Antimicrobial Activity of *Scutellaria Baicalensis* Extract with Different Solvents against *Escherichia coli*

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Abstract:

Background: Huang Qin (*Scutellaria baicalensis, S. baicalensis*) has been used to treat various diseases such as fever, diarrhea, and dysentery. *Escherichia coli* (*E. coli*) is a standard part of intestinal microbiota and the common cause of several diseases that come with diarrhea, stomach cramps, and fever.

Objectives: This paper aimed to determine the antimicrobial activity of *S. baicalensis* extract with different solvents (water, ethanol, and ethyl acetate) against *E. coli*.

Materials and Method: *S. baicalensis* is ground into powder and macerated in solvents until exhausted and extracted via evaporation under vacuum. The water extract *S. baicalensis* (WHQ), ethanol extract *S. baicalensis* (EtOHHQ), and Ethyl Acetate extract *S. baicalensis* (EtOAcHQ) dissolved in dimethyl sulfoxide (DMSO). The agar wall diffusion method was used to test antimicrobial activity. The microdilution method determined the minimum inhibitory concentration (MIC) of the extractions. The extractions' minimum bactericidal concentration (MBC) was evaluated from the agar plate, and no microbial growth area was observed.

Results: The average inhibition zone in MIC of EtOHHQ was 7.33 ± 0.58 mm, EtOAcHQ was 7.67 ± 0.58 mm, Baicalein was 7.67 ± 0.58 mm, while Gentamicin showed 16.33 ± 0.58 mm. MIC of EtOHHQ, EtOAcHQ, and Baicalein were > 2,000 μg/ml, while MIC of Gentamicin was 6.25 μg/ml. MBC of EtOHHQ, EtOAcHQ, and Baicalein were > 2,000 μg/ml, while MBC of Gentamicin was 6.25 μg/ml. WHQ and Baicalin did not show antimicrobial activity against *E. coli*.

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Conclusion: *S. baicelensis* extraction can inhibit the growth of *E. coli* with a high concentration.

Keywords: *Scutellaria Baicalensis, Escherichia coli*, Ethanol, Ethyl acetate, Anti-microbial

Introduction

S. baicalensis is a flowering plant in the Lamiaceae family and is widely used in traditional Chinese medicine (TCM). It is mainly distributed in East Asia, Europe, and America; China remains the primary producer for medical purposes.[1] In TCM, *S. baicalensis* is known for clearing heat, removing dampness, and calming the fetus. It is important in various TCM formulas, such as Xiao Chai Hu decoction, Ban Xia Xie Xin decoction, and Huang Lian Jie Du decoction. Clinical applications mainly use the plant's roots as a medicine to treat diseases related to diarrhea, inflammation, and respiratory infections.[2]

S. baicalensis has been isolated and identified using various methods to find the compounds' content. The Chemical constituents of *S. baicalensis* are divided into five categories: flavonoids, volatile oils, terpenoids, polysaccharides, and other components. The major compounds of *S. baicalensis* are flavonoids and glycosides.[3] 126 small molecule compounds and six polysaccharides have been isolated from *S. baicalensis*, with baicalein and baicalin being the main active compounds of *S. baicalensis*.[4]

S. baicalensis and its major compounds exhibit significant anti-microbial activities. The water extract of S. baicalensis could inhibit a broad spectrum of oral bacteria (MIC, 15.7-62.5 MBC, 20-125 mg/ml), including *Streptococcus sanguis II*, *S. salivarius*, *Actinomyces viscosus*, *A. naeslundi*, *A. odontolyticus*, two strains of *Capnocytophaga*, *Bacteroides melaninogenicus ss intermedius*, *B. gingivalis*, *Fusobacterium nucleatum*, and *Actinobacillus actinomycetemcomitans*.[5] It could also inhibit the growth of *Candida albicans* at a concentration of 5 mg/ml and 2.5 mg/ml.[6] *S. baicalensis* extracts have shown substantial antibacterial effects against *Bacillus*, *cereus*, *E. coli*, *Listeria monocytogenes*, *Salmonella anatum*, and *Staphylococcus aureus* in a previous study.[7]

