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Antimicrobial activity of oridonin

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Abstract

Oridonin is an enantiomer-kaurene tetracyclic diterpenoid compound, which is the main active component of *Rabdosia rubescens*, a herb used in traditional Chinese medicine. It has been reported to exert anti-tumor, anti-inflammatory, proapoptotic, anti-angiogenic, neuroprotective, and other pharmacological effects. Owing to the overuse of antibiotics, currently, the medical and food industries are facing drug resistance challenges, which have severely impacted food and medical safety. Thus, new antibacterial agents must be identified. As an important active component of *Rabdosia rubescens*, oridonin has been extensively and deeply studied in antimicrobial aspects. This paper reviews the antimicrobial activity of oridonin and its underlying mechanism. In addition, its safety and application as an antibacterial agent were briefly introduced. Finally, the current problems and challenges of the application of oridonin and the prospects were also elucidated.

Keywords: oridonin; antimicrobial activity; antibacterial mechanism; Rabdosia rubescens; drug resistance.

Practical Application: Oridonin is widely used because of its pharmacological and biological activities. Here, we reviewed its antimicrobial activity and the underlying mechanism. Studies have shown that the antibacterial effect of oridonin is multidimensional, which can reduce the generation of drug-resistant bacteria. Thereby, it is expected that the remarkable antimicrobial activity of oridonin made it possible as a promising candidate for the development of novel agents which can be used in food preservation or functional foods.

1 The challenge of antibiotic-resistant microorganisms

Owing to antibiotic overuse in the medical, fishery, and livestock and poultry breeding industry, several antibioticresistant bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Streptococcus pneumoniae (MDRSP), and vancomycin-resistant Enterococcus (VRE) have emerged, posing new challenges to food hygiene and safety and efficacy of medicines (Gomes et al., 2022; Kim & Ahn, 2022; Le et al., 2022). To overcome the challenges posed by the increasing emergence of drug-resistant bacteria and their strong environmental adaptability, researchers are using a combination of antibiotics to treat bacterial infections (Beardmore et al., 2017; Li et al., 2022b; Pabon et al., 2022). In recent years, many researchers have focused on identifying natural antibacterial substances. Compared with conventional antibiotics, Chinese herbal medicine shows unique antibacterial characteristics in controlling the invasion of pathogenic bacteria. Many active ingredients of traditional Chinese medicine can not only directly inhibit the growth of and kill bacteria but also help in the defense against the invasion of pathogenic bacteria by enhancing the immunity of an organism. In addition, it can also inhibit bacterial colony formation to achieve an antibacterial effect, thereby reducing the use of drugs, especially antibiotics. Bacteria cannot easily gain resistance to traditional Chinese medicine (AlSheikh et al., 2020). Traditional Chinese medicine has played a comprehensive role in regulating and preventing the invasion of pathogenic microorganisms. Therefore, the

antibacterial research of active ingredients in Chinese herbal medicine has become a hotspot.

2 Traditional Chinese medicine Rabdosia rubescens

Rabdosia rubescens is a characteristic medicinal plant in the Taihang Mountain area of the Henan Province, China, and is often used as a botanical Chinese herbal medicine and dietary supplement (Khan et al., 2019). It contains several active ingredients including flavonoids, alkaloids, amino acids, organic acids, monosaccharides, and terpenoids, among others (Li et al., 2022a; Yang et al., 2020). The extract from the fresh leaves of Rabdosia rubescens has an antibacterial effect on Escherichia coli, S. aureus, Streptococcus albicans, Bacillus subtilis, and Pseudomonas aeruginosa, and its antibacterial activity against gram-positive bacteria is better than that against gram-negative bacteria (Feng & Xu, 2014; Kim et al., 2020). In the study on the separation and identification of ethyl acetate extract from Rabdosia rubescens and its antibacterial activity, the separated components were mainly diterpenoids, oridonin; phenolic acids, rosmarinic acid, caffeic acid, salicylic acid, ferulic acid, and vanillic acid; among which oridonin, salicylic acid, and ferulic acid showed antibacterial activity against the tested strains, and salicylic acid and ferulic acid had lower antibacterial activity than oridonin (Li et al., 2014). Based on the property that oridonin is easily soluble in organic solvents and has a low water extraction rate, combined with the antimicrobial activity of natural diterpenoid phenolic

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compounds, oridonin is considered the main antibacterial active ingredient in *Rabdosia rubescens* (Han et al., 2000; Saha et al., 2022; Wei et al., 2022).

