bacterial infections and the individual components of those medicines this information was used to identify gaps in the current research that require further study. **Results:** Traditional Chinese medicine contain multiple components and function via multiple pathways against multiple targets. Many of these pathways and concepts may be difficult for non-Chinese due to their complexities. However, an evaluation of TCMs for antibacterial activities is an attractive option for antibiotic discovery and development as they generally have low toxicity, low side effects and as combinational therapies, there is no inherent drug resistances in human bacterial pathogens towards these drugs. This study reviews the current status of bacterial resistance, the mechanism of traditional Chinese medicine against bacterial infections, and the adoption progress of Chinese herbal medicines in the treatment of resistant bacterial infections. **Conclusion:** TCM can inhibit the growth of bacterial pathogens and can participate in mediating the immune function of multiple bodily aspects. Therefore, Chinese herbal medicine may provide new leads to treat drug-resistant bacterial infections.

**Key words:** Chinese herbal medicine, Resistant bacteria, Synergy, Combinational therapies, MRSA, ESBL, Bacterial pathogens.

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## INTRODUCTION

The development of antibiotic resistance in bacterial pathogens has decreased sensitivity to those drugs and greatly lessened their efficacy.[1] In recent years, with the over and incorrect use of antibiotics, multi-drug resistant pathogens and "super bacteria" have gradually emerged and new and effective therapies are desperately required.[2] Medical research has shifted focus to an evaluation of traditional medicines, including traditional Chinese medicine (TCM), to discover new drug candidates for the treatment of drug-resistant bacteria. TCM has been adopted in disease treatment for thousands of years and it has the advantages of containing multiple components, as well as having multiple targets, multiple effects, and low side effects. TCM may therefore provide prospects for the development of novel therapies that are effective against antibiotic resistant bacterial strains. The current status of drug-resistant bacteria, the mechanism of bacterial resistance, and the treatment of drug-resistant bacteria by TCM are reviewed in this manuscript.

### A brief history of Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) has a long history and has evolved over thousands of years. Indeed, the first English language pharmacopeia was published in London in 1618. In comparison, the earliest known Chinese medicine publications are believed to be 'The Yellow Emperor's Canon' and 'Treatise on Cold Damage', both of which are attributed to the Yellow Emperor who is thought to have ascended to the throne of China in 2698BC. However, it is likely that the development of many of the notions such as yin-yang and five phases that are pivotal to modern TCM are rooted much older, and are in fact rooted in the Shang dynasty period ($14^{th}$-$11^{th}$ century BC). However, that period is less well documented and today, the oldest surviving TCM documents are those of the Yellow Emperor (during the Han dynasty).

In the centuries following the Han dynasty, multiple other books were written on Chinese medicinal theory and practice, although most of these were summaries of the earlier texts. However, in 1578AD, Li Shizhen (a noted pharmacologist and physician of that era) published 'Pen Tsao' (Compendium of material Medica), which listed comprehensive details about more nearly 11000 TCMs, consisting of over 1800 different natural materials (including plants, animals and minerals). Many of the medicines and components used in their preparation do not appear in earlier works. Furthermore, this document meticulously describes the plants used and includes 1160 illustrations to aid in plant identification. As such, the Pen Tsao is the most comprehensive record of TCM use and preparation.

Whilst TCM has been used continuously used since antiquity, it saw a resurgence in its usage during the Chinese Cultural Revolution (1966-1978). The Chinese government invested substantial amounts of money in the development and promotion of TCM during this period as a means of providing affordable and effective health care. This period of TCM revitalisation was particularly beneficial for rural areas, where the provision of effective health care was often beyond the means of many residents. It was also during this period that non-Chinese people were exposed to TCM, although many people from Western cultures are yet to accept the basis of its efficacy. More recent efforts, particularly by Chinese researchers, have attempted to validate and understand the basis of TCM through laboratory testing.

### Philosophical Background of TCM

TCM is a general term and encompasses a variety of mind and body techniques (e.g. tai chi, acupuncture, cupping therapy, massage, exercise and diet), as well as the use of herbal medicines.[3] The philosophy of TCM is based on several fundamental philosophies including yin-yang, qi and wuxing. Yin and yang are ancient concepts originating in the Shang dynasty of China (1699-1100BC). Essentially, it is believed that every aspect of the universe can be divided into two complementary but opposite aspects (e.g. male/female, moon/sun, inside/outside, cold/hot, moist/dry).[3] The body is also represented by yin and yang, with the lower parts of the body considered to be yin, whilst the upper parts and the back are considered to be yang. Thus health is seen in TCM as a balance between yin-yang, whereby an imbalance through lack or over-abundance of any aspect can lead to characteristic symptoms. For example, cold and hot sensations are considered to be yin and yang symptoms respectively and medicines can be provided to treat these symptoms by reinforcing either the yin or the yang.

Another tenet of TCM is that the bodies vital energy (qi) circulates throughout the body via channels known as meridians and the correct flow of qi is vital for the functions of specific organs and functions (e.g. breathing, body temperature etc).[3] An individual's qi is believed to be generated by air, the food they consume and can be inherited. Thus, poor diet, exercise and bad breathing can contribute to wellbeing, as can genetic aspects. In treating a medical complaint, TCM practitioners will examine the symptoms and assign medicines based on yin-yang and qi, amongst other aspects. Generally, TCMs contain multiple components and are individual to every patient, and often contain different components between individuals. This concept is difficult for Westerners to understand and it is best to think of TCMs as combinational therapies that are treating multiple aspects of the one illness.

## MATERIALS AND METHODS

This study aimed to review TCMs used to treat bacterial-induced diseases in humans. Google-Scholar, Science-Direct, PubMed and Scopus electronic databases were searched to identify original research studies and TCM books using the following terms as filters, and were searched both alone and as combinations: "traditional Chinese medicine", "TCM", "traditional medicine", "bacterial infection" and "antibiotic resistant bacteria". Through this study, we aim to foster further research into TCMs (and their individual plant species components) as treatments for bacterial infections in humans.