E. coli bacteria typically reside in the intestines of humans and animals.[8] Most types of *E. coli* are harmless, but a few strains of *E. coli* can cause severe gastroenteritis, urinary tract infections, neonatal meningitis, hemorrhagic colitis, and Crohn's disease. Common symptoms include abdominal cramps, diarrhea with blood, and vomiting.[9] Most people get well within 5 to 7 days, but some can become severe or life-threatening. Approximately 5 to 10% of people who are diagnosed with *Shiga toxin-producing E. coli* (STEC) infection develop a potentially life-threatening complication known as hemolytic uremic syndrome.

Consumption of fresh vegetables can expose individuals to enteric pathogens, which include *Salmonella, Shigella, Listeria monocytogenes,* and pathogenic *E. coli*.[10,11] In Thailand, the dietary habit of consuming uncooked vegetables might be a risk to people's *E. coli* infection. An investigation by Leelaporn et al. reported that Enterotoxigenic *E. coli* (ETEC) was 11.6% and STEC was 2.2% among 181 isolated pathogens.[12] Another study by Chomvarin et al. reported 140 *E. coli* obtained from 186 food samples from various categories in Khon Kaen province, Thailand, and reported the occurrence of 140 *E. coli*.[13] Nawattanapaibool et al. found *E. coli* and STEC in 11.00% and 9.67% of 300 fruits and vegetables samples in Bangkok.[14]

This research aimed to determine the antimicrobial activity of *S. baicalensis* extract with different solvents against *E. coli* and provide a choice of natural medicine to inhibit the growth of *E. coli*. The research gaps of this study are comparing the antimicrobial activity differences between three types of *S. baicalensis* extracts.

Materials and Method

S. Baicalensis preparation

The root of *S. baicalensis* will be collected from the Chinese herbal store "Tong Hua" in Chiangrai, Thailand, and authenticated by the Chinese Medicine expert from Chengdu University of Traditional Chinese Medicine Affiliated Hospital. Ethanol and ethyl acetate were purchased from Union Science Co., Ltd. Baicalin and Baicalein were purchased from Life Science AP Co., Ltd. All materials were deposited at the School of Integrative Medicine TCM laboratory at Mae Fah Luang University.

The root of *S. baicalensis* was washed and dried in a hot air oven at 45°C.[15] Once dried, it is ground into powders and macerated in distilled water, ethanol, and ethyl acetate until exhausted, using a ratio of 100g of powder with 400g of solvent (1:4). The resulting extract evaporates under vacuum. The yield was weighted, recorded, and stored at -20°C.

Antimicrobial activity

The *S. baicalensis* extract dissolved in dimethyl sulfoxide (DMSO). The agar well diffusion method was used to test antimicrobial activities.[16] Laboratory strain *E. coli* (Code: dmst4212) was grown on Mueller Hinton agar (for bacteria) and then incubated at 37°C for 24 hours. The turbidity of the culture was modulated to about 0.5 McFarland standard and suspended in 0.85% sodium chloride. The assay was performed using the double agar layer technique. One hundred of the suspension was added to 3 ml of sterile seeds agar, and then, it was poured on sterile base agar and offered all plates dried at room temperature. A sterile cork borer (6mm) was applied to punch holes on agar plates. Added 20 µl of *S. baicalensis* extracts (200 mg/ml), 20 w DMSO as a negative control, and 10 µl of Gentamicin (10 mg/ml) as positive controls in each well, respectively. Incubated for 24 hours. The diameters of the inhibition zone were measured. Each sample was tested in triplicate.

Minimum inhibitory concentration and minimum bactericidal concentration.

