Review Article

Ethnopharmacology, Phytochemistry and Pharmacological Properties of Cortex Phellodendri Chinensis: A Comprehensive Review

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pharmacology
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Abstract

Ethnopharmacological Relevance: Cortex Phellodendri Chinensis (CPC), a traditional Chinese medicine known as “HuangBai” in China, are being widely employed as its health benefits. CPC has the function of clearing heat and expelling dampness, purging fire and removing toxin, detumescencing and removing necrotic tissue, which have the treatment for a variety of diseases.

Aim of The Study: The present review is intended to summarize the current researches on the phytochemistry, pharmacological significances and medicinal uses of CPC, hoping to provide reference and scientific basis for the research of bioactive ingredients, quality markers of CPC, as well as further development and utilization in treatment of human diseases with CPC.

Materials and Methods: Extensive search of various documents and electronic databases such as Pubmed, Royal Society of Chemistry, Science Direct, Springer, Web of Science, and Wiley, etc., were done to obtain data. Other online academic libraries, e.g. Google Scholars, Scopus and national pharmacology literature were also been employed to learn more information about CPC. Additional information was derived from herbal classic books, Chinese pharmacopoeia, Postgraduate theses, China national knowledge internet, etc.

Results: The comprehensive analysis of the electronic database and literatures demonstrated that CPC is a valuable herbal medicine with multiple pharmacological effects. Phytochemical and pharmacological analysis indicated alkaloids are the major bioactive ingredients in CPC. However, there are no reports on the research of quality markers of CPC, which means in a short time, there will emerge many studies to fill this gap. Under the guidance of traditional Chinese medicines theory, CPC is usually combined with other traditional Chinese medicines into prescriptions for various clinical use.

Conclusions: This review summarized the results from current researches about the basic characteristics of CPC, such as bioactive constituents, pharmacological effect and mechanism of action, which are still being studied and explored in order to realize the optimal medical practice. Meanwhile, it points out the existed problems of the current researches of CPC and puts forward some suggestions for the future research of CPC.

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Introduction

Cortex Phellodendri Chinensis (CPC), a famous herbal medicine, is the Phellodendron chinense Schneid.of Rutaceae family or the drying bark of Phellodendronamurense Rupr., which widespread in the world. The property of CPC was bitter and cold, moreover, it had the function of clearing away heat, reducing swelling and relieving pain. CPC usually grows in the mountains, riverside, streams and forests. It also widely distributed in China and other Asian regions [1]. Phellodendron chinense cortex is often called “Chuan HuangBai”, and the main producing areas

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are Sichuan, Guizhou, Hubei, Yunnan, Shaanxi, and Guangxi province in China. *Phellodendri amurensis* cortex is usually named as “Guan HuangBai”, and Liaoning, Jilin, Heilongjiang, Hebei province, and Inner Mongolia are the main producing areas (Figure 1).

**Figure 1:** The major production areas of *Cortex Phellodendri Chinensis* in China.

The blue font represents the main producing areas of “Chuan Huang Bai (CHB)”. The red font represents the main producing areas of “Guan HuangBai (GHB)”

The main effective components of CPC are alkaloids, and significant differences in alkaloid species and components existed between *Phellodendri chinense* cortex and *Phellodendri amurensis* cortex. The main components of *Phellodendri chinense* cortex are berberine and phellodendrine, while berberine and palmatine are the main constituents in *Phellodendri amurensis* cortex, moreover, the berberine content in *Phellodendri chinense* cortex is much higher than that in *Phellodendri amurensis* cortex [2-4]. Although the 2005 edition of <Pharmacopoeia of the People's Republic of China> divided CPC into two kinds of medicinal materials, the description function of “Chuan HuangBai” and “Guan HuangBai” are the same.

With Yoyo Tu won the 2015 Nobel Prize in medicine, the researches on herbal medicine has gradually increased. CPC was first recorded as high grade in <Shen Nong Ben Cao Jing>, originally known as “Bo Mu”, having a wide range of clinical effects, such as anti-inflammatory anti-cancer anti-bacterial immunosuppression etc. [5-8]. There have been many studies on the chemical compositions and pharmacological activities of CPC, the medicinal herbs itself and its derived formulas have been widely recognized and used in clinical applications, such as Huanglian Jiedu Decotion (HLJDD), which is not only widely used in China, but also in Japan [9].

In view of the plentiful pharmacological activities of CPC, it is believed that the discovery and clinical application of new drugs based on CPC will have a far-reaching impact on human health through future studies. After consulting literatures, there were no relatively comprehensive reviews on CPC. In the present review, we exhibit a comprehensive overview on the current state of CPC’s medicinal properties, phytochemical composition, pharmacological effects, and its participation in clinical commonly used prescription, both highlighting the potential medicinal benefits of CPC which laying a scientific foundation for the wide application of CPC in clinical practice in future, and assessing the deficiencies of current researches and providing the direction for future CPC studies.

**Phytochemical Constituents**

With the earliest began in 1926, the Japanese scholar isolated berberine and palmatine from the Japanese production of *Phellodendri amurensis cortex*, hereafter, other chemical composition of CPC has been reported consecutively of which mainly include alkaloids, limonoids, flavonoids and so on (Table 1). Other chemical constituents such as lactones also enrich the diversity of chemical constituents of CPC. It is convinced that with the continuous progress of analytical techniques, more components will be detected and identified. The more components are identified, the research of CPC will be more thorough.

**Table 1:** Chemical compounds isolated and characterized from CPC.

<table>
<thead>
<tr>
<th>Category</th>
<th>Chemical compound</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
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<tr>
<td></td>
<td><em>Protoberberines</em></td>
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<td></td>
<td>Berberine 1</td>
<td>[1]</td>
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<td></td>
<td>Berberastine 2</td>
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<td>Palmatine 3</td>
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<td>Jatrorrhizine 4</td>
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<td></td>
<td>Phellodendrine 5</td>
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<td>Tetrahydrojatrorrhizine 7</td>
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<td>8-Oxoberberine</td>
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<td>8-Oxoepiberberine</td>
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<td>Magnoflorine isomer</td>
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<td>Lotusine</td>
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<td>(-)-Oblongine</td>
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<td>Evodiamine</td>
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<td>Dihydrocyclobuxine D</td>
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<td>N-Methylflindersine</td>
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<td>Bis-[4-(dimethylamino)phenyl]methanone</td>
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<td>4-Dimethylamino-4′-isopropylbenzophenone</td>
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<td>3,4-Dihydro-1-[(4-hydroxyphenyl)methyl]-7-methoxy-2-methyl-8-isoquinolinol</td>
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<td>3,4-Dihydro-1-[(4-hydroxyphenyl)methyl]-7-methoxy-2-methyl-6-isoquinolinol</td>
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<td><em>Limonoids</em></td>
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<td>Obaculactone</td>
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<td>12α-Hydroxylimonin</td>
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<td>Limonexic acid</td>
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Hispidol B 70  [96]
Melianone 71  [98]
24-methylenecycloartanol 72  [97]
[(21R,23R)epoxy-21α-ethoxy-24-hydroxy]tirucalla-7-en-3-one 73  [99]
Fridelin 74  [97]
[(21S,23R)epoxy-24-hydroxy-21β,25-diethoxy]tirucalla-7-en-3-one 75  [99]
[(21R,23R)epoxy-24-hydroxy-21α,25-diethoxy]tirucalla-7-en-3-one 76  [99]
Toonaclilatin K 77  [100]
(21R,23R)-epoxy-21R-ethoxy-24S,25-dihydroxyapotirucalla-7-en-3-one 78  [100]