## RESULTS

### Current status of bacterial infections in China

Drug-resistant bacteria have become a serious global problem, with reports of multi-drug-resistant bacteria and extensively drug-resistant bacteria rapidly increasing in recent years.[1,4] From October 2017 to September 2018, a total of 3,234,372 cases of antibiotic resistant bacteria were reported in infected patients in China (the data includes 1353 hospitals, with 349 secondary hospitals and 1004 tertiary hospitals).[5] Gram-positive bacteria accounted for 29.4% of these infections (952,023 strains), whilst Gram-negative bacteria accounted for the remaining 70.6% (2282349 strains). The five most prevalent antibiotic bacterial species of Gram-positive bacteria and Gram-negative bacteria in China are indicated (Figure 1). The top five species of resistant Gram-positive bacteria were *Staphylococcus aureus* (32.5%), *Streptococcus pneumoniae* (10.7%), *Staphylococcus epidermidis* (10.5%), *Enterococcus faecium* (9.6%), and *Enterococcus faecalis* (9.5%). The top five reported antibiotic-resistant Gram-negative bacteria species were *Escherichia coli* (28.9%), *Klebsiella pneumoniae* (20.4%), *Pseudomonas aeruginosa* (12.4%), *Acinetobacter baumannii* (9.9%) and *Enterobacter cloacae* (4.0%).

Additionally, a 2019 tertiary hospitals bacterial resistance monitoring study[4] reported the difference between the number of bacterial strains isolated from inpatients and outpatients in emergency departments from 2009 to 2019 (Figure 2). Interestingly, the number of resistant bacterial strains isolated from hospitalized patients in each year was always higher

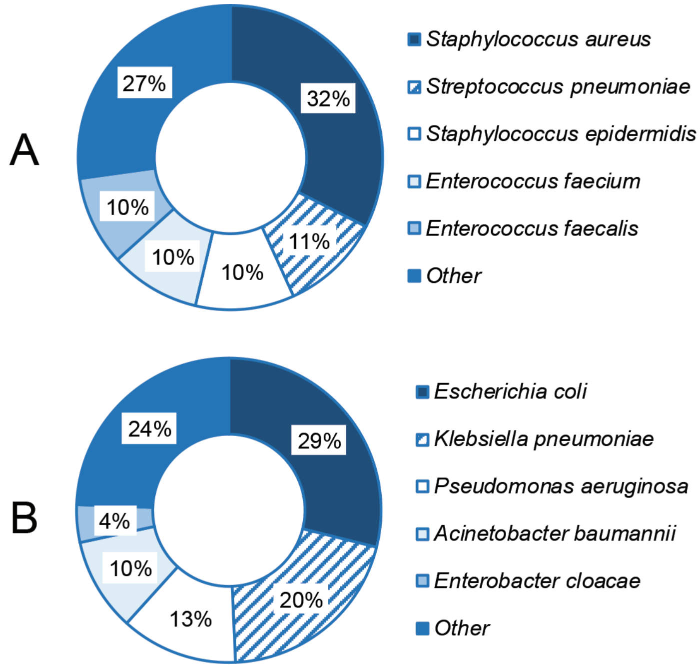


**Figure 1:** The proportion of resistant bacteria detected in the top 5 of Gram-positive bacteria (A) and Gram-negative bacteria (B).[4-6]

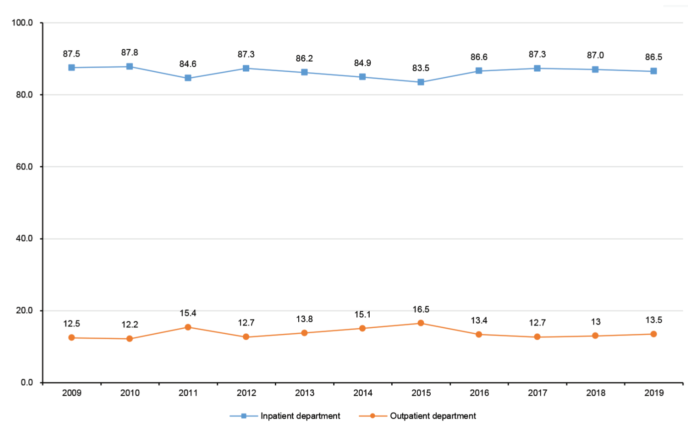


**Figure 2:** The proportion of resistant bacterial strains isolated from inpatients and outpatients in tertiary hospitals from 2009 to 2019.[4-6]

than 80% of the total reported bacterial species reported. In contrast, the number of resistant bacterial strains isolated from outpatient and emergency patients was between 11% and 16%, demonstrating that the probability of resistant bacterial infection in inpatients was significantly higher than that in outpatient and emergency departments, indicating that nosocomial infections with antibiotic-resistant bacteria is a major and increasing problem in China.[5]

The differences in the proportion of resistant Gram-positive and Gram-negative bacteria strains isolated from patients in tertiary hospitals from 2009 to 2019 were also compared in that study (Figure 3). The number of resistant Gram-negative bacterial strains was always higher than 60%, whilst the number of resistant Gram-positive bacteria was around 30%. These results are consistent with the monitoring results announced in the 2018 National Bacterial Resistance Monitoring Report.[5,7]

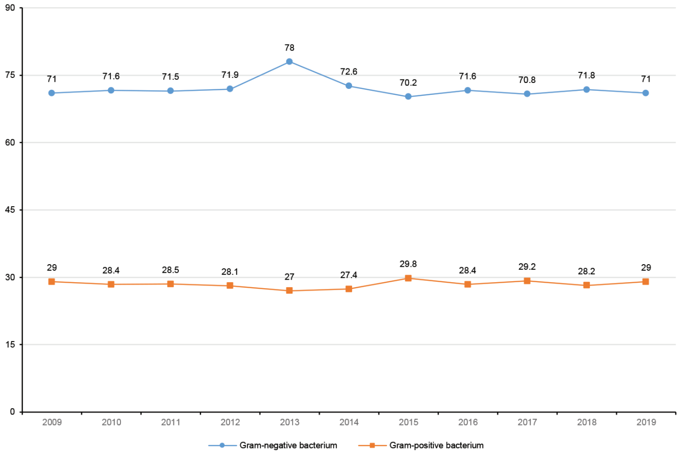


**Figure 3:** The proportion of resistant Gram-positive and Gram-negative bacterial strains isolated from tertiary hospitals from 2009 to 2019.4-6