3 The main active ingredient of *Rabdosia rubescens*: Oridonin

Oridonin is the main medicinal component of Rabdosia rubescens (Li et al., 2021). It is a light-yellow crystalline powder with a slight odor and bitter taste. It has a melting point of 248 °C-250 °C, solubility in water of 0.75 mg/mL, and a chemical molecular formula of $C_{20}H_{20}O_{c}$. Its molecular structure is shown in Figure 1. It belongs to enantiomer-kaurene diterpenoids (Li et al., 2021). Oridonin is commonly used to relieve inflammation and pain caused by cancers such as liver cancer, breast cancer, gallbladder cancer, cervical cancer, and oral cancer and to treat these cancer diseases because of its anti-angiogenesis effect and regulating functions of signal pathways such as autophagy, apoptosis, and cell cycle arrest of cancer cells (Abdullah et al., 2021; El-Baba et al., 2021; Xu et al., 2017). Oridonin also has anti-inflammatory and antioxidant effects. Oridonin can protect the liver from toxic compounds, such as bisphenol A, reduce uric acid levels, and exhibit other health functions (Wang et al., 2021b; Xu et al., 2018). Based on these reports, the potential of oridonin as a safe and natural antibacterial agent for food must be explored.

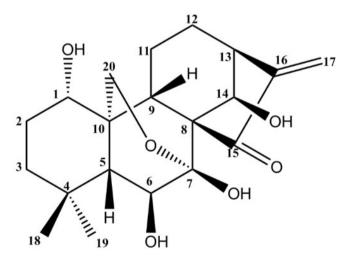


Figure 1. Chemical structure of oridonin.

Table 1. Antimi	icrobial ad	ctivity of	oridonin.
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4 Antimicrobial activity of oridonin

Studies on the antimicrobial activity of oridonin mainly focus on the inhibition of bacteria and less on fungi. Oridonin had a low inhibitory activity on the hypha and spore germination of fungi such as Botrytis cinerea, Colletotrichum gloeosporioides, Fusarium oxysporum, and Verticillium dahliae but had antibacterial activity against bacteria such as S. aureus, B. subtilis, and Bacillus cereus (Wang et al., 2010). Table 1 shows the antibacterial activity of oridonin against common pathogenic microorganisms: the MIC value of oridonin against *B. subtilis* was 31.2 µg/mL, only about 4 times that of the effective antibiotic chloramphenicol. Oridonin could inhibit the growth of S. aureus, although its MIC value was about 10 times that of antibiotic chloramphenicol against S. aureus (Li et al., 2016). Oridonin could inhibit the biofilm formation of S. aureus (Jiu et al., 2020), and it has the same activity against methicillin-resistant S. aureus (Yuan et al., 2019). Oridonin has strong antibacterial ability to Aeromonas hydrophila which is resistant to gentamicin, neomycin, amoxicillin and tetracycline (Miao et al., 2021). Oridonin can inhibit the quorum sensing of Chromabacterium violaceum at 31 µg/mL to achieve antibacterial effect. And based on the same quorum sensing inhibition effect, it could inhibit the growth and reproduction of Pseudomonas aeruginosa. In addition, it had an effective inhibitory activity on *Mycobacterium phlei* at 16 µg/mL (Huang, 2018; Xu et al., 2014a).