MIC was determined by the micro-dilution method in 96 microtiter plates.[17] All test solutions, including extracts and controls, were analyzed in triplicate for reproducibility. Serial two-fold dilutions of the test extract or positive control were prepared across wells in columns 1 to 10. Column 11 was negative control, while column 12 contained only broth media as sterility control. Each well was filled with 50 µl of tested solutions in broth and 50 µl microbial suspended in broth and incubated at 37°C for 24 hours. MIC was recorded at the last well, which showed a clear solution. Streaked clear inoculate broth on Mueller Hinton agar (for bacteria), then incubated the agar plate at 37°C for 24 hours. The determination of MBC was evaluated from the agar plate, which showed no microbial growth. All tested solutions were analyzed in triplicate. In the agar plate, the inhibition zone is the area that is not entirely clear of microbial growth but clearer than the areas of the plate with uninterrupted microbial growth. When considering the anti-microbial results, the killing zone was counted as the anti-microbial substance to kill the microbial entirely and not only reduce it.

High performance liquid chromatography (HPLC)

WHQ, EtOHHQ, and EtOAcHQ compounds were determined using versatile high-performance liquid chromatography (Agilent 1260 infinity II, USA). Baicalin and Baicalein were determined as standard compounds. The column (particle size 5 µm, 150 mm x 4.6 mm) was used. The flow rate was 1.0 ml/min at 35 °C. The mobile phase comprised acetonitrile and phosphoric acid (20:80, v/v).[18]

Results

Antimicrobial activity

Figure 1 shows the agar plate for inhibiting *S. baicalensis* against *E. coli*. Gentamicin (G) showed a clear kill zone of Gentamicin. At the same time, EtOHHQ (T1), EtOAcHQ (T2), and Baicalein (B2) showed an inhibition zone against *E. coli*. WHQ (T3) and Baicalin (B1) did not show a kill zone and inhibition zone against *E. coli*.

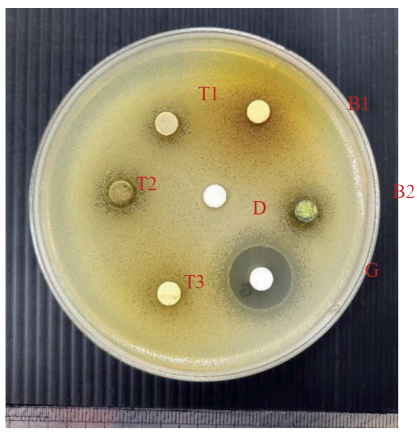


Figure 1 Inhibition zones against *Escherichia coli (T1:EtOHHQ,T2:EtOAcHQ, T3: WHQ, B1: Baicalin, B2: Baicalein, G: Gentamicin, D: DMSO)*

The inhibition effects of *S. baicalensis* extracts on *E. coli* are shown in Table 1 and Figure 2. EtOHHQ, EtOAcHQ, and baicalein showed the inhibition effects on *E. coli*, but WHQ and baicalin did not show the effects on *E. coli* inhibition and clearing. EtOHHQ had an average 7.33 ± 0.58 mm inhibition zone, and EtOAcHQ and baicalein had an average 7.67 ± 0.58 mm inhibition zone.

Table 1 Inhibition zones against Escherichia coli using agar diffusion method

	Tested substance	Inhibition zone (mm) (Mean ± SD)
T1	EtOHHQ (100 mg/ml)	7.33 ± 0.58
T2	EtOAcHQ (100 mg/ml)	7.67 ± 0.58
T3	WHQ (100 mg/ml)	N/A
B1	Baicalin (100 mg/ml)	N/A
B2	Baicalein (100 mg/ml)	7.67 ± 0.58
G	Gentamicin (1 mg/ml)	16.33 ± 0.58
D	DMSO	N/A