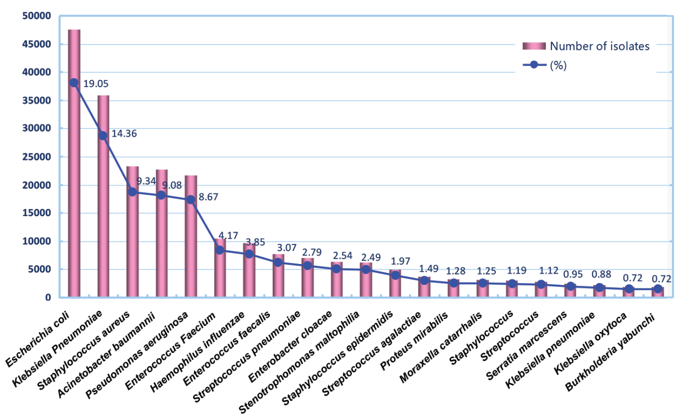


**Figure 4:** Distribution of main clinical isolates of bacteria in tertiary hospitals in 2019 (top 20).[4-6]

The distributions of the 20 most prevalent bacterial species obtained from major clinical isolates in 2019 were further analyzed in that study (Figure 4). It was found that the proportions of both *Escherichia coli* and *Klebsiella pneumonia* were more than 14%. *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* each accounted for more than 8% of the total resistant bacteria infections. Changes in the isolation rate of main Gram-negative bacilli from 2009 to 2019 were further analyzed (Figure 5). The isolation rate of resistant *Escherichia coli* has remained high in recent years whilst the reporting of resistant *Klebsiella pneumoniae* has increased annually. In contrast, the levels of antibiotic-resistant *Pseudomonas aeruginosa* strains has decreased in recent years.

One of the main pathogenic substances of *Escherichia coli* is plasma coagulase, which causes diarrhoea in gastrointestinal *E. coli* infections. *E. coli* gastrointestinal infections can be further classified into 5 types: enterotoxigenic, intestinal invasive, intestinal pathogenicity, intestinal aggregation adhesion, and intestinal hemorrhagic.[8] In contrast, *Klebsiella pneumoniae* mainly exists in the upper respiratory tract and intestinal tract of the human body. When the body's immunity is reduced, *Klebsiella pneumoniae* can enter the body's lung tissue, leading to confluent consolidation of the large lobes or lobules.[9]

*Staphylococcus aureus* is a common food-borne pathogen and it is widely present in the natural environment.[10] This bacterium can produce

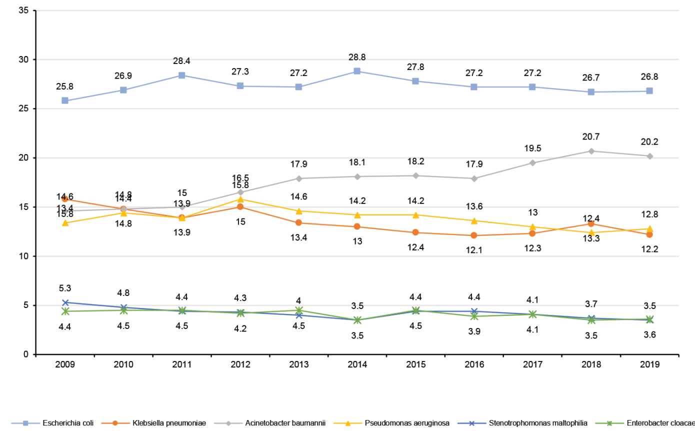


**Figure 5:** Changes in the ratio of major resistant Gram-negative bacterial strains isolated from tertiary hospitals from 2009 to 2019.[4-6]

enterotoxins under specific conditions, and these toxins can cause food poisoning in infected individuals. Moreover, food poisoning incidents caused by this bacteria account for more than 25% of the total food-borne microbial food poisoning incidents.[11] *Acinetobacter baumannii* is the most common type of bacteria in hospital infections, especially in intensive care units. It can cause diseases such as bacteremia, pneumonia, meningitis, and skin infections.[12] The prevalence of *A. baumannii* reported in China in the previous study is believed to be due to incorrect and over use of antibiotics, resulting in the generation of multi-drug resistant *A. baumannii* strains, with their resistance to antibiotics increasing annually.[13]

*Pseudomonas aeruginosa* is one of the main pathogens of infection in hospitals. An important condition for the survival of *Pseudomonas aeruginosa* is a humid environment and *P. aeruginosa* infections are relatively common in patients with metabolic diseases, hematological diseases, and malignant tumors. This bacterium can also cause post-operative wound infections. In addition, infected lesions can lead to blood dissemination, resulting in bacteremia and sepsis.[14] Notably, when burn patients are infected with *Pseudomonas aeruginosa*, it can result in death.[15]

With the mis and overuse of broad-spectrum antibacterial drugs, increasing numbers of bacteria are developing enhanced drug resistance. The infection rate caused by the emergence of multi-drug-resistant bacteria and extensively drug-resistant bacteria has also shown a significant upward trend each year. Therefore, the development of "super antibacterial drugs" that can treat drug-resistant bacterial infections is of great significance for preventing and controlling the increase in the rate of drug-resistant bacterial infections.