5 Antibacterial activity of oridonin derivatives

The hydrophobicity of oridonin limits its bioavailability (Zhang et al., 2020). To overcome the disadvantages of low solubility and poor bioavailability of oridonin, researchers have explored a variety of structural modification strategies. For example, the introduction of a thiazole ring on the C(1)and C(2) of oridonin A ring can significantly improve water solubility, esterification modification of C(14) amino acids can improve the chemical stability of oridonin, pegylation of C(14)can improve the water solubility of oridonin and prolong its halflife, these modification methods can improve the bioavailability of oridonin in different degrees. In addition, glycosylation at the C(6) position of oridonin is also a potential modification pathway to improve its water solubility and targeting, and thus improve its bioavailability (Cheng et al., 2019; Ding et al., 2013). Through modification, the solubility and bioavailability of oridonin were improved, and the antibacterial activity was retained, even the antibacterial activity of some derivatives was significantly improved. The derivatives of oridonin containing trans-cinnamic

Bacterial species	MIC [µg/mL]	MBC [µg/mL]	References
Bacillus subtilis CMCC63501	31.20	-	Li et al. (2016)
Staphyloccocus aureus ATCC29213	31.20	-	Li et al. (2016)
Staphyloccocus aureus ATCC6538	25.00	50.00	Jiu et al. (2020)
Methicillin-resistant Staphylococcus aureus USA300	64.00	512.00	Yuan et al. (2019)
Aeromonas hydrophila CW: MN428791	256.00	512.00	Miao et al. (2021)
Chromabacterium violaceum CV026	31.25	-	Huang (2018)
Psmdomonas aeruginosa PA01	125.00	-	Huang (2018)
<i>Mycobacterium phlei</i> ATCC355	16.00	-	Xu et al. (2014a)

MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration.

acid units could inhibit the growth of Mycobacterium phlei at 0.5 µg/mL. Some derivatives showed enhanced antibacterial effect (MIC = $17.1 \,\mu\text{g/mL}$) against *Mycobacterium tuberculosis* H₂₇Rv. Although the antibacterial activity was weaker than that of isoniazid (INH) and rifampicin (RIF), it was better than that of oridonin itself, and the MIC value was reduced by about half (Xu et al., 2014b). In research by Li et al. (2016), the R group was substituted with an aliphatic compound, and its MIC value for S. aureus and B. subtilis was 3.9 µg/mL, which was better than that of oridonin itself. The derivative with R being substituted by indole had a MIC value of 3.9 µg/mL for S. aureus, which was the same as that of chloramphenicol, and 2.0 µg/mL for B. subtilis, which was lower than that of chloramphenicol by 7.8 µg/mL. In the future, the bioavailability of oridonin could be further improved using advanced techniques and combining microparticles, embedding bodies, liposomes, and nanoparticles (Yang et al., 2021).

6 Antibacterial mechanism of oridonin

The antibacterial mechanism of oridonin against S. aureus and P. hydrophila was similar (Yuan et al., 2019; Miao et al., 2021). Oridonin can increase the permeability of bacterial cell membrane and cell wall, destroy the barrier between cell cytoplasm and the external environment, and make the internal environment of bacteria unbalanced, thus interfering with the growth and metabolism of bacteria. Moreover, results of the scanning and transmission electron microscopy showed that oridonin treatment could lead to membrane damage, bacterial deformation, separation of the cell membrane and cell wall, loss of cell contents, and internal cavitation. Moreover, the 4;6-diamidino-2-phenylindole (DAPI) staining results of S. aureus and P. hydrophila demonstrated that the membrane permeability of bacteria increased, and intracellular nucleic acid was lost after oridonin treatment (Yuan et al., 2019; Miao et al., 2021). Oridonin can also inhibit the respiratory metabolism of S. aureus through the tricarboxylic acid circulation pathway, including the inhibition of succinate dehydrogenase (SDH) and malate dehydrogenase (MDH) (McNeil et al., 2014; Takahashi-Iniguez et al., 2016). In the respiratory metabolism of S. aureus and P. hydrophila, oridonin mainly reduces the activity of lactate dehydrogenase during anaerobic metabolism, resulting in bacterial energy metabolism disruption. Energy metabolism disorder will further lead to protein synthesis obstruction and nucleic acid metabolism disorder (Chen & Nielsen, 2019). Thus, the total soluble protein content of S. aureus and P. hydrophila treated with oridonin showed a decreasing trend with the increase in mass concentration compared with that of the blank control (Yuan et al., 2019; Miao et al., 2021). And oridonin inhibited protein synthesis and interfered with the metabolism of bacteria. The above reports indicate that the antibacterial effect of oridonin on bacteria is multi-dimensional, which is different from the single target antibacterial effect of antibiotics, and can reduce and slow down the generation of drug-resistant bacteria.