**Lignans**

(±)-Syringaresinol-4,4′-bis-O-β-D-glucoside 79  [101]
(±)-Lyoniresinol 80  [101]
(±)-5,5′-Dimethoxyariciresinol4′-O-β-D-glucoside 81  [101]

**Flavonoids**

Phellodenols D 82  [102]
Phellodenols E 83  [102]
Phellodensin G 84  [102]
Phellamurin 85  [85]
Armuresin 86  [85]
Dihydrophelloside 87  [85]
Phelloside 88  [85]
Noricarise 89  [85]
Phellavin 90  [85]
Hyperoside 91  [85]
Dihydrokaepferol 92  [97]
Phellochinin A 93  [97]

**Phenol derivatives**

Amurenlactone A 94  [103]
Amurenamido A 95  [103]
Coniferin 96  [86]
Ferulic acid 97  [86]
Cinnamylate 98  [104]
Methyl 3-O-feruloyl-quinate 99  [104]
Cyclohexanecarboxylic acid 100  [104]
Syringaresinol di-O-β-D-glucopyranoside 101  [86]
Phellolactone 102  [97]
Vanilloloside 103  [86]
3-O-feruloylquinicacid 104  [101]
I Phytochemical Constituents and Corresponding Extraction

Method of Alkaloids

Many studies have reported the alkaloids are the active constituents of CPC which demonstrate a variety of biological and pharmacological activities, including antimicrobial antimalarial and anti-diarrhea etc. [10-12]. These alkaloids mainly include protoberberine, aporphine, furoquinoline, canthinone, indolopyridoquinazoline, etc. The structures of these components were shown in (Figures 2 & 3).

Figure 2: The structures of protobberines from CPC.

4-O-feruloylquinic acid 105  
5-O-feruloylquinic acid 106  
7-O-β-D-glucopyranoside 107  
rel-(15Z,2R,3R)-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1-(methoxycarbonylmethyl)-indane-2-carboxylic acid methyl ester (α-di(methylferulate)) 108  
rel-(1R,2R,3R)-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1-(methoxycarbonylmethyl)indane-2-carboxylic acid methyl ester (γ-di(methyl ferulate)) 109  
Chlorogenic acid 110  
Neochlorogenic acid 111  
4-Dicaffeoylquinic acid 112  
Salidroside 113  
Ferulic acid methylester 114  
4-Hydroxyphenethyl alcohol 116  
(6S)-dehydrovomifoliol 117  
(6R,7R)-epiloliolide 118  

4-O-feruloylquinic acid 105  
5-O-feruloylquinic acid 106  
7-O-β-D-glucopyranoside 107  
rel-(15Z,2R,3R)-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1-(methoxycarbonylmethyl)-indane-2-carboxylic acid methyl ester (α-di(methylferulate)) 108  
rel-(1R,2R,3R)-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1-(methoxycarbonylmethyl)indane-2-carboxylic acid methyl ester (γ-di(methyl ferulate)) 109  
Chlorogenic acid 110  
Neochlorogenic acid 111  
4-Dicaffeoylquinic acid 112  
Salidroside 113  
Ferulic acid methylester 114  
4-Hydroxyphenethyl alcohol 116  
(6S)-dehydrovomifoliol 117  
(6R,7R)-epiloliolide 118  

I Phytochemical Constituents of Alkaloids

Many studies have reported the alkaloids are the active constituents of CPC which demonstrate a variety of biological and pharmacological
**Figure 3:** The structures of aporphines, furoquinolines, canthinone, indolopyridoquinazolines, and other alkaloids from CPC. A) The structures of aporphines from CPC, B) The structures of furoquinolines from CPC, C) The structures of canthinone and indolopyridoquinazolines from CPC, D) The structures of other alkaloids from CPC. 

**ii) Extraction Method of Alkaloids**

Alkaloids can be extracted from CPC by multiple extraction techniques and solvents. Traditional technology used for extraction is liquid-liquid extraction, and the solvent is mixed reagents, such as different proportions of water and methanol, water and ethanol. With the progress of technology, substantial innovative methods for alkaloids extracting were emerged, and its extraction effect was greatly improved. Zhang et al. developed a simple poly ether ether ketone (PEEK) tube-based solid phase microextraction method for the extraction alkaloids in CPC [13]. This proposed method functionalized the chemically resistant surface of the PEEK tube and synthesized the poly acrylamideethylene glycol dimethacrylate inside the tube, and chemically bonded together with the surface. It showed the detection sensitivity was increased by about 400-folds, and also suitable for the extraction of complex samples.

Ionic liquids is a novel type of solvent, characterized by all the liquid composed of ions with the possibility of adjusting the solvation properties over a very wide range. Wang et al. developed a simple poly ether ether ketone (PEEK) tube-based solid phase microextraction method for the extraction alkaloids in CPC [13]. This proposed method functionalized the chemically resistant surface of the PEEK tube and synthesized the poly acrylamide-ethylene glycol dimethacrylate inside the tube, and chemically bonded together with the surface. It showed the detection sensitivity was increased by about 400-folds, and also suitable for the extraction of complex samples.

Ionic liquids is a novel type of solvent, characterized by all the liquid composed of ions with the possibility of adjusting the solvation properties over a very wide range. Wang et al. employed four ionic liquids with the Box-Behnken design to optimal extract alkaloids from CPC [14]. Finally, ultrasonic assisted extraction and ionic liquids (1-butyl-3-methylimidazolium bromide) selected as solvent, the ultrasonic power was set to 100W, extraction time was 75 min and the proportion of solvent to raw material was 1:14. This new approach is more efficient and environmentally friendly than traditional methods. The rapid development of nanomaterials has injected new vitality into analytical chemistry. Shi et al. adopted one-step self-polymerization reaction to directly grafted polydopamine onto Fe$_3$O$_4$ to enrich and extraction berberine [15].

Various extraction conditions have been optimized, for instance, the amount of polydopamine-coated nanoparticles, desorption solvent, desorption time, and equilibrium time [15]. The content of berberine extracted from CPC was 91.3% higher than that of 9.5% in the extract. Meng et al. investigated a novel magnetic nanomaterial with a molecularly imprinted polymers for protoberberine alkaloids extraction in CPC [16]. Molecularly imprinted polymers were prepared on the surface of Fe$_3$O$_4$ nanoparticles, acetonitrile and water as porogen, acrylamide as functional monomer, ethylene glycol dimethacrylate acrross-linking agent [16]. The magnetic molecularly imprinted polymers were acted as the sorbent to extract berberine, jatrorrhizine, and palmatine.