## Current status of drug-resistant bacterial infections

Bacterial resistance can be divided into two types: inherent resistance and acquired resistance (Figure 6). When bacteria are exposed to an environment containing antibiotics for extended periods, drug-sensitive bacteria can be inhibited. However, natural or acquired resistant bacteria may survive and spread their resistance genes.[16] Thus, resistant strains with a selective advantage can outcompete antibiotic sensitive strains and become the most prevalent strains. Currently, the most common drug-resistant bacterial strains in China include methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem resistant enterobacteriaceae (CRE), and carbapenem resistant *Acinetobacter baumannii* (CR-AB).[17,18] The changes in the numbers of methicillin-resistant *S. aureus* reported from 2009 to 2019 (Figure 7) and interestingly the detection rate of MRSA has recently shown a downward trend, whilst the report rate of

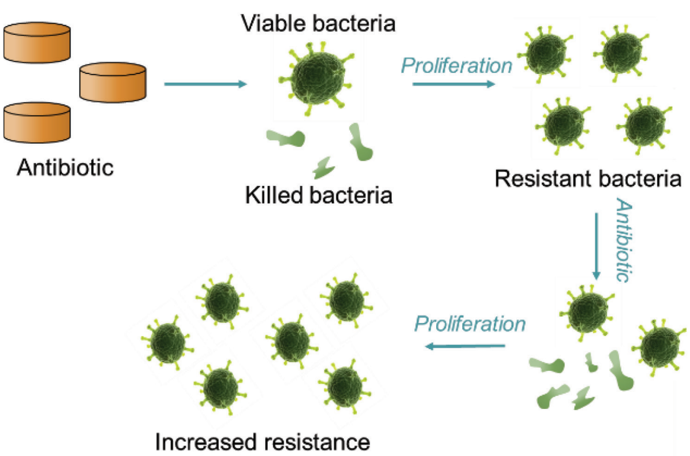


**Figure 6:** The process of acquiring induced bacterial resistance.

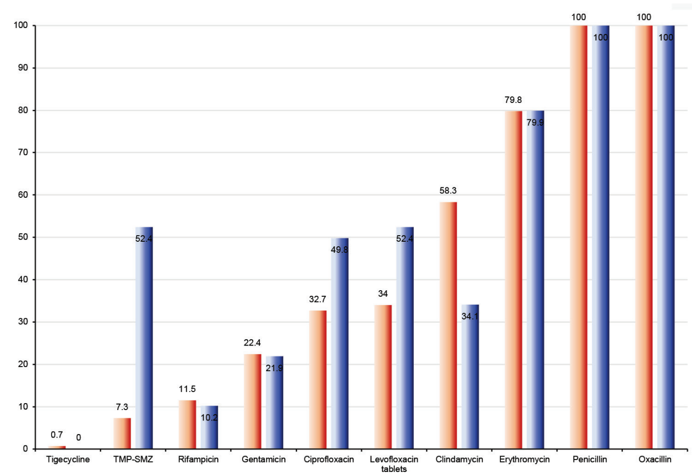


**Figure 8:** Antimicrobial resistance rates of MSSA and MSSE.[4-6]

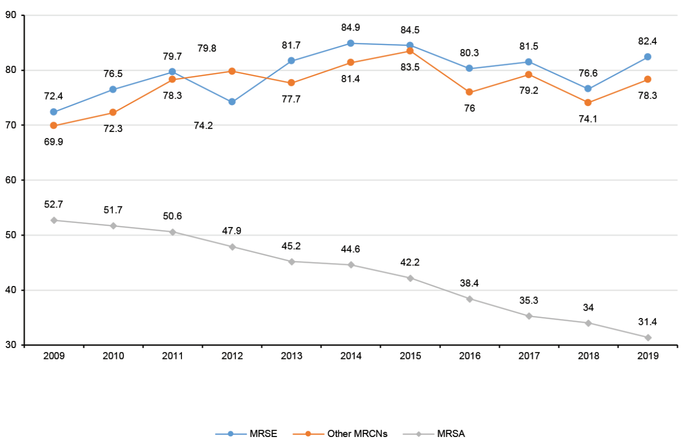


**Figure 7:** Changes in the detection rate of methicillin-resistant Staphylococcus from 2009 to 2019 (Other MRCNS referred to MRCNS in other *Staphylococci excepted Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus pseudointermedia and Staphylococcus Schneider*).[4-6]

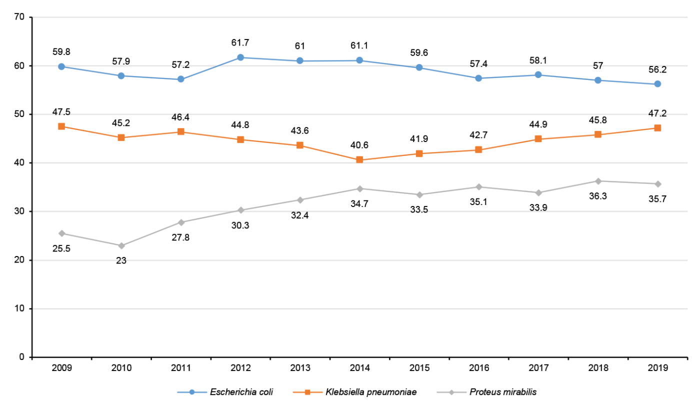


**Figure 9:** Changes in the detection rate of cefotaxime or ceftriaxone-resistant bacteria in Enterobacter from 2009 to 2019.[4-6]

methicillin-resistant *Staphylococcus epidermidis* (MRSE) had remained high. The detection rate of other methicillin-resistant coagulase-negative *Staphylococci* (MRCNS) has also increasing yearly.

The difference between methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-susceptible *Staphylococcus epidermidis* (MSSE)'s resistance to different antimicrobial drugs was further analyzed and compared in that study (Figure 8). Interestingly, methicillin-sensitive *S. aureus* (MSSA) and methicillin-sensitive *S. epidermidis* (MSSE) had high resistance rates to quinolones and other antibiotics.[19] Indeed, the resistance rate to penicillin and oxacillin were reported to be 100% in that study. However, MSSA and MSSE were not resistant to vancomycin, linezolid, and teicoplanin. Therefore, these antibiotics are useful for the treatment of MSSA and MSSE in clinic. However, whilst those drugs are still useful against these sensitive strains, other strains are resistant to their effects.

The changes in the detection rate of cefotaxime or ceftriaxone resistant Enterobacteria spp. from 2009 to 2019 were also compared and analyzed (Figure 9). In recent years, the detection rate of resistant *E. coli*, *K. pneumoniae*, and *Proteus mirabilis* was been substantially higher than 15%. The detection rate of drug-resistant *E. coli* had stabilized above 50%, and the detection rate of drug-resistant *K. pneumoniae* is higher than 40%. The detection rate of other drug-resistant enterobacteria is also gradually increasing.