*Mean ± SD, Ø 6 mm of disc, N/A = no activity

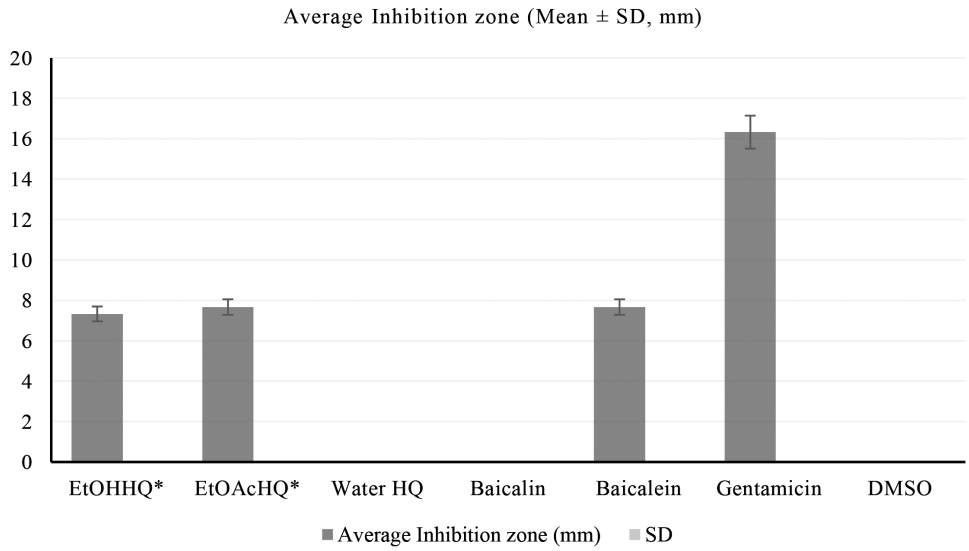


Figure 2 Inhibition zones of EtOHHQ, EtOAcHQ, WHQ, Baicalin, Baicalein, Gentamicin, and DMSO on *E. coli*

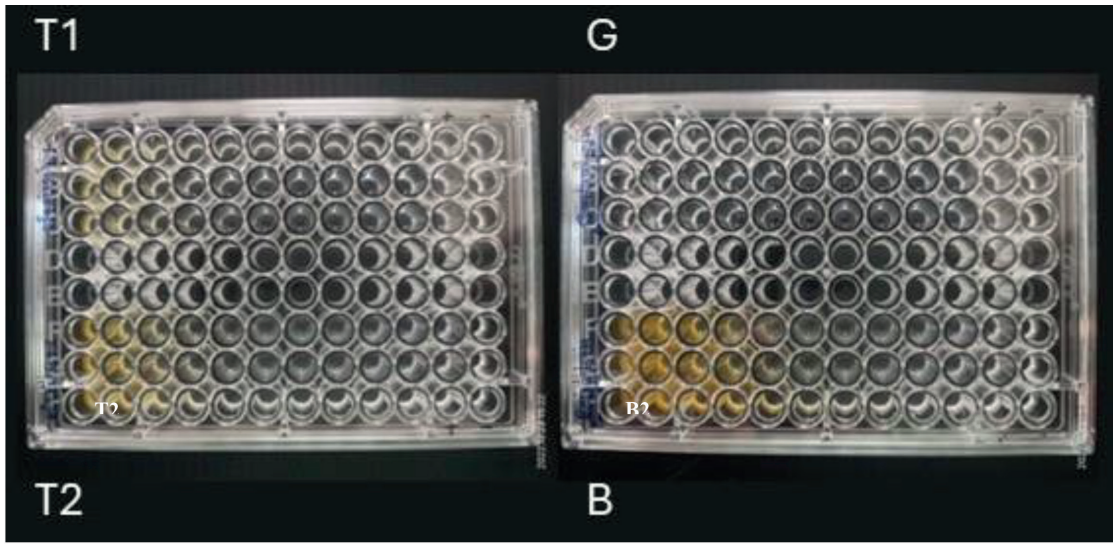
Minimum Inhibition Concentration

The reduction in anti-microbial effects with lower concentrations of the herbal infusion was tested. Table 2, Figure 3, and Figure 4 show the MIC and MBC of *S. baicalensis* extracts against *E. coli*. MIC and MBC of EtOHHQ, EtOAcHQ, and Baicalein were > 2,000 µg/ml. MIC and MBC of Gentamicin were 6.25 µg/ml. Meanwhile, the research did not show MIC and MBC of WHQ and Baicalin.