This novel extraction method can also be used for the extraction of protoberberine alkaloids in biological samples. Jiang et al. used aptamer functionalized Fe$_3$O$_4$ nanoparticles for selective extraction of berberine from CPC [17]. The aptamer-functionalized Fe$_3$O$_4$ nanoparticles were
served not only as identification elements for the recognition and acquisition of the target berberine, but also could use an external magnet to support the quick separation and purification of the bound target. The purity of berberine extracted from CPC was 98.7% compared with that of 4.85% in the extract. These reports indicated that different functionalized Fe₃O₄ nanoparticles were effective for the alkaloids enrichment and separation from CPC. Although the above-mentioned extraction method of alkaloids in CPC are novel and tremendously improved the extraction efficiency, they were still not widely accepted, and the reproducibility and extraction rate need further verification and investigation. Future extraction methods must be concise, efficient and easy to operate.

II Limonoids

Limonoids is a class of highly oxidized tetranortriterpenoid. The structure was shown in (Figure 4A).

III Triterpenoids

The structure of triterpenoids was shown in (Figure 4B).

IV Lignans

The structure was shown in (Figure 5A).

V Flavonoids

Flavonoids are another major component of CPC, which has high medicinal value. Therefore, the optimization of extraction technology of flavonoids can provide scientific theoretical basis for the rational development and utilization of CPC resources. Zhang et al. investigated the extraction technology of total flavonoids from *Phellodendri amurensis cortex* and its antioxidant activity in vitro [18]. The results showed that the extraction rate of total flavonoids from *Phellodendri amurensis cortex* was 2.31% under the optimum extraction conditions. The inhibitory concentration (IC₅₀) values of total flavonoid extracts from *Phellodendri amurensis cortex* were 2.9525 mg/L, 1.6827 mg/L and 1.3951 mg/L for OH, O₂⁻ and DPPH, respectively, showed a strong antioxidant activity. Although the extraction yield is not high and lacking real pharmacological studies to verify the antioxidant of flavonoids, the results of this study suggested the possible medicinal value of flavonoids in *Phellodendri amurensis cortex*, which might indicate the broad prospects of exploitation and utilization of CPC resources. Thus, the
pharmacological studies of flavonoids in CPC need to be further implemented. The structure of flavonoids from CPC was shown in Figure 5B.

Figure 5: The structures of lignans and flavonoids from CPC. A) The structures of lignans from CPC, B) The structures of flavonoids from CPC.

Figure 6: The structures of phenols and their derivatives from CPC. j:rel-(1S,2R,3R)-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1-(methoxycarboxymethyl)-indane-2-carboxylic acid methyl ester (α-di(methyl ferulate)) (108), k:rel-(1R,2R,3R)-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1-(methoxycarboxymethyl)indane-2-carboxylic acid methyl ester (γ-di(methyl ferulate)) (109).
VI Phenols and Their Derivatives

The structure was shown in (Figure 6).

Pharmacology of Cortex Phellodendri Chinensis

Numerous pharmacological studies have manifested that CPC have various pharmacological effects, which ascribed to some of its bioactive components, such as alkaloids. The pharmacological activities mainly include anti-inflammatory activity, anti-microbial activity, anti-cancer activity, anti-diabetic activity, anti-ulcer activity, antioxidant activity, and neuroprotective effect (Table 2).

Table 2: Pharmacological activities of CPC.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Part of plant (extract)</th>
<th>Model or assay</th>
<th>Treatment</th>
<th>Result</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Anti-inflammatory activity</td>
<td>Boiled water extract</td>
<td>Female, specific-pathogen free ICR mice</td>
<td>p.o., 200 mg/kg for three consecutive days, 1, 10, or 100 μg/mL</td>
<td>Down-regulated LPS-induced IL-6, IL-1β and MCP-1 in serum; inhibited iNOS, NF-κB by degradation and phosphorylation of IκBα, and attenuated phosphorylation of MAPKs.</td>
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<td>Ethanol extracts</td>
<td>Murine macrophage cell line RAW 264.7</td>
<td>1, 10, or 100 μg/mL</td>
<td>MPO activity, ROS level were significantly decreased, the levels of TNF-α, IL-1β, IL-6 and COX-2 were remarkably inhibited.</td>
<td>[24]</td>
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<td>Demethylenberberine (chemical components)</td>
<td>TPA-induced ear edema in male ICR mice</td>
<td>200, 400 mg/kg</td>
<td>MPO activity, the levels of IL-6, TNF-α, IFN-γ were diminished, activation of NF-κB signaling pathway were inhibited. ROS production and pro-inflammation cytokines were markedly inhibited in vitro.</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>80% methanol extracts</td>
<td>Acute colitis female C57BL/6 mice model</td>
<td>p.o., 15 mg/mL and 30 mg/mL, 10, 20, and 40μM</td>
<td>CPC inhibited osteoarticular cartilage and chondrocyte destruction by inhibiting proteoglycan release and type II collagen degradation, down-regulating aggreganases, MMP activity and phospho-ERK1/2, JNK and p38 MAP kinase signaling, and up-regulating TIMP-1 activity.</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>50% ethanol extracts</td>
<td>Pelvic inflammatory female C57BL/6J mice model</td>
<td>25 mg i.c. twice</td>
<td>TNF-α, IL-1β were diminished, indicated the mechanisms involved in reducing inflammation.</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>Methanol extracts</td>
<td>Culture of human osteoarthritis chondrocytes</td>
<td>40, 100, 200 μg/mL</td>
<td>CPC inhibited osteoarticular cartilage and chondrocyte destruction by inhibiting proteoglycan release and type II collagen degradation, down-regulating aggreganases, MMP activity and phospho-ERK1/2, JNK and p38 MAP kinase signaling, and up-regulating TIMP-1 activity.</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>Specific pathogen-free male ICR mice</td>
<td>Limonin and obakunone identified in the CPC non-alkaloid fraction suppressed NO production, exhibiting IC50 values of 16 and 2.6μM, respectively.</td>
<td>Limonin and obakunone identified in the CPC non-alkaloid fraction suppressed NO production, exhibiting IC50 values of 16 and 2.6μM, respectively.</td>
<td>[21]</td>
<td></td>
</tr>
<tr>
<td>Anti-microbial activity</td>
<td>Berberine (chemical components)</td>
<td>Staphylococcal strains</td>
<td>1-500 μg</td>
<td>Berberine showed antimiicrobial activity against all tested strains of MRSA. Minimum inhibition concentrations of berberine against MRSA ranged from 32 to 128μg/mL.</td>
<td>[10]</td>
</tr>
<tr>
<td>Activity</td>
<td>Extract/Component</td>
<td>Species/Cell Lines</td>
<td>Concentration/Culture Conditions</td>
<td>Treatment/Activity Description</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Anticancer activity</td>
<td>75% methanol extract</td>
<td>Male BALB/c-nude mice</td>
<td>i.g. 1.6 g/kg daily for 28 days</td>
<td>CPC could observably reverse the disturbed metabolites and have obvious therapeutic effect against prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Anticancer activity</td>
<td>Nexrutine (chemical components)</td>
<td>Male Wistar rats COLO205 and HCT-15 cells</td>
<td>300, 600 ppm 2.5, 5, and 10 μg/mL</td>
<td>Dietary exposure of nexrutine significantly reduced the number of azoxymethane-induced aberrant crypt foci in rats. In vitro studies, nexrutine decreased cell survival and colony formation while inducing G0/G1 cell cycle arrest and apoptosis in colon adenocarcinoma cells COLO205 and HCT-15.</td>
<td></td>
</tr>
<tr>
<td>Anti-diabetic activity</td>
<td>Berberine (chemical components)</td>
<td>3T3-L1 preadipocytes</td>
<td>0-200 μmol/L</td>
<td>Berberine increases glucose uptake through a mechanism distinct from insulin, and activated adenosine monophosphate-activated protein kinase seems to be involved in the metabolic effect of berberine.</td>
<td></td>
</tr>
<tr>
<td>Anti-diabetic activity</td>
<td>Berberine (chemical components)</td>
<td>Glomerular mesangial cells</td>
<td>30, 90 μmol/L</td>
<td>Berberine might inhibit fibronectin and collagen synthesis partly via p38MAPK signal pathway in rat glomerular mesangial cells exposed to high glucose.</td>
<td></td>
</tr>
<tr>
<td>Anti-ulcer activity</td>
<td>50% ethanol extract</td>
<td>Male Sprague-Dawley rats</td>
<td>i.g., 10 mg/kg/day, 30 mg/kg/day, 90 mg/kg/day</td>
<td>Total alkaloids of Cortex Phellodendri Chinensis exerts a beneficial gastroprotective effect and the involved mechanism is likely neurohumoral regulation.</td>
<td></td>
</tr>
<tr>
<td>Anti-oxidant activity</td>
<td>Demethyleneberberine (chemical components)</td>
<td>HepG2 cells</td>
<td>50 μM</td>
<td>Demethyleneberberine suppressed CYP2E1, HIF-1a, and iNOS, which contributed to ethanol-dependent oxidative stress</td>
<td></td>
</tr>
<tr>
<td>Neuroprotective effect</td>
<td>Phellodendrine isolated from CPC</td>
<td>Zebrafish embryos</td>
<td>100 μg/mL</td>
<td>Phellodendrine down-regulated Akt, MAPK1, and up-regulated NF-κB and IKK</td>
<td></td>
</tr>
<tr>
<td>Neuroprotective effect</td>
<td>Ethanol extract</td>
<td>Beta-amyloid (Aβ)-induced neurotoxicity in PC12 cells</td>
<td>0.1 and 1 μg/ mL</td>
<td>CPC can significantly increase the cell viability, and markedly elevate the ratio of the protein and mRNA levels of Bcl-2/Bax, while remarkably decrease the release of cytochrome c, and the protein and mRNA expression of caspase-3.</td>
<td></td>
</tr>
</tbody>
</table>
I Cytotoxic Effect

