Research Article

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Research Progress on Antibiosis Activity of Scutellaria Flavonoids

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ABSTRACT

Scutellariae (Huangqin) is a traditional medicine that is widely applied in China for the treatment of cold and fever, and nowadays research found that it can against pathogenic microorganism. Flavonoids is the main active constituent isolated from Scutellariae and possesses outstanding antibiosis activity. Scutellaria flavonoids displayed antiseptic actions and anti-resistance, including but not limited to destroy bacterial biofilm, suppressed activity of the DNA enzyme, restrain efflux pump and quorum-sensing system. This paper highlights and discusses the antibiosis activity of Scutellaria flavonoids, along with possible mechanisms of its action. hoping to providing basis and evidence for clinical application.

Keywords: Scutellaria; Scutellaria flavonoids; Bacteria; Antibiosis

INTRODUCTION

Scutellariae (Huangqin),the dried root of *Scutellaria baicalensis* Georgi, is a widespread used herb in clinic to treat cold, fever, and infectious diseases in china [1]. In the past decades, researchers found that scutellariae display various bioactivity including anti-inflammatory, antiviral, neuroprotection and antibiosis [2]. Flavonoids are class of compounds with rich pharmacological activities and have excellent antibacterial performance,which is main active constituent of scutellariae [3]. Nowadays, baicalin has been regarded as one of the index components in scutellariae, and its content should not be less than 8.0% percent in scutellariae according to Pharmacopoeia of the People's Republic of China [1]. Modern research has found baicalin can inhibit the growth of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candidicoccus albicans*, which via destroying the bacterial biofilm, reduce the expression of bacterial virulence factors. Not only baicalin but also baicalein and wogonoside have excellent antibacterial effects, and their chemical structure is shown in Figure 1. Herein, the antibiosis of Scutellariae flavonoids were discussed, and even more the mechanism。

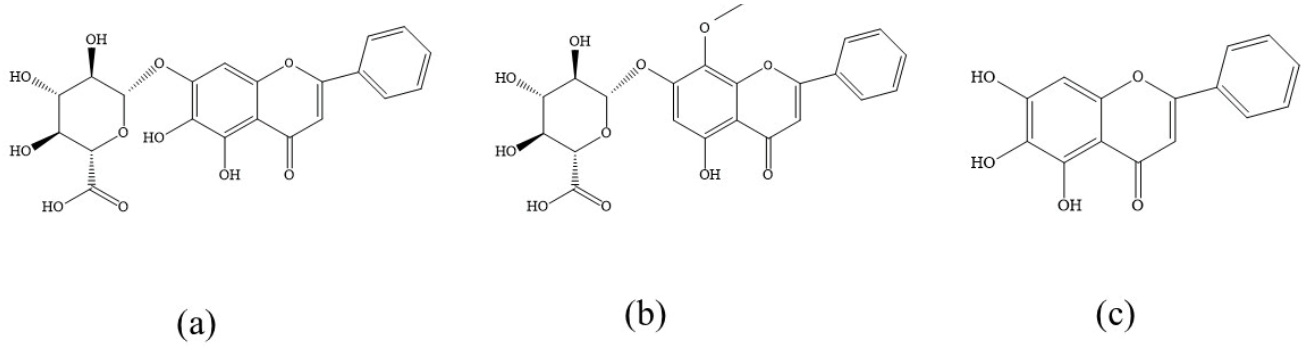

Figure 1: The chemical structures of Baicalin (a), Wogonoside (b) and Baicalein (c).

Staphylococcus aureus

Staphylococcus aureus (SA) is a conditionally pathogenic gram-positive bacterium, which causing infectious diseases such as pericarditis, cephalomeningitis and septicemia [4]. The minimum inhibitory concentration(MIC) of baicalin and baicalein were 1mg/mL and 0.25mg/mL [5]. Baicalin can increase the conductivity of and nucleic acid leakage of SA in the concentration of 1g/mL, at the same time, thallus were withered and broken [6]. Baicalin can suppressed the formation of biofilm and damage the cell membrane of SA [7]. Baicalin can inhibit the expression of many virulence factors of SA. Wang et al.found that baicalin were interaction with residues Asn^{92} and Tyr^{128} which directly binds to the active center of the key virulence factor, Sortase B (SrtB) [8]. Moreover, baicalin impeded the cell lysis activity of α-hemolysin (Hla) by way of combining with the Y148, P151, and F153 of Hla [9]. In animals, it was enhanced bacterial clearance and survival rate via attenuating the expression of inflammatory factors, increasing the number of lymphocytes and dendritic cells and inhibiting the apoptosis of tissue cells [10-12].