Oridonin could inhibit the biofilm formation of S. aureus by interfering with quorum sensing (Jiu et al., 2020). The mechanism schematic is shown in Figure 2. Stimulation with oridonin could regulate the expression of *agrA* and *sarA* (Thompson & Brown, 2021). AgrA and SarA regulate the expression of *ica* operon and cid operon, respectively. The icaA gene encodes acetylglucosamine transferase, which is responsible for the synthesis of intercellular polysaccharide adhesin (PIA) (Atkin et al., 2014). The cidA gene mediates programmed death and cell lysis of bacterial cells and then secretes environmental DNA (eDNA) (Arciola et al., 2015). eDNA and PIA are the main substances for bacteria to produce and form biofilm (Peterson et al., 2013). The expression levels of agrA, sarA, icaA, and cidA in S. aureus decreased significantly after being treated with oridonin, thus reducing the synthesis of PIA, inhibiting the secretion of eDNA, further changing the permeability of bacterial biofilm, and intervening with the biofilm formation to achieve an antibacterial effect. The antibacterial effect of oridonin on the biofilm formation of *P. aeruginosa* was similar to that of S. aureus. Oridonin can cause the downregulation of *lasR* and *rhlR* that are related to its quorum sensing system, and inhibit the formation of rhamnolipid and biofilm of P.

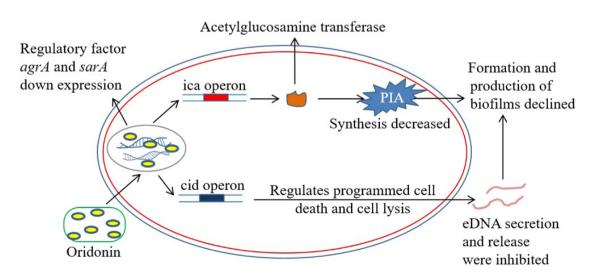


Figure 2. Mechanism diagram of the intervention of oridonin on the formation of S. aureus biofilm.

aeruginosa. Also, oridonin could affect the activity of hydrolytic protease and elastase, and reduce the adhesion of the bacterial attachment surface and the drug permeation barrier caused by the biofilm (Huang, 2018). It can also improve drug sensitivity to achieve better antibacterial effect. Many food-borne pathogenic bacteria could contaminate food and endanger the health of consumers by forming biofilms on the surfaces of food. Given the antibacterial effect of oridonin on *S. aureus*, it can be used in the food industry to reduce the attachment and spread of pathogenic bacteria on food production and processing devices as well as the possibility of food being contaminated by bacteria to a certain extent. Thus, oridonin can be developed as a surface bactericide. However, it is still necessary to explore and consider the preparation and safety of appropriate dosage forms.

7 Antifungal mechanism of *Rabdosia rubescens* extract

At present, there is no report on the antifungal mechanism of oridonin, but there is a study on the inhibition mechanism of the oridonin n-butanol extract against Ascochyta molleriana wint (Li, 2020). The antifungal mechanism of Rabdosia rubescens extract is shown in Figure 3. The extract achieves the antifungal effect mainly by destroying the cell membrane and inhibiting the synthesis and metabolism of intracellular substances. *R. rubescens* extract can destroy the mycelium morphology of Ascochyta molleriana wint and increase the permeability of the cell membrane, which is mainly reflected as the increase in the conductivity and polysaccharide content of the mycelium solution. The propidium iodide (PI) staining results show that the transfection rate of the extract treatment group increased as the concentration increased, reaching 100% at 5 mg/mL, whereas the protein content in the mycelium solution first increased, and then decreased, which is different from the trend of the extracellular protein content, which increased when the permeability of the bacterial cell membrane increased. This is related to the way of obtaining nutrition through the mycelium during the growth of the fungi (Johns et al., 2021). However, the