On the basis of current knowledge, the toxicity of CPC is low and their use in herbal prescriptions is considered safe. The cytotoxic effects against cancer cell lines of methanol extracts (thirteen compounds, that are 1, 32, 33, 35, 42, 54, 56, 57, 58, 94, 104, 108, and 109) of CPC were evaluated [1]. In B16 melanoma cell lines, compounds 27, 28, 36, and 48 exhibited almost no toxicity. Compounds 1, 33, 35, 108, and 109 displayed cytotoxicities against HL60, AZ521, SK-BR-3 cell lines with half maximal IC50 values at the range of 2.6-90.0 μM (Table 3). It is worth noting that the IC50 values of compound 1 (berberine) against AZ521 and SK-BR-3 were 2.6 μM and 21.0 μM, which were superior to or similar with that of the reference cisplatin (9.5 μM and 18.8 μM). In zebrafish embryos, the median lethal dose of compound 5 was 500 μg/mL [19].

Table 3: Cytotoxic activities of compounds isolated from the extracts of CPC.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cytotoxicity, IC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HL60 (Leukemia)</td>
</tr>
<tr>
<td>1</td>
<td>29.4±3.0</td>
</tr>
<tr>
<td>33</td>
<td>29.3±2.3</td>
</tr>
<tr>
<td>35</td>
<td>31.4±1.7</td>
</tr>
<tr>
<td>108</td>
<td>90.0±1.0</td>
</tr>
<tr>
<td>109</td>
<td>56.6±4.5</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>4.2±1.1</td>
</tr>
</tbody>
</table>

Trypan blue, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and flow cytometry were employed to investigate the cytotoxicity of CPC and other herbs on human corneal epithelial cells, CPC showed no cytotoxicity after 5 minutes exposure to concentrations up to 5% which indicated CPC may have the potential for ocular preparations [20]. No cytotoxicity was found among the tested herbs when trypan blue and MTT method were used, while flow cytometry uncovered the cell membrane damage of Rhizoma Coptidis, which indicated it is very important to choose a sensitive method for detecting cytotoxicity. Meanwhile, it also suggested that a variety of research methods should be adopted in toxicity study to ensure the credibility of the results. In our present review study, we found the cytotoxic effects of CPC were not fully researched, thus, it suggested that a variety of research and research methods should be adopted in toxicity study to extend and ensure the credibility of the results.

II Anti-Inflammatory Activity

Anti-inflammatory activity of CPC was demonstrated in many studies, which has been proven the main effective components are alkaloids [21]. Choi et al. reported the anti-inflammatory effect of CPC is related with down-regulation of NO production and inducible nitric oxide synthase (iNOS) expression via degradation nuclear factor (NF-κB) and attenuated phosphorylation of mitogen-activated protein kinases (MAPK), as well as inhibition of cytokines such as interleukin (IL)-6, IL-1β and macrophage chemo-attractant protein-1 [22]. Chen et al. also investigated that CPC alleviate inflammation mainly through the regulation of NF-κB pathway and Th cells homeostasis [23]. In the model of colitis, demethyleneberberine, a component of CPC, can significantly decrease pro-inflammatory cytokines IL-6 and tumor necrosis factor (TNF)-α in vivo, and inhibit the activation of NF-κB pathway.

In addition, the level of interferon-γ was also decreased, and IL-4 concentration was increased in splenocytes. Reactive oxygen species (ROS) production and pro-inflammatory cytokines were remarkable inhibited by demethyleneberberine in RAW264.7 cell line in vitro. Xian et al. studied the anti-inflammatory effect of the ethanol extracts of CPC in the 12-O-tetradecanoylphorbol-acetate-induced mouse model [24].