Interestingly, baicalein also showed significant inhibition on methicillin-resistant Staphylococcus aureus (MRSA),the MIC were 0.64μg/mL [13]. Further studies showed, it embeds and binds DNA to inhibit the activity of DNA isomeric topoisomerase, resulting in DNA replication and transcription abnormalities and loss of biological function in vivo, but does not affect the integrity of MRSA cells and cell walls [14,15]. Reversal of bacterial resistance to β-lactam antibiotics against MRSA at a baicalein dose of 5mg/mL [16]. This effect caused by restraining NorA efflux pump, suppressing MRSA-specific pyruvate kinase lead to deficiency of ATP and attenuating SOS-response [17,18]. Baicalein integrates with Asp-75 and Lys-80 residues binding to Von Willebrand factor-binding protein(vWbp) which affected bacteria proliferation [19]. chen et al. found that baicalein treatment reduced staphylococcal enterotoxin A (SEA) and Hla levels, downregulated the quorum-sensing system regulators agrA, RNAIII, and sarA, and gene expression of ica [20]. Baicalein inhibited the accessory gene regulator system, reducing the expression of SEA, thus lowering CRP and PCT levels [21].

Pseudomonas aeruginosa

Pseudomonas aeruginosa (PA), is a conditionally pathogenic Gram-negative bacterium,which induced infectious disease including endocardial infection, urinary tract infection, gangrene pustulosis [22]. Baicalin inhibited the growth of PA biofilm and reduced bacterial adhesion at 0.625mg/mL;baicalin (3.75mg/ml) diminished the expression of LasR, RhlR and PvdQ in quorum-sensing (QS)systems system, which is closely related to biofilm formation of PA. baicalin (15.65mg/mL) can destroy biofilm of Pseudomonas aeruginosa; When the concentration reaches 32.25 mg/L, baicalin had significant effects in interfering with the biofilm formation of PA, reducing the yield of polysaccharide-protein complexes, and inhibiting the expression of (QS)Las1m RNAm [23-26]. In addition, baicalin attenuated the expression of 3-oxo-C12-HSL and C4-HSL of QS signaling [27]. Moreover, baicalin suppressed the functional genes of PA such as virulence genes,quorum sensing genes and motility related genes [28].

Baicalein inhibited the formation of bacterial biofilm and suppressed the adhesion of PA at a concentration of 2μg/mL [29]. When the concentration were increased to 64μg/mL,it suppressed that clust movement and twitching movement ability of PA [30,31]. Baicalein reduces the secretion of inflammatory factors in macrophages by inhibiting the activation of PA-infected macrophage MAPK and NFκB signal transduction pathways [32].

Escherichia coli

Escherichia coli (E. coli), is a gram-negative bacterium which is an important strain of human intestinal flora, but at the same time, it can cause diarrhea, abdominal pain, fever and other diseases [33]. The MIC of baicalin were 512mg/mL, it were hindered the formation of E. coli biofilm and significantly reduce the adhesion gene fliC [34]. Moreover, baicalin attenuated cytotoxicity of E. coli via forming a pentamer with Shiga toxins 1 and 2 (Stx1 and Stx2) [35]. When the concentration were 4-40 mM, baicalein promoted hydrolysis of receptor TraR protein [36]. Baicalein can inhibit the activity of ATP synthase and the synthesis of ATP in E. coli [37].

Helicobacter pylori

Helicobacter pylori (Hp), a microaerobic Gram-negative bacteria, was first isolated from the gastric mucosa by Australian scholars Warren and Mashall in 1983. Hp is closely related to the occurrence of a variety of digestive diseases, which can lead to stomach cancer, gastric mucosa-related lymphoma, whereupon the World Health Organization therefore identified it as a Class I carcinogen in 1994 [38]. The MIC90 and MIC50 of jaundice for 10 clinical Hp strains were 1.31mg/mL, 1.05mg/mL, and the MIC for multi-drug-resistant Hp strains was 25-200mg/mL [39,40]. Baicilin inhibits the pyroenose of Hp, which binds to the flap region of the pyroenose, preventing the flap region from shutting down [41]. And through the thiohydro bond with the space with the key with the customs Cys321 located on the mobileflap [42]. High expression of hefA gene, one of the coding active exosotysis systems, is associated with HP's resistance, and baicilin can

reduce the expression of the hefA gene [43]. Baicalin and baicalin inhibited the expression of Hp vacuolating cytotoxin A (vacA), a type of gastric epithelial cell that causes the gastric epithelial cells to bubble [44]. In Hp-induced human gastric epithelial GES-1 cells, baicalin(60mg/L) reduces the inflammation factors secreted by GES-1 cells infected with HP, promotes cell proliferation and reduces apoptosis. Further studies demonstrated that this is associated with inhibition of p38 MAPK pathways [45].

Acinetobacter baumannii

Acinetobacter baumannii (AB), a Gram-negative bacterium, which is a strict oxygen demand, non-lactose fermentation condition pathogenic bacteria [46]. The MICs of baicalein and wogonoside were 0.625 and 0.125mg/mL, and baicalein restrained the biofilm of AB [47]. Further research observed that baicalein stimulated the expression of adeA, adeR, adeS genes of efflux pump, OXA-23,OXA-51 genes of β-lactamase, and CarO,OmpAv of membrane protein [48].