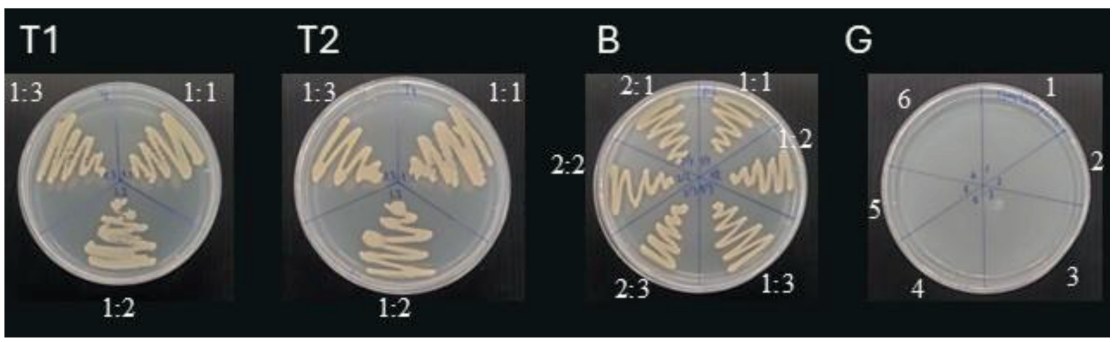
Table 2 Antimicrobial activity against *Escherichia coli* using broth microdilution method

Tested substance	MIC	MBC
EtOHHQ	> 2,000 µg/ml	> 2,000 µg/ml
EtOAcHQ	> 2,000 µg/ml	> 2,000 µg/ml
WHQ	N/A	N/A
Baicalin	N/A	N/A
Baicalein	> 2,000 µg/ml	> 2,000 µg/ml
Gentamicin	6.25 µg/ml	6.25 µg/ml
DMSO	N/A	N/A

* N/A = no activity



T1 = EtOHHQ, T2 = EtOAcHQ, B = Baicalein, G = Gentamicin
Figure 3 Antimicrobial activity against *Escherichia coli* (MIC)



T1 = EtOHHQ, T2 = EtOAc HQ, B = Baicalein, G = Gentamicin
Figure 4 Antimicrobial activity against *Escherichia coli* (MBC)

HPLC

The contents of Baicalin and Baicalein of WHQ, EtOHHQ, and ETOAcHQ were tested. Table 3 shows the content of Baicalin and Baicalein in WHQ, EtOHHQ, and EtOAcHQ. WHQ has more Baicalin compounds than EtOHHQ and EtOAcHQ. EtOHHQ has more Baicalein compounds than WHQ and EtOACHQ.

Table 3 Baicalin and Baicalein in S. Baicalensis extracts analyzed by HPLC.

Baicalin (% w/w)	Baicalein (% w/w)	MBC
WHQ	18.46 ± 0.06	0.93 ± 0.01
EtOHHQ	1.70 ± 0.01	13.80 ± 0.06
EtOAcHQ	2.64 ± 0.1	3.07 ± 0.05

Discussion

EtOH and EtOAc extracts of *S. baicalensis* showed inhibition activity against *E. coli*, significantly different from WHQ. The area of baicalein showed the inhibition zone of *E. coli*. However, the area around baicalin did not show the inhibition area, which means that the active compound that inhibits the growth of *E. coli* in *S. baicalensis* was Baicalein. The results of MIC showed that EtOHHQ and EtOAcHQ required a high concentration to produce a reduction zone of *E. coli*. The results suggest that *S. baicalensis* affects *E. coli* growth inhibition but needs to be with high concentration.

The inhibition and antimicrobial activity of *E. coli* by *S. baicalensis* extraction had been shown in another study.[19] The research showed that *S. baicalensis* extraction brought an average 5mm killed zone, which proved the antimicrobial and inhibition activity of *S. baicalensis* extraction on *E. coli*. Research showed that Baicalin had an inhibitory effect on *E. coli* in vitro; the MIC of Baicalin against *E. coli* isolated from mastitis in dairy cattle was 4000 μg/ml, and antimicrobials such as streptomycin, ciprofloxacin, and ampicillin had synergistic effects in combination with Baicalin. The combination could significantly increase the susceptibility to *E. coli*.[20,21]