The distribution of carbapenemase in the carbapenam-resistant *E. coli* strain (CRE) was also analyzed (Figure 10). Carbapenemase producing strains KPC-2 (isolated from adult patients with *K. pneumonia* infections), NDM (isolated from *E. coli* infected patients) and OXA-48-all were reported.[20] Notably, carbapenemase resistant *Klebsiella pneumoniae* was more widely distributed in children's hospitals. The distribution of blaNDM enzymes in *E. coli* and *K. pneumoniae* increased, as did the incidences of blaKPC and blaOXA-48-like enzymes. In general hospitals, blaKPC enzyme was the most widely distributed carbapenemase, followed by blaNDM. Notably, super-resistance due to NDM-1 spans multiple bacterial species.[21,22]

Finally, a comparative analysis of the resistance rate of carbapenem-resistant *K. pneumoniae* to antibacterial drugs has been reported (Figure 11). Notably, tetracycline resistance in *K. pneumonia* strains, which are also carbapenem-resistant to tetracycline, recently reached more than 45%. Furthermore, the drug resistance rate to quinolones, cephalosporins, biapenem and other antibiotics had reached more than 90%.[23]

## Novel treatments for antibiotic-resistant infections

The mechanism of bacterial resistance is constantly changing. A variety of strategies for the treatment of drug-resistant bacterial infections without antibiotics have been explored clinically, with varied success.

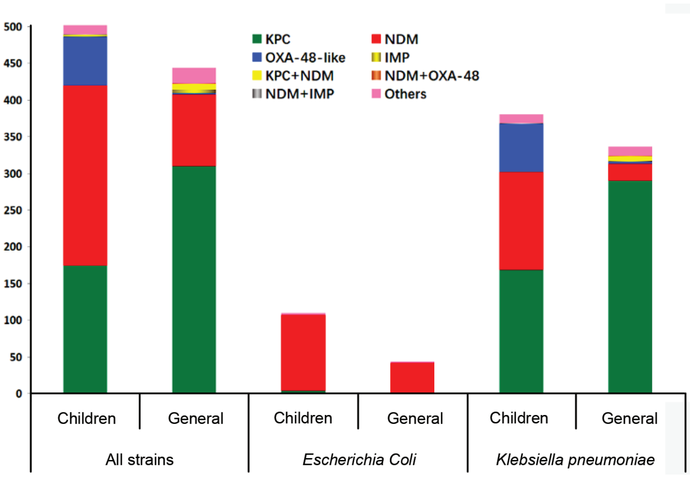


**Figure 10:** Distribution of carbapenemase in CRE strains in children's hospitals and general hospitals.[23]

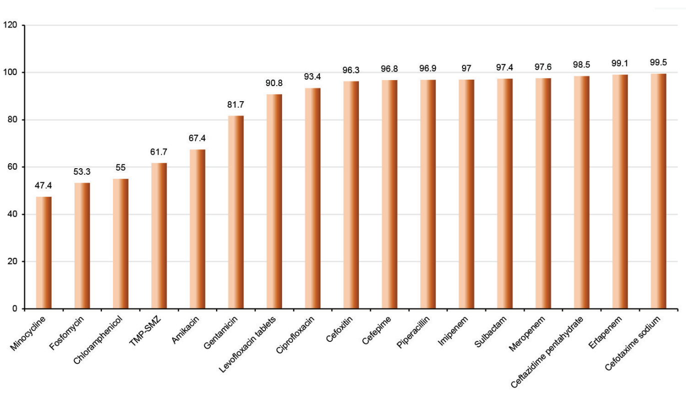


**Figure 11:** Resistance rate of carbapenem-resistant *Klebsiella pneumoniae* to antibiotics.[23]

## Targeted therapies for drug-resistant bacteria

Historically, β-lactam antibacterial agents and β-lactamase inhibitors have been the most successful antibacterial drugs used clinically for the treatment of bacterial pathogens.[24] However, many bacterial strains have developed the ability to produce the enzyme β-lactamase, which degrades β-lactam antibiotics. Furthermore, some bacteria contain efflux pumps that expel antibiotics from the cell, thereby blocking its effects. Thus, drugs that target these (and other) resistance mechanisms have the potential of improving the antibacterial activity of the existing antibiotics, even in bacterial strains otherwise resistant to their effects.

## Toxicological targets

"Friendly" and "mild" antimicrobial chemotherapy may cause bacteria to become incapacitated. Some scholars have devoted themselves to the exploration of bacterial virulence secretion systems aiming to develop drugs that can make bacteria lose their virulence.[25] This strategy causes selective pressure on the bacteria. Indeed, anti-virulence treatments that don't kill the bacteria may speed up the development of resistance.

## Phage therapy

Bacteriophages that can target and kill specific bacterial pathogens (Figure 12) hold great promise for the development of novel antibacterial therapies. However, they have generally not been utilized clinically to date. This may be due in part to the requirement for strict characterization between phages and bacteria. Additionally, limited research has been published on bacteriophage therapy and this has also limited its uptake as a therapy. However, this method of inhibiting bacterial growth has promise and much more work is required. As well as providing novel therapeutic options, phage treatment can be utilized in the search for new antibacterial targets.[26]