phenomenon wherein the soluble protein content in the mycelium decreases is consistent with the performance of the bacteria, the antifungal activities, and antifungal mechanisms of effective antibacterial components of R. rubescens were the same in the effect of soluble protein on thallus. The polysaccharide content in the mycelium solution increases, and the content of total polysaccharides in bacteria decreases. The decrease in ergosterol level shows that the R. rubescens extract has an inhibitory effect on the synthesis of the intracellular substances of fungi (Oktay Başeğmez et al., 2021). The antifungal effect of R. rubescens extract on Ascochyta molleriana wint is achieved by damaging the cell membrane and inhibiting the synthesis of protein, which is consistent with the antibacterial mechanism clarified by other natural antibacterial agents and has a guiding significance for the antifungal research of oridonin in R. rubescens (Ju et al., 2020; Meng et al., 2020; Yin et al., 2021). On this basis, we can conduct antifungal research on oridonin, a single component from Rabdosia rubescens, especially its influence on the fungal gene level to explore the antifungal mechanism and target of oridonin to make oridonin more broad-spectrum and effective.

8 Synergistic antimicrobial activity of oridonin

Studies have shown that oridonin combined with other drugs, such as fluconazole, itraconazole, and voriconazole, could reduce the dosage of drugs and the drug resistance of bacteria (Chen et al., 2021). Compared with that the treatment of four kinds of azole-resistant *Candida albicans* with azole drugs alone, the addition of 8 μ g/mL oridonin could lessen the MIC values of fluconazole, itraconazole, and voriconazole by 128 times, 64 times, and 250 times, respectively, which significantly reverses the drug resistance of azole-resistant *C. albicans*. Oridonin can significantly reduce the expression of efflux-related genes *CDR1* and *CDR2* caused by azole drugs, which could inhibit drug efflux and reverse the drug resistance of pathogenic microorganisms, raising the question that if it can be used for food preservation. Can oridonin improve the sensitivity

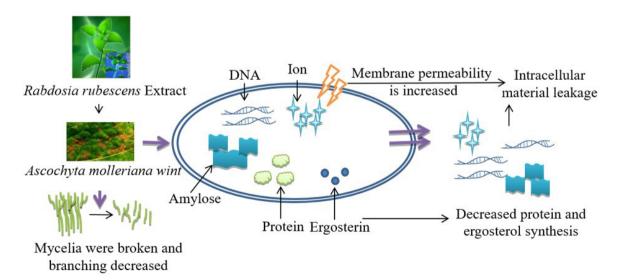


Figure 3. Schematic depicting the mechanism of Rabdosia rubescens extract against Ascochyta molleriana wint.

of pathogenic bacteria and reduce the dosage of drugs when combined with other preservatives? If so, oridonin treatment can reduce the use of additives in food while achieving the purpose of bacteria inhibition and food preservation to make food safer and healthier.

9 Security research status

Oridonin is safe and non-toxic in many studies, but it may show adverse effects or even toxicity under certain conditions such as high-dose administration. Oridonin showed a significant effect on the expression and activity of cytochrome P450 in HepaRG cells and induces the expression of mRNA and protein of the main member of CYP450s (Zhang et al., 2018). Li et al. administered the alcohol extract of Rabdosia rubescens to rats by intragastric administration and found that a high dose of oridonin could lead to adverse reactions such as loss of appetite in rats (Li et al., 2013). After pathological examination, it was found that rats had liver and kidney injuries, and the degree of the lesions was dose-dependent. Tian et al. evaluated the biological safety of oridonin with the help of a zebrafish model and monitored the physiological activities of zebrafish and conducted fluorescent quantitative PCR on the RNA samples of zebrafish embryos, juvenile zebrafish, and adult zebrafish (Tian et al., 2019). Oridonin promoted movement and increased the hatching rate of the zebrafish at a low dose and inhibited the movement and hatching rate at a high dose. Oridonin also caused obvious teratogenic damage to embryos. Consistent with this, the results of qRT-PCR of the RNA samples showed that oridonin had adverse effects on zebrafish embryo development by down-regulating the expression of the VEGFR3 gene, which indicated that oridonin was not completely harmless. In future, the key point for oridonin application is to reduce the dosage to avoid toxicity or modify it to improve its biological safety.