However, Wang X. K. found that the active compound that effected antimicrobial activity of the root of *S. baicalensis* was Baicalein.[22] Baicalein can reduce the pathogenic bacteria such as *S. aureus* and *E. coli* by disrupting the cell wall integrity, reducing bacterial enzymatic activities, and inhibiting bacterial energy production and nucleotide synthesis.[23] Baicalin increased the permeability of *E. coli* cell membrane by causing damage, leading to the infiltration of bacterial, and achieving the bacteriostatic effect.[24]

The results of HPLC showed that WHQ has the most Baicalin than the other two extracts, but it has the least Baicalein, which is less than 1% w/w. EtOHHQ has the most Baicalein than the other two extractions (13.8% w/w) but with the least Baicalin compound. EtOAcHQ has almost the same amount of Baicalin and Baicalein, with 2.6% w/w and 3.1% w/w. EtOH and EtOAc can extract more Baicalein from *S. baicalensis*, which makes the extraction more effective in inhibiting *E. coli* while compared with WHQ. However, EtOHHQ and EtOAcHQ did not showed significantly different which suggests that the inhibition zone might be the at the functional saturation point.

EtOH and EtOAc are common solvents in plant compound extraction and product making. EtOH is considered a universal solvent due to its molecular structure, allowing it to dissolve polar, hydrophilic, and nonpolar, hydrophobic compounds. The chemical formula of ethanol is CH3CH2OH. EtOAc is the ester of EtOH and acetic acid, manufactured on a large scale as a solvent with low cost, low toxicity, and agreeable odor.[25] The chemical formula of EtOAc is C4H8O2. These solvents showed a difference in the extraction of *S. baicalensis*; EtOAc might be more suitable for baicalein extraction. *S. baicalensis* was widely regarded as a safe and nontoxic herb in China. Jinsu Lim's[26] study showed that water extract *S. baicalensis* had a lower value in total phenolic and total flavonoid content, which caused lower antioxidant activities. The result is similar to the result of this study; this could be the reason for the lack of anti-microbial in WHQ.

Research tested the acute toxicity of the *S. baicalensis* extraction.[27] The results showed that the maximal tolerated dose of the aqueous extracts of *S. baicalensis* in mice was 72.0 g/kg, and the median lethal concentration value of 80.0% ethanol

extracts of *S. baicalensis* was 39.6g/kg. There are no obvious adverse events on in-vivo *S. baicalensis*. The study showed that the aqueous extracts of *S. baicalensis* had no significant changes in body weight, clinical symptoms, and mortality in rabbits and guinea pigs during dermal stimulation/ corrosion and skin sensitization tests.[28] Another study showed 300 mg/kg, 1250 mg/kg, and 2500 mg/kg of ethanol extracts of *S. baicalensis*; only 2500 mg/kg per day, the liver tissue of the rats showed some reversible inflammatory changes.[29]

In previous studies, *S. baicalensis* did not show many toxicity activities or serious adverse events but showed the effects on antimicrobial activities and treatments in clinical applications. It has been a practical choice for the application in hospitals to antimicrobial and treat patients. Baicalein protected Vero cells from cytotoxicity of Stx1 and Stx2 by binding to the cytoplasmic membrane of the cell and altering its function.[30] *S. baicalensis* has the effect of *E. coli* inhibition with high concentration, making it a potential option for *E. coli* infection.

Conclusion

S. baicalensis extracted by EtOH and EtOAc has the potential to inhibit the growth of *E. coli*. The results showed the difference between water extracts and organic solvent extracts of *S. baicalensis* and the effect of antimicrobials against *E. coli*. This has given a key to the importance of extraction methods in maximizing the pharmacological potential of herbal medicines. Future research should prioritize optimizing extraction, such as ethanol or ethyl acetate extraction, to enhance the yield of hydrophobic compounds. Future studies should also explore synergistic combinations of *S. baicalensis* flavones with conventional antibiotics to lower the effective dose and overcome resistance in Gram-negative pathogens. The findings point toward the potential use of *S. baicalensis* compounds as complementary agents in antimicrobial therapy.

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Conflict of interest

Authors declare that no conflict of interest in the research.

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