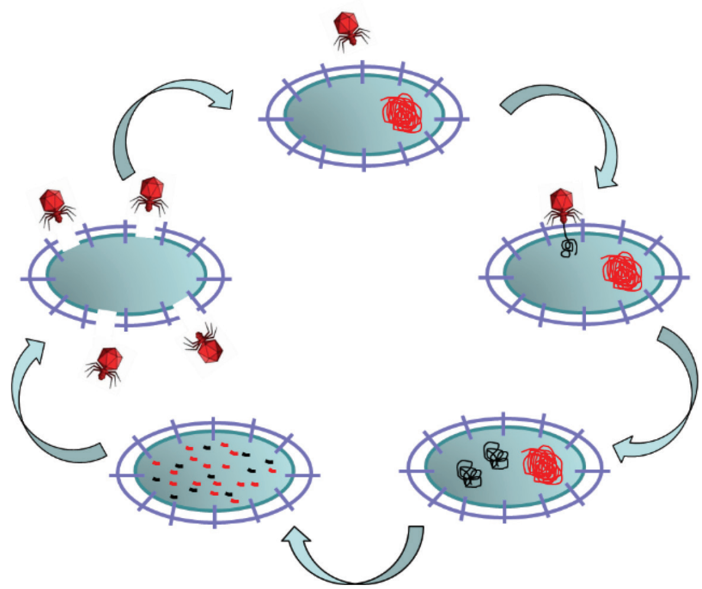

**Figure 12:** Bbacteriophage function in killing specific bacterial pathogens.

## Chinese herbal medicines to treat bacterial infections

The theory of 'combined treatment of bacteria and toxin' was proposed in 1975 by Professor Jinda Wang, who combined TCMs and Western medicines to treat severe bacterial infections. TCMs have been used in combination antibiotics with good efficacy for the treatment of resistant bacterial strains. Professor Jinda Wang activated blood circulation and removing blood stasis as a means to treat blood stasis syndrome. Additionally, heat-clearing and detoxicating remedies were utilized for the treatment of toxic heat syndrome, and the supporting the healthy energy method was utilized for the treatment of acute deficiency syndrome.[27] That study also used TCMs for the treatment of clinical infectious patients with multiple organ failure, significantly reducing the fatality rate of the disease.

The destruction of intestinal barrier function is increasingly seen as a major cause of the endogenous transmission of bacteria. This destruction increases the incidence of severe infectious multiple organ failures.[28] The authors of that study combined three syndromes and three treatment methods, with the belief that diseases of the lung and the large intestine are related. They believed that using 'tongli gongxia' (restoring normal bowel movement) is effective for treating the obstruction of qi and organs, thereby creating a four syndromes and four methods treatment method.

The theory of "combined treatment of bacteria and toxin" combines treatments for pathogen infections, endotoxins and inflammatory mediators from allopathic medicine, with TCMs used for congestion, heat and toxicity. The mortality of patients with critical and severe infectious multiple organ failure in clinical settings was reduced, which also provided new strategies for the clinical adoption of TCM in the treatment of bacterial infectious diseases.

## Treatment of blood stasis promoting blood circulation

Patients with blood stasis often present with dark faces, dark or purple lips and fingers, with blue veins and pain in their lower extremities, dark purple tongues, as well as several other symptoms. Injection with xuebijing (a Chinese medicine use to remove the blood stasis) has been reported to be effective at promoting blood circulation. Xuebijing is composed of five traditional Chinese medicines: *Carthamus tinctorium* L. (hong hu, 红花 in Chinese), *Paeonia veitchii* Lynch（chi shao, 赤芍 in Chinese), *Ligusticum striatum* DC. (chuan xiong, 川芎in Chinese), *Angelica sinensis* Diels (dang gui, 当归in Chinese) and *Salvia miltiorrhiza* Bunge (dan she, 丹参in Chinese). It promotes blood circulation, removes blood stasis, clears heat and dredges meridians. Studies have confirmed in animal models that xuebijing injection has strong anti-endotoxin effects. It improves the ability to clot blood, whilst also improving immune function. Other studies have confirmed that activating blood circulation and removing blood stasis can regulate the immune capacity of patients with multiple organ failure, to restore the disorder of the patient's inflammatory response.[29]

Clinically, use of TCM to promote blood circulation and remove blood stasis (PBCRBS) has been widely adopted in the treatment of clinical cardiovascular and cerebrovascular diseases.[30] In comparison with Western chemotherapies for thrombus treatment, PBCRBS drugs have mild antithrombotic effects, function via multiple pathways, have multiple targets treatment and low adverse reactions. Analysis of the interaction among the core Chinese medicine components in PBCRBS drugs (Figure 13) reported that *S. miltiorrhiza*, *C. tinctorium*, and *L. striatum* were the core components of this Chinese medicine.

*Salvia miltiorrhiza* Bunge, *Cochlospermum tinctorium* Perr. Ex A.Rich. and *Trifolium striatum* L. have been reported to regulate levels of the inflammatory molecules $NOS_2$, $NOS_3$, $PTGS_2$, and inflammatory factors IL-6, IL-10, TNF-α, and IL-1β (Figure 14). These inflammatory mediators correlate closely with atherosclerosis signalling pathways, suggesting that promoting blood circulation and removing blood stasis may inhibit inflammation and therefore have anti-inflammatory effects.

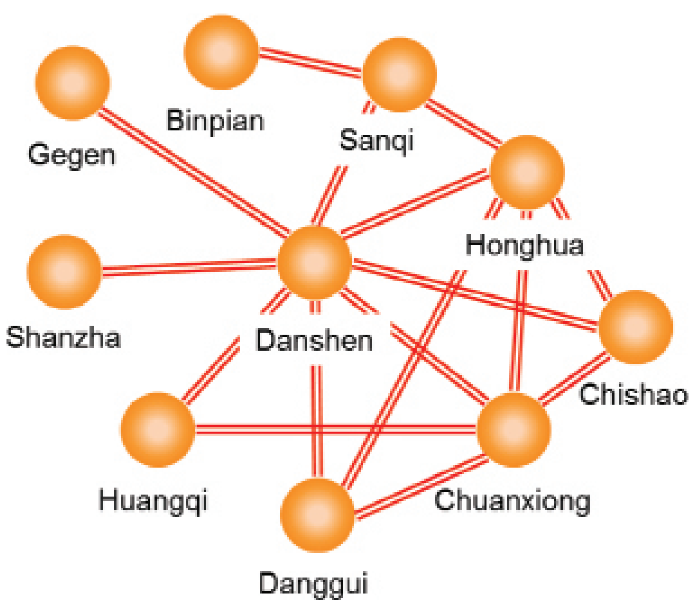


**Figure 13:** The action network of the core traditional Chinese medicine for promoting blood circulation and removing blood stasis. The species names for TCMs are: Gegenm = *Pueraria montana var. lobate*; Binpian = *Dryobalanops aromatic*; Sanqi = *Panax notoginseng*; Shanzha = *Crataegus pinnatifida*.[30]