![Figure 7: Summary of CPC anti-inflammatory mechanism.](image)
It showed that the activity of myeloperoxidase and the reactive oxygen species level can be significantly decreased by CPC. Moreover, the protein and the mRNA levels of IL-1β, IL-6, TNF-α, and cyclooxygenase (COX)-2 were also outstandingly inhibited. Ario Fujii clearly indicated that NO was decreased by the non-alkaliol fraction of CPC, limonin and obakunone of which can effectively reduce NO and iNOS gene expression mainly by means of NF-κB pathway [21]. Because of the anti-inflammatory effect of CPC, Oh et al. attempted to treat pelvic inflammatory disease with CPC in order to discover its new clinical utility [25]. The extractions of CPC were dissolved in saline for administration for female C57BL/6J mice. Cytokine determination of uterine tissue indicated that CPC can down-regulated the inflammatory cytokine levels of IL-1β and TNF-α, and the results of histopathological lesion scores also supported this result. This is the first trial to use CPC for the treatment of pelvic inflammatory disease, more researches were needed to clarify the mechanisms. Two signaling pathways were mainly involved in the anti-inflammatory effects of CPC was briefly summarized in (Figure 7).

CPC can also protect human osteoarthritic cartilage and chondrocytes. Kim et al. studied the effect of water extract of CPC on human osteoarthritic cartilage explants, taking celecoxib as the positive control medicine [26]. IL-1β-mediated degradation of glycosaminoglycan and type II collagen were notably inhibited by CPC in a concentration-dependent way. While celecoxib unable remarkably restrain glycosaminoglycan can release and only slightly lessened type II collagen. In the present study, CPC inhibits the destruction of osteoarticular cartilage and chondrocyte mainly depends on the inhibition of the proteoglycan release and type II collagen degradation, as well as down-regulating aggrecanase-1 and -2, matrix metalloproteinase-1, -3 and -13, phosphorylation of extracellular signal regulated kinase (ERK)1/2, Jun NH2-terminal kinase and p38 MAPK signal pathway, and up-regulating metalloproteinase activity. The anti-inflammatory activity of CPC has been universally acknowledged, but its anti-inflammatory components need to be further elucidated, which is helpful for the following systemic and comprehensive study of the anti-inflammatory activity of CPC.

III Anti-Microbial Activity

Wong et al. studied twenty traditional Chinese medicines (TCM) to evaluate their anti-microbial activity against Porphyromonas gingivalis, Streptococcus mitis, Streptococcus mutans, and Streptococcus sanguis [27]. CPC showed the antimicrobial activity of Streptococcus sanguis and Porphyromonas gingivalis. Although the present study demonstrated the antimicrobial activity of CPC against two types of bacteria, the associated active components and corresponding mechanism remained to be studied. Yu et al. investigated the anti-methicillin-resistant Staphylococcus aureus (anti-MRSA) activity of CPC [10]. The results indicated that berberine is the main antimicrobial component with the potential of restore the effectiveness of β-lactam antibiotics to MRSA, as well as suppress MRSA adhesion and intracellular invasion in human gingival fibroblasts. CPC also has the inhibitory effect on Helicobacter pylori and is widely used in the treatment of gastrointestinal disorders, but few studies elucidated the potential mechanism [28]. Li et al. reported the urease can be inhibited by CPC, which is usually considered to be an important target in the development of anti-Helicobacter pylori agents, and the main mechanism is the interaction with the sulphydryl group [7].

Seneviratne et al. studied eight types of TCM to assess the underlying anti-Candida species activity [29]. Here, the antifungal activity of TCM were screened by standard agar diffusion assay, and the potent antifungal activity of CPC were showed on three different non-albicans Candida species, including C. krusei, C. glabrata and C. tropicalis, which implied its potential therapeutic function. Although the aforementioned studies all reflect the anti-microbial effect of CPC, there is few in-depth studies on its antimicrobial mechanism, only the initial exploration has been carried out. Moreover, further research models are critically needed to confirm these anti-microbial activities in vivo and in humans. With the extensive use of antibiotics in recent years, drug resistance occurred frequently, and the choice of clinical medicines has also been greatly limited. All the above studies indicated the anti-microbial activity and potential anti-microbial value of CPC, in the meantime, provided references for the comprehensive development and utilization of CPC.

IV Anti-Cancer Activity

With the increase of population growth and aging, cancer has become the main cause of death, especially in less developed countries [30]. Owing to the little toxicity and adverse reaction of TCM, the anti-cancer effect of TCM gradually aroused people’s attention. Anti-cancer activity is also one of the pharmacological activities of CPC. Li et al. employed a chinnedomics platform to screen the active components of CPC for treating prostate cancer [31]. It was reported that berberine, magnoflorine-O-glucuronide, magnoflorine, jatrorrhizine, menisperine-O-glucuronide, menisperine, obaculactone, obacunone, and (p-hydroxybenzyl)-6,7-dihydroxy-N-methyletetrahydro iso-quinoline-7-O-p-D-glucopyranosid highly correlated with the treatment of CPC against prostate cancer. The above-mentioned components displayed the treatment effects mainly via regulating the following metabolic pathways: citrate cycle, purine metabolism, retinol metabolism, arachidonic acid metabolism, glycerophospholipid metabolism, and sphingolipid metabolism.

In present study, a novel method was adopted to delineate not only the active components of CPC, but also its mechanism. Mitani et al. probed the therapeutic effect of berberine on lymph node metastasis of murine lung cancer [32]. After oral administrated berberine for 14 days, spontaneous lymphatic metastasis of murine lung cancer was significantly inhibited, while the growth of the implanted lung cancer were not affected. In addition, the combination of berberine and CPT-11 (an anticancer drug) can result in significant anti-tumor effects compared with the individual treatments alone, which means that CPC can be used as a compatibility agent with other anticancer drugs in order to achieve better efficacy.

Bin et al. used a computational and experimental approach to explore the potential proteins involved in the anti-melanoma effects of berberine [33]. In this study, molecular docking and molecular dynamics exhibited that berberine could bind with four proteins, including p38 MAPK, 3-phosphoinositide-dependent protein kinase 1, dihydrofolate dehydrogenase, and glucocorticoid receptor. Cellular experiments displayed that berberine could inhibited cell proliferation, increased
phosphorylation of p38 MAPK and glucocorticoid receptor, as well as inhibited the activity of dihydrofolate reductase in A375 human melanoma cells. It is the first time that identified dihydrofolate reductase as one of the direct anti-melanoma targets of berberine, which opened up a new target for the treatment of melanoma.

Alam et al. explored the mechanism of nexrutine on chemopreventive/chemotherapeutic effects against colon cancer and found oral administrated with nexrutine can significantly lessened the abnormal crypt lesions in rats induced by oxidized methane [34]. Furthermore, significant inhibition of oxidized methane-induced cell proliferation was also observed. Nexrutine can remarkable enhanced the apoptosis of colon cells of the oxidized methane treated rats. The present study suggested that nexrutine may be a useful drug candidate for the chemoprevention and treatment of colon cancer. CPC as observed with potent anti-cancer activities should be taken into next research stage to ensure its less side effects and can be safely used in cancer-related patients, which may further help ease the burden and mortality rate for cancer.