Klebsiella pneumoniae

Klebsiella pneumoniae (Kpn) has capsuleis, is a Gram-negativeand and opportunistic pathogen that is native to the gastrointestinal tract and the pharynx [49]. The MIC of baicalin were 6.250 mg/mL,and it suppressed biofilm formation [50,51]. CTX-M is a dominant gene for antibiotic resistance to β-lactamase in broad-spectrum β-lactamase Kpn,the combination therapy of baicalein and cefotaxime can remarkably decrease transcribed mRNA level of CTX-M-1 [22].

Salmonella typhimurium

Salmonella typhimurium (S. Typhimurium) is a Gram-negative, spore-less anaerobic bacteria, which is closely related to diarrhea [52]. Baicalien diminished S. Typhimurium on epithelial cells by hindering S.Typhimurium pathogenicity island-1 (SPI-1) type III secretion system (T3SS) and translocase at 50M [53]. And baicalien attenuated the levels of tumor necrosis factor α(TNF-α), nitrate, and lactate dehydrogenase (LDH) from S. typhimurium-infected Caco-2 cells [54]. Moreover,baicalin and baicalein can significantly restrain the transcription levels of sopB, sopE, and sopE2 genes which are associated with the Salmonella pathogenicity island 1 virulence S. Typhimurium [54].

Mycobacterium tuberculosis

Mycobacterium tuberculosis (Mtb), is the main pathogen of tuberculosis [55]. Baicalin has a significant inhibitory effect on Mtb, the MICs were 0.75~12mg/m [56]. For clinically resistant bacteria, the MICs of baicalin for 37 clinically isolated strains was 1.5g/L, with a maximum greater than 48 g/L [57]. The concentration of baicalin increased the morphological change of Mycobacterium tuberculosis, and the degree of damage was increasing [58]. Further studies have found that baicalin is not only attached to the surface of Mtb, but also in the inside of Mtb to play a role, the site of action is cytoplasm [59]. In Mtb infected mice, baicalin activate inflammasomes and inducing autophagy of host macrophages [60].

Candidicoccus albicans

Candidicoccus albicans (C.albicans), a single-celled eukaryote, most exists in the body's gastrointestinal tract, mouth, and urethra [61]. The MIC of baicalin were 1.0 mg/mL, it inhibits the formation and adhesion of the C.albicans tube [25,62]. Baicalin affected the synthesis of DNA, RNA, and proteins by inhibiting leucine in bacteria [63]. Baicalin induced the nuclear solidification and fragmentation of C.albicans cell, and it lowed the expression of mitochondrial membrane potential(MMP) ,and enhanced the CAP1,SOD2 and TRR1 genes which are relevant to redox and the level of reactive oxygen species (ROS) [64,65]. Besides, baicalin affected the cell cycle and ultra-microstructure of candida biofilm cells, hindered cell growth cycles, and disrupted their mitochondrial function, even induced biofilm apoptosis via activating Cytochrome C(Cyt C) and metacaspase [66,67]. The combination with fluconazole reduces hydrophobicity on the surface of the biofilm [68]. In addition, the MICs of baicalein ranged from 13 to 104μg/mL of six C.albicans [69].

Bacteria associated with periodontitis

The MICs of baicalin were 1.0,2.0 and 2.0 g/L, and the MBCs were 2.0, 8.0 and 4.0 g/L of *Porphyromonas gingivalis* (P.g), *Fusobacterium nucleatum* (F.n) and *Aggregatibacter actinomycetemcomitans* (A.a) [70]. When the concentration of baicalin reached 500 μg/mL,it hindered formation biofilm of *streptococcus mutans* which is the main caries pathogen, and inhibited the production of acids [71]. In periodontitis rats, baicalin reduced inflammatory responses in rats with laboratory periodontitis and the alveolar bone loss via inhibition toll-like receptor 2(TLR2) and toll-like receptor 4 (TLR4) expression and downstream signaling [72].

CONCLUSION

In recent years, as an antibacterial and treatment of infectious diseases, Chinese medicine has received widespread attention because of its good efficacy and its difficulty in producing drug resistance. The growth of bacteria and the formation of biofilms are inhibited by flavonoids of scutellariae. Of note, flavonoids inhibited the activity of enzymes in DNA, affecting the metabolism of bacteria and the synthesis of

macromolecular substances. More importantly, for resistant bacteria, flavonoids inhibited efflux pump and quorum sensing. In animals, flavonoids diminished adhesion to the host and increased the removal rate of host bacteria, also reduces the host's inflammatory response. This makes it promising to be a clinically innovative drug. However, more data from preclinical studies are needed,including pharmacokinetics and pharmacodynamics. As well as its modern pharmacological research is limited to in vitro and animal experiments, has not been widely used and clinical, which to a certain extent limits the drug value.

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