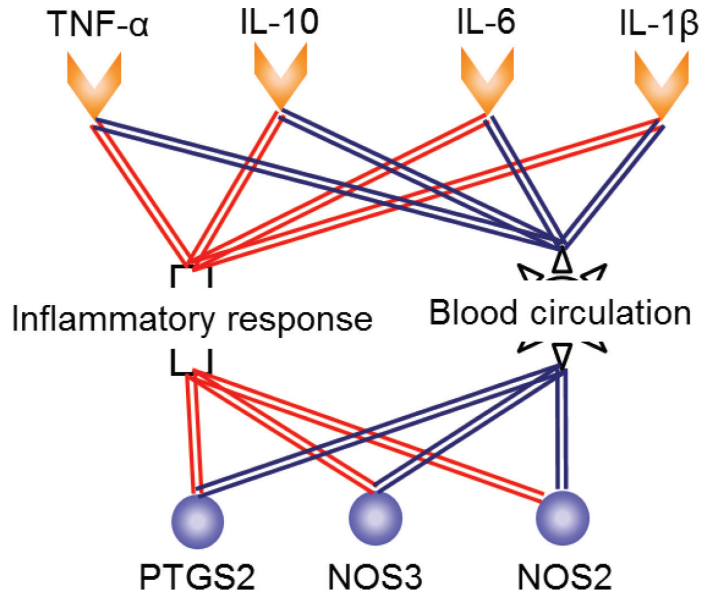


**Figure 14:** The interaction of inflammatory molecules in the immune response and the effect of promoting blood circulation and removing blood stasis.[30]

## Clearing heat and toxic material to cure fever

Patients with toxic heat syndrome usually present with high fever, cold preference, red face and warm limbs. Patients with severe toxic heat syndrome will also show dry mouths, thick yellow coating on the tongue, thick yellow phlegm, as well as other symptoms. Clinical laboratory evaluations of patients with febrile disease found that the serum calcitonin levels, as well as white blood cell neutrophil counts in these patients were significantly higher than those in healthy populations.[31] These patients also had increased levels of toxins and inflammatory mediators in their blood. Studies revealed that using TCMs to heat clear and detoxify are important treatments for patients with toxic heat syndrome and can reduce the activation level of neutrophils and the expression of TNF-α and IL-6 pro-inflammatory cytokines.[32]

*Forsythia suspensa* Vahl. has been shown to clear heat and detoxify the body, thereby reducing swelling. It is widely used clinically in TCM as a heat-clearing and detoxification treatment. Modern pharmacological studies have demonstrated that clinical indications of *F. suspensa* related to its anti-inflammatory pharmacological activity.[33] There are 114 known phytoconstituents in *F. suspensa*, among which the most important for their therapeutic properties are the flavonoids, triterpenes, lignans, and lignans glycosides. The therapeutic targets of *F. suspensa* in TCM are mainly targeted at chronic obstructive pulmonary disease, inflammation, and tuberculosis.[34] Notably, the pathogenesis of both chronic obstructive pulmonary disease and tuberculosis is closely related to inflammatory responses. Thus, *F. suspensa* can play its antipyretic and detoxifying effect via its anti-inflammatory pharmacological action. Other reports have proposed a regulatory network for the interaction between therapeutic targets and inflammatory-regulatory molecules in *F. suspensa* (Figure 15). Six *F. suspensa* constituents can regulate the levels of eight inflammatory factors ($NOS_2$, $NOS_3$, $MMP_2$, $MMP_9$, $CMA_1$, $STAT_1$, $PARP_1$, and $HMOX_1$). These results confirm that the heat-clearing and detoxifying effects of *F. suspensa* was due to the anti-inflammatory pharmacological action of the plants chemical constituents.

## Treatment of acute deficiency supporting healthy energy

Patients with acute deficiency syndrome often show symptoms including mental exhaustion, spontaneous sweating, night sweats, dizziness,

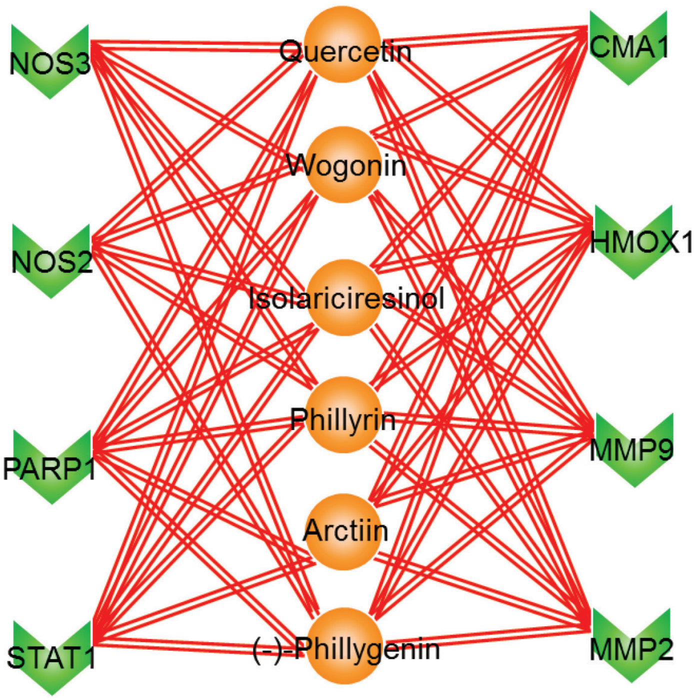


**Figure 15:** Composition of *F. suspensa* and its treatment target.[30]

palpitations, and insomnia. In the treatment of patients with multiple organ failure, some TCM practitioners have adopted the method of combining traditional Chinese and western medicine. Interestingly, combinations of Chinese and Western medicine could improve the immunosuppressive status of patients with acute deficiency syndrome. Indeed, compared with the effect of using Western medicine alone, the combinations significantly improved the balance between pro-inflammatory and anti-inflammatory activities.[35] Additionally, other studies revealed that buyang huanwu decoction (a TCM used to promote blood circulation) can reduce the rate of cell apoptosis and improve the immunosuppression status of patients with sepsis.[36] This medicine consists of a combination of several other TCMs (huangqi, danggui, chishao, dilong, chuanxiong, honghua, taoren) and the roles of each in the therapeutic properties of buyang huanwu decoction are yet to be fully evaluated.