V Anti-Diabetic Activity

Diabetes is a metabolic disease characterized by high blood glucose. Persistent hyperglycemia and long-term metabolic disorders can lead to systemic organ damage. Following cardiovascular disease and cancer, diabetes has become the third non-communicable disease in developed countries [35]. Many researchers reported CPC can prevent or postpone the development of diabetes. Yin et al. employed HepG2 cell line to explore the effect of berberine to the glucose-lowering compared with troglitazone and metformin in vitro [36]. With the increase of glucose concentration, the glucose-reducing effect of berberine was decreased, and this effect is independent of insulin level, which was similar to metformin, while, unlike troglitazone. βTC3 cell line was also employed for insulin release test, while no secretory effect was observed by CPC.

These results indicated that CPC has glucose-reducing effect, which is independent of insulin and has no influence on insulin secretion. In Shen’s research, berberine can induce a reversible concentration-dependent inhibition of insulin gene transcription in NIT-1 cells, thus resulting in the decrease of the number of insulin and mRNA expression and protect the islet cells [37]. Zhou et al. exhibited that berberine can induce glucose transport by a different mechanism of insulin in 3T3-L1 adipocytes, which has the capacity of glucose-free glucose transport and GLUT4 expression [38]. Berberine was found to stimulate glucose uptake in a dose- and time-dependent way and activated ERK 1/2. Different from that of insulin, the effect of berberine on glucose uptake was insensitive to SB203580 and wortmannin. Here, berberine works mainly by increasing the phosphorylation of AMPK and acetyl-CoA carboxylase.

As one of the most serious complications of diabetes, diabetic nephropathy is regarded as the main cause of end-stage renal disease. Liu et al. proved the effect of berberine on rat glomerular mesangial cells under high glucose condition [39]. Here, the cell proliferation, collagen synthesis and protein expression were detected by MTT assay, 3H-proline incorporation assay and western blot analysis, respectively. The present study exhibited that berberine can remarkably restrain fibronectin and collagen synthesis through p38MAPK signal pathway in high glucose-treated mesangial cells. Furthermore, p38 phosphorylation may be directly inhibited by berberine, and the pathway may be affected via anti-oxidation.

All of the aforementioned studies were carried out in vitro, further in vivo studies and research models, particularly comparative studies using the already reported drugs in order to compare the activity. Diabetic patients need to take medicine for a long time. The adverse reactions of western medicine are relatively great. If CPC can be used as an alternative or adjuvant drug, it will benefit the majority of diabetic patients. All of the aforementioned studies were carried out in vitro, further in vivo studies and research models, particularly comparative studies using the already reported drugs in order to compare the activity should be explored.

VI Anti-Ulcer Activity

Gastric ulcer is the most common gastrointestinal disease in the world, and its incidence is increasing with each passing year as human diet diversified. CPC as a famous TCM can also play a protective role of gastric ulcer. Wang et al. investigated the anti-ulcer effect of total alkaloids in CPC of acetic acid-induced gastric ulcer rat model [40]. Ulcer area, ulcer inhibition rate and epidermal growth factor were used to assess the anti-ulcer effect of the total alkaloids. The levels of norepinephrine and serotonin were used to indicate the gastro protective mechanism of total alkaloids.

The results manifested that the anti-ulcer effect of total alkaloids is better than omeprazole, and can significantly enhance the level of growth factors, as well as accelerate ulcer healing.Takase et al. reported that the CPC in HLJDD can inhibit the decrease of gastric surface potential caused by ethanol, but has no effect on the basal gastric surface potential [41]. The CPC here can prevent the secretion of gastric acid induced by 2-deoxy-D-glucose and has a greater effect on pentagastrin compared with than the other three TCM of the decoction. The gastric mucosal protection is mainly due to CPC and Rhizoma Coptidis by strengthening the mucosal barrier resistance via endogenous sulfhydryl compounds [42].

VII Antioxidant Activity

ROS are continuously produced in the process of oxidative metabolism of life activities. Normally, the production and elimination of free radicals in human body are in a dynamic equilibrium state. When this balance is broken, the phenomenon of “oxidative stress” usually occurs, which induce various diseases. The antioxidant ability of CPC has attracted more and more attention of scientific researchers. Demethylenberberine is a novel cationic antioxidant, could be guided into the mitochondrion by the high negative potential inside the mitochondrion. It was reported that binge drinking could significantly reduce mitochondrial glutathione (GSH) and glutathione peroxidase activity and further elevated thiobarbituric acid reactive substances formation in binge-drinking mice model.

After the treatment of demethylberberine, the results of H&E exhibited ethanol-mediated mitochondrial swelling can be alleviated,
and ultrastructural damages of mitochondria can also be profoundly ameliorated [43]. The inhibitory effects of expression at the protein or mRNA level of phosphorylated AMPK, and PGC-1α were also reversed. A novel mechanism of demethylenberberine involving the attenuation of hepatic oxidative stress and steatosis, partially through mitochondria targeted antioxidant, down regulation of CYP2E1, and activation of the Siruin 1/AMPK/peroxisome proliferator-activated receptor-γ coactivator-1α pathway-associated fatty acid oxidation were verified.

Phellodendrine is one of important characteristic ingredients of CPC and was firstly found by a Japanese scholar. It was found that phellodendrine isolated from CPC had the ability of antioxidant through regulating the Akt/NF-κB pathway in zebrafish embryo mainly by reversing the expression of ROS-dependent JNK, MAPK1, p38 MAPK, Akt and NF-κB signaling pathways which were abnormally changed by AAPH-induced oxidative stress [19].

VIII Neuroprotective Effect

Neurological degenerative diseases have become a major problem affecting human health and quality of life. Frequent reports on the neuroprotective effects of berberine have prompted researchers to explore the mechanism of neuroprotective effects of CPC from a scientific perspective. Berberine can decrease the activity of neurons and mitochondria-related caspase pathway, and significantly reverse the damage and apoptosis of primary hippocampal neurons induced by amyloid-β [23,31] (Aβ [25,30]) [44].

The ethanol extract of both Phellodendri chinense cortex and Phellodendri amurenensis cortex can significantly increase the cell viability in Aβ-treated PC12 cells, as well as elevated the ratio of the protein and mRNA expression of Bel-2/Bax, while remarkably decrease the release of cytochrome c, and the protein and mRNA expression of caspase-3 [45]. The report also pointed out Phellodendri amurenensis cortex had better protective effect than Phellodendri chinense cortex against Aβ-induced neurotoxicity in PC12 cells. This neuroprotective effect may be mediated by inhibition of cellular apoptosis.

Acetylcholinesterase is a known therapeutic target for early stages of the most general form of dementia, Alzheimer’s Disease. Dorothea et al. tested 80 TCM plants for their in vitro anti-acetylcholinesterase activity, and the methanol, dichloromethane, and aqueous crude extracts of CPC substantially inhibited acetylcholinesterase [46]. Furthermore, the ethanol extract and water extract of CPC had no cytotoxicity at the inhibitory concentration of acetylcholinesterase. It was found that the combination of some alkaloids such as berberine, berberine and palmatine could synergistically enhance the inhibition of acetylcholinesterase which might provide new leading compounds for the treatment of neurological diseases.

Cortex Phellodendri Chinensis in Formula

Formula was consisted with a variety of TCMs, such combinations can reduce or neutralize the toxicity produced by certain herbs, as well as facilitate and improve the synergistic and additive effects of the herbs in the formulation [47]. Many classical medicine literatures have records of CPC, and the treatment effect is remarkable. A list of some other commonly known prescriptions including CPC is shown in (Table 4).

<table>
<thead>
<tr>
<th>Prescription Name</th>
<th>Type</th>
<th>Main compositions</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baidai Wan</td>
<td>Pill</td>
<td>Cortex Phellodendri Chinensis Ailanthi Cortex Pacoiae Radix Alba Angelica Sinensis</td>
<td>Clearing heat, removing dampness, arresting leukorrhea</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyperi Rhizoma Pulsatillae Radix Taraxaci Herba Scutellariae Radis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baipuhuang Pian</td>
<td>Tablet</td>
<td>Cortex Phellodendri Chinensis Pinelliae Rhizoma Praeparatum Gastrodiae Rhizoma</td>
<td>Clearing heat and expelling dampness, detoxifying, blood-cooling</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astragali Radix Preparata Cum Melle Ginseng Radix et Rhizoma Atractylodis Rhizoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atractylodes Macrocephala Citri Reticulatae Pericarpium Alismatis Rhizoma Liu Shen Qu</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hordei Fructus Germinatus Cortex Phellodendri Chinensis Rehmanniae Radix Preparata</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salt Anemarrhenae Rhizoma Salt Cortex Phellodendri Chinensis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salt Cortex Phellodendri Chinensis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: The commonly used prescriptions including CPC.
<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Ingredients</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danggui Longhui Wan</td>
<td>Pill</td>
<td>Angelicae Sinensis Radix, Gentianae Radix et Rhizoma, Aloe, Indigo Naturalis, Gardeniae Fructus, Coptidis Rhizoma, Scutellariae Radix, Cortex Phellodendri Chinensis, Rhei Radix et Rhizoma, Aucklandiae Radix, Artificial Moschus</td>
<td>Discharging fire and relaxing the bowels</td>
<td>[85]</td>
</tr>
<tr>
<td>Fufang Huangbaiye Tuji</td>
<td>Embrocation</td>
<td>Forsythiae Fructus, Cortex Phellodendri Chinensis, Lonicerae Flos, Taraxaci Herba, Sclopendra</td>
<td>Clearing heat and removing toxicity, reducing swell and removing necrotic tissue</td>
<td>[85]</td>
</tr>
<tr>
<td>Fuke Zhidai Pian</td>
<td>Tablet</td>
<td>Ailanthi Cortex, Schisandrae Chinensis Fructus, Cortex Phellodendri Chinensis, Testudinis Carapax et Plastrum, Poria, Asini Corii Colla, Dioscoreae Rhizoma</td>
<td>Clearing away heat and Drying dampness, astringency and arresting leucorrhea</td>
<td>[85]</td>
</tr>
<tr>
<td>Fenqing Wulin Wan</td>
<td>Pill</td>
<td>Akeiae Caulis, Plantaginis Semen, Scutellariae Radix, Poria, Polyporus, Cortex Phellodendri Chinensis, Rhei Radix et Rhizoma, Polygonum Aviculare, Dianthi Herba, Anemarrhenae Rhizoma, Alismatis Rhizoma, Gardeniae Fructus, Glycyrrhizae Radix et Rhizoma, Talcum</td>
<td>Clearing heat and purging fire, inducing diuresis for treating stranguria</td>
<td>[85]</td>
</tr>
<tr>
<td>Fengtong’an Jiaonang</td>
<td>Capsule</td>
<td>Radix Stephaniae Tetrandrae, Tetrapanacis Medulla, Cinnamomi Ramulus, Curcumae Longae Rhizoma, Gypsum Fibrosum, Coicens Semen, Chaenomelis Fructus, Cortex Erythrinae, Lonicerae Japonicae Caulis</td>
<td>Clearing heat and promoting diuresis, promoting blood circulation to remove meridian obstruction</td>
<td>[85]</td>
</tr>
<tr>
<td>Name</td>
<td>Type</td>
<td>Ingredients</td>
<td>Functions</td>
<td>Ref.</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Gonglao Quhuo</td>
<td>Tablet</td>
<td><em>Cortex Phellodendri Chinensis</em>, <em>Forsythiae Fructus</em>, <em>Mahoniae Caulis</em></td>
<td>Clearing heat and producing sound</td>
<td>[85]</td>
</tr>
<tr>
<td>Jiusheng San</td>
<td>Powder</td>
<td><em>Cortex Phellodendri Chinensis</em>, <em>Scutellariae Radix</em>, <em>Gardeniae Fructus</em></td>
<td>Detoxification swelling, dry wet itching</td>
<td>[85]</td>
</tr>
<tr>
<td>Muxiang Binglang Wan</td>
<td>Pill</td>
<td><em>Aucklandiae Radix</em>, <em>Arecae Semen</em>, <em>Aurantii Fructus</em>, <em>Citri Reticulatae Pericarpium</em>, <em>Citri Reticulatae Pericarpium Viride</em>, <em>Cyperi Rhizoma</em>, <em>Sparganii Rhizoma</em>, <em>Curcumae Rhizoma</em>, <em>Coptidis Rhizoma</em>, <em>Cortex Phellodendri Chinensis</em>, <em>Rhei Radix et Rhизма</em>, <em>Pharbitidis Semen</em>, <em>Natrii Sulfas</em></td>
<td>Promoting Qi circulation and removing food stagnation, purging heat and relaxing the bowels</td>
<td>[85]</td>
</tr>
<tr>
<td>Qianlietong Pian</td>
<td>Tablet</td>
<td><em>Vaccariae Semen</em>, <em>Astragali Radix</em>, <em>Plantaginis Semen</em>, <em>Phellodendri Amurensis Cortex</em>, <em>Anemones Raddreanae Rhizoma</em>, <em>Taraxaci Herba</em>, <em>Lycopi Herba</em>, <em>Star Anise oil</em>, <em>Cinnamomi oil</em></td>
<td>Removing dampness and clearing away turbidness, dispersing blood stasis and removing stasis</td>
<td>[85]</td>
</tr>
<tr>
<td>Qinlian Pian</td>
<td>Tablet</td>
<td><em>Scutellariae Radix</em>, <em>Forsythiae Fructus</em>, <em>Coptidis Rhizoma</em>, <em>Cortex Phellodendri Chinensis</em>, <em>Paoniae Radix Rubra</em>, <em>Glycyrrhizae Radix et Rhizoma</em></td>
<td>Clearing heat and removing toxicity, relieve swelling and pain</td>
<td>[85]</td>
</tr>
<tr>
<td>Qingfei Yihuo Wan</td>
<td>Pill</td>
<td><em>Scutellariae Radix</em>, <em>Gardeniae Fructus</em>, <em>Anemarrhenae Rhizoma</em>, <em>Fritillare Thunbergii Bulbus</em>, <em>Cortex Phellodendri Chinensis</em>, <em>Sophorae Flavescentis Radix</em>, <em>Platyodonis Radix</em>, <em>Peucedani Radix</em>, <em>Trichosanthis Radix</em>, <em>Rhei Radix et Rhизма</em></td>
<td>Cleaning lung-heat and stopping cough, resolving sputum and relaxing the bowels</td>
<td>[85]</td>
</tr>
<tr>
<td>Sizhi Xiangfu Wan</td>
<td>Pill</td>
<td><em>Cyperi Rhizoma</em>, <em>Rehmanniae Radix Preparata</em>, <em>Angelicae Sinensis Radix</em>, <em>Chuanxiong Rhizoma</em>, <em>Atractylodis Macrocephalae Rhizoma</em></td>
<td>Regulating vital energy and nourishing blood, regulate menstruation</td>
<td>[85]</td>
</tr>
<tr>
<td>Wei’an Capsule</td>
<td>Capsule</td>
<td>Cortex Phellodendri Chinensis</td>
<td>Dongre Capsis</td>
<td>Nourishing Yin and benefiting stomach, regulating liver and relieving pain</td>
</tr>
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</tr>
<tr>
<td>Wumei Wan</td>
<td>Pill</td>
<td>Mume Fructus</td>
<td>Zanthyloxyli Pericarpiaum Asari Radix et Rhizoma Coptidis Rhizoma Cortex Phellodendri Chinensis Zingiberis Rhizoma Aconiti Lateralis Radix Praeparata Cinnamomi Ramulus Ginseng Radix et Rhizoma Angelicae Sinensis Radix</td>
<td>Regulating the heat in the upper and cold in the lower</td>
</tr>
<tr>
<td>Wushe Zhiyang Wan</td>
<td>Pill</td>
<td>Zaocys Saponisokoviae Radix Cnidii Fructus Cortex Phellodendri Chinensis Atractylodis Rhizoma Ginseng Radix et Rhizoma Rubra Mouan Cortex Snake bile Sophorae Flavescentis Radix Bovis Calculus Artifactus Angelicae Sinensis Radix</td>
<td>Nourishing the blood to expel wind, eliminating dampness and relieving itching</td>
<td>[85]</td>
</tr>
<tr>
<td>Xiao’er Ganyan Keli</td>
<td>Granule</td>
<td>Artemisiae Scopariae Herba Gardeniae Fructus Scutellariae Radix Cortex Phellodendri Chinensis Crataegi Fructus Sojae Semen Germinatum Curcumae Radix Tetrapananis Medulla</td>
<td>Clearing heat and eliminating damp, relieving depression and pain</td>
<td>[85]</td>
</tr>
<tr>
<td>Xiao’er Qingre Pian</td>
<td>Tablet</td>
<td>Cortex Phellodendri Chinensis Junii Medulla Gardeniae Fructus Uncariae Ramulus Cum Uncis Realgar Coptidis Rhizoma Cinnabaris Gentianae Radix et Rhizoma Scutellariae Radix Rhei Radix et Rhizoma Peppermint Oil</td>
<td>Clearing heat and removing toxicity, dispelling wind and relieving convulsion</td>
<td>[85]</td>
</tr>
<tr>
<td>Zhizi Jinhua Wan</td>
<td>Pill</td>
<td>Gardeniae Fructus Coptidis Rhizoma Scutellariae Radix</td>
<td>Clearing heat and purging fire, cooling blood and eliminating toxins</td>
<td>[85]</td>
</tr>
</tbody>
</table>
### I Ermiao San and Ermiao Wan

Ermiao San or Ermiao Wan, a traditional formula according to <Dan Xi Xin Fa>, containing the equivalents of *Atractylodis Rhizoma* and CPC, has been widely used to treat gout and hyperuricemia via excreting dampness, eliminating heat and anti-edema [48, 49]. Kong et al. explored the effects of Ermiao San on lessening serum uric acid levels in hyperuricemia mice and the activities of mouse liver xanthine dehydrogenase and xanthine oxidase [50]. In the hyperuricemia model, Ermiao Wan was more effective than that of CPC alone, and the use of *Atractylodis Rhizoma* cannot produce the hypouricemic effect. Here, *Atractylodis Rhizoma* assisted and enhanced the effect of CPC on the lessening serum uric acid levels in hyperuricemia mice according to the theory of TCM that CPC is the main ingredient, and *Atractylodis Rhizoma* adjuvant ingredient in Ermiao Wan.

Chen et al. evaluated the anti-inflammatory activity and the molecular mechanism of Ermiao San in mouse RAW264.7 macrophages [51]. The production of NO in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages can be suppressed by Ermiao San, while, CPC and *Atractylodis Rhizoma* alone cannot. The production of TNF-α, IL-1β, macrophage chemotacticprotein-1, p38 phosphorylation, inhibitor of NF-κB (IkBα), phosphorylated p65 and NF-xB DNA-binding activity can also be inhibited. The inactivation of the MAPK and NF-xB pathway was the key to the inhibition of inflammatory response in the LPS-stimulated RAW264.7 macrophages.

Chen et al. also further investigated the effects of Ermiao San extracts on TNF-α-induced matrix metalloproteinases-1 expression in human dermal fibroblasts [51]. Ermiao San can reduce the level of nuclear p65 protein while stabilizing the IkB content without suppressing MAPK phosphorylation. The results demonstrated that Ermiao San exerted the anti-inflammatory activity mainly by inhibiting NF-xB pathway rather than MAPK pathway in human dermal fibroblasts. These studies reconfirmed the anti-inflammatory effect of CPC from the prescription point of view.

### II Sanmiao San and Sanmiao Wan

Sanmiao San was recorded in *Yi Xue Zheng Zhuan* in Ming Dynasty which composed of CPC, *Atractylodis Rhizoma* and *Achyranthes Bidentatae Radix* with equal proportion. Sanmiao San is usually employed in the treatment of *Bi Zheng*, which is a painful obstructive syndrome mainly caused by the invasion of external pathogenic factors into muscles, bones and joints of the suffer [52-55]. Sanmiao Wan has been used to treat gout via the elimination of heat and excretion of dampness [56, 57].

Wang et al. explored the hypouricemic effects and its potential mechanism of Sanmiao Wan in potassium oxonate-induced hyperuricemic mice model [57]. The present study demonstrate that Sanmiao Wan could reduce uric acid production by inhibiting liver xanthine oxidase and decrease urate reabsorption meanwhile increase urate excretion by down-regulating renal urate transporter 1. Thus, the dual hypouricemic function of Sanmiao Wan could decrease the uric acid level, while has no effect on normal mice. The effect of Sanmiao Wan on hyperuricemia rat model was evaluated by metabolomics techniques which can characterize hyperuricemia-related metabolic profiles [56].

Thirteen serum metabolites associated with hyperuricemia were identified, mainly involving tricarboxylic acid cycle, purine metabolism, glycerophospholipid metabolism, arginine and proline metabolism, phenylalanine metabolism, and tryptophan metabolism. After treatment with Sanmiao Wan, the above-mentioned perturbed metabolic pathways were partially regulated to reverse the pathogenesis of hyperuricemia except for glycerophospholipid metabolism. The study utilized another perspective to investigate the potential efficacy and mechanisms of Sanmiao Wan in treating hyperuricemia.