10 Antibacterial application of oridonin

Oridonin is widely used because of its pharmacological and biological activities and plant origin. It has a positive effect on the intestinal flora of animals. Thus, in broilers infected with Salmonella, researchers added oridonin to the diet. Results showed that oridonin could significantly reduce the population of Salmonella in the intestinal flora of broilers and significantly increase the population of lactic acid bacteria, which produced antibacterial and anti-inflammatory effects, protected intestinal health of broilers, and improved the immunity of broilers (Wu et al., 2018). In the aspect of food preservation, oridonin has been used in food packaging because of its broad-spectrum antibacterial effect. For meat preservation, a study showed that an oridonin/chitosan composite membrane can be used for the preservation of chilled chicken breast (Wang et al., 2021a). By inhibiting the growth of microorganisms and blocking direct contact with the environment, oridonin delayed the change in the color of the chicken and its elasticity and reduced the generation of mucus and bad odor, thereby prolonging the preservation period of the chicken breast. In an experiment where fresh fruits such as oranges, apples, and peaches were infected with Penicillium, Colletotrichum gloeosporioides, Aspergillus Niger, and yeast, Rabdosia rubescens extract significantly reduced the infection rate of fruits, inhibited the spread of infected parts of the disease spots, and controlled further spread of diseases in fruits (Niu, 2014). For clinical use, based on the promising activity of oridonin and Rabdosia rubescens components in inhibiting MRSA growth, an antibacterial cream was made for external use by combining the oridonin-based Rabdosia rubescens extract with penetration enhancers, such as green thorn fruit oil (Chen, 2013). Experiments to evaluate anti-infective activity were carried out in guinea pigs inoculated with S. aureus and Duroc mini-pig models inoculated with MRSA, smear this antibacterial cream on the wound that has been artificially infected with MRSA. It was found that the skin in the non-infected parts of the animals had no redness and peeling after administration, and the redness and swelling of the skin in the infected parts disappeared after smearing this antibacterial cream. The number of bacteria in the infected parts showed a decreasing trend with the antibacterial cream treatment time, which indicated that the cream was safe and non-irritating and had a local anti-bacterial effect (Tian et al., 2016). There are studies on whitening antibacterial toner prepared based on the antibacterial activity of Rabdosia rubescens and functional beverage prepared by compounding with other Chinese herbal medicines, all of which reflected the development and application value of oridonin's antibacterial activity (Zang, 2019). At present, the development of antibacterial and fresh-keeping products with oridonin is limited. Once the antibacterial mechanism has been identified, we could develop various antibacterial products, improve and optimize the above existing antibacterial agents, and further broaden the application of oridonin, such as its application as a food preservative or edible fresh-keeping film, or combining it with other drugs or preservatives for bacterial inhibition and food preservation to improve the utilization rate and economic benefits of oridonin.

11 Conclusions and prospects

Oridonin has shown great application potential in the antibacterial field, which makes it a good candidate as a food preservation component. Oridonin can change the permeability of the cell membrane and alter the genetic information by influencing the physiological activities, such as protein synthesis, respiratory metabolism, and secretion of substances related to biofilm formation. Therefore, oridonin is expected to be widely used in the preservation of meat, fruit, and vegetable. However, to the best of our knowledge, studies on the antifungal activity of oridonin have not been reported; thus, its related mechanism and practical application need to be further studied, especially on the following aspects:

The antibacterial spectrum needs to be improved. Although oridonin has broad-spectrum antibacterial properties, the main model bacteria used for oridonin research were *S. aureus* and *P. hydrophila*. Antibacterial research about pathogenic bacteria, such as *Vibrio parahaemolyticus*, pathogenic *E. coli*, and *Listeria monocytogenes*, needs to be carried out.

The antimicrobial mechanism needs further study. The antimicrobial mechanism of oridonin is mainly focused on its antibacterial effect, and there is a lack of research on its fungicidal effect and antifungal mechanism. Whether oridonin has similar antifungal activity to its antibacterial activity without triggering oridonin-resistant needs further research.

In some cases, the *in vivo* administration of high-dose oridonin showed some adverse effects on animal livers, kidneys, or early embryo development. Therefore, the biological safety of oridonin cannot be ignored for its wider application in food industry or medical field.

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