TCMs are said to improve patients' symptoms by removing pathogenic factors" but also are used for "righting the wrongs" (as described in *Huangdi neijing*, an ancient Chinese medicine book). These early text also state that to "keep healthy, then do not be evil". TCMs are often used for dispelling evils. After "dispelling evil", if the patient is still unable to achieve good qi, the patient will be unable to overcome the evil spirits, and will remain ill. For TCM practitioners, qi is relevant to all blood disorders. If the qi is adequate and in balance, people will have good health. Not doing evil in TCM refers to maintaining a healthy mind and making attitude adjustment as required. Therefore, for TCM practitioners, the treatment of patients with deficiency disorders should not be limited to dispelling pathogenic factors, clearing away heat and removing blood stasis, etc, but can also be achieved by restoring vital energy (qi) and regulating a patient's defense functions. The herbs most commonly used in TCM for these purposes are *Glycyrrhiza* spp., *Atractylodes* spp. and ginseng. *Glycyrrhiza* spp. (particulatly *G. glabra* L.) are well known for their anti-inflammatory, anti-tumor and immuno-regulatory activities. Indeed, the use of *Glycyrrhiza* spp. reduces the expression of pro-inflammatory factors when used to treat colitis. Ginseng also plays a role in regulating the immune function of the body and its adoption in the treatment of intestinal inflammation can significantly improve the symptoms of diarrhoea. Similarly, atractyloids (isolated from *Atractylodes* spp.) have anti-inflammatory, intestinal mucosal repair and immunological regulation effects and are therefore useful in treating these conditions. Studies have also shown that atractyloids can inhibit the synthesis of macrophages, thus reducing inflammatory symptoms.

## Tongli gongxia method for treating fu-qi obstruction

Clinically, the obstruction of fu-qi generally presents as the inability to defecate and is often accompanied by vomiting. Clinical laboratory tests showed significant increases in blood endotoxin levels in these patients. Tongli gongxia refers to a group of herbs that are indicated for gastrointestinal disorders. The most common TCM tongli gongxia medicine is dachengqi decoction (a TCM made of dahuang, zhishi, houpu, mangxiao). Patients with multiple organ failure that were treated with dachengqi decoction show reduced serum levels of the pro-inflammatory mediators IL-6, IL-10, IL-1, and TNF-α, corresponds to improved patient symptoms.[37] This suggests that the intestinal function of patients with multiple organ failure can be improved by the pass-through tapping method, which also maintains the balance of pro-inflammatory and anti-inflammatory responses.

## Adoption of Chinese herbal medicine in the treatment of antibiotic resistant bacterial infections

Many studies have explored the effect of TCM in the treatment of bacterial (including drug-resistant bacteria) infection. Li *et al*.[38] prepared nanoparticles of berberine and flavonoid glycosides and applied them to a mixed bacterial population. The proliferation rate of the bacterial population and their ability to generate biofilms was also significantly reduced. A metadata TCM study used for the treatment of acne[39] reported that combinations of either qing-Shang-fang-feng-Tang or Zhen-Ren-Hua-ming-yin, combined with *F. suspense,* were the most commonly used TCM therapies for acne. These findings suggest anti-inflammatory and antibacterial effects for these medicines. Furthermore, qingdaisan can reduce the number of inflammatory cells in oral ulcer tissues.[40] Interestingly, when qingdaisan was applied to animal models of oral ulcer, it produced significant anti-inflammatory effects, but poor antibacterial activity. In a separate study, gingyo-san was applied to respiratory pathogens to examine the antibacterial activity of this drug.[41] It inhibited the growth of *Bacillus subtilis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae*. Huang *et al*.[42] also tested combinations of TCM and Western medicines in the treatment of bacterial sepsis. They reported that combinations of TCMs and Western medicine had substantially better anti-inflammatory activity than pure Western medicine treatments alone.

In addition, traditional Chinese medicine has been applied in the antibacterial treatment of drug-resistant bacteria.[43] Compounds derived from several TCM medicines were effective againstdrug-resistant bacterial infections. This is a noteworthy finding as the effective treatment of drug-resistant bacteria has become less effective using conventional antibiotics and new therapies are urgently required.[44] However, an increasing number of studies have reported that TCM can significantly reduce the mortality and inflammatory indicators in sepsis patients. Therefore, the adoption of TCM in the treatment of drug-resistant bacterial infection has promise. Another study combined Chinese herbal medicines and antibiotics for the treatment of extensive drug-resistant Enterobacteria infections.[45] The combination of TCM and Western medicine was substantially better than conventional antibiotic therapy alone. Furthermore, the white blood cell count and the proportion of neutrophils in the blood of the patients were decreased in response to the combinational therapy (compared to conventional therapy alone). Liu *et al.*[46] tested the TCM fuzheng qingre formula against uropathogenic *Escherichia coli* and reported that it could significantly reduce the number of bacteria in the kidney and bladder in animal models of urinary tract infection, further highlighting the potential of TCM's to treat resistant bacterial infections.

## CONCLUSION

The over and incorrect use of antibiotics has led to an increase in the incidence of drug-resistant bacterial infections. In recent years, the incidence of drug-resistant bacteria has seriously threatened human health and the development of new antibacterial drugs is a priority for medical science. Studies have confirmed that some TCMs can inhibit bacteria growth, and can mediate immune function in multiple body tissues. Many studies have reported that the active ingredients in Chinese herbal medicine have anti-inflammatory and antibacterial abilities. Furthermore, the combination of TCMs with conventional antibiotics may improve their efficacy. Therefore, TCMs may provide new leads for the treatment of antibiotic-resistant bacterial infections.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**CRE:** Carbapenam-resistant *E. coli;* **ESBL:** Extended-spectrum beta lactamase; **MRCNS:** Methicillin-resistant coagulase-negative Staphylococci; **MRSA:** methicillin resistant *S. aureus*; **TCM:** Traditional Chinese Medicine.

## SUMMARY

- Traditional Chinese Medicines (TCMs) has successfully been used to treat bacterial infections for thousands of years.
- The prevalence of antibiotic resistant bacterial pathogens has increased dramatically in China in recent years.
- This study reviews the use of TCMs to treat antibiotic resistant bacterial infections.
- The combinational approach of TCM is well suited to the treatment of antibiotic resistant bacteria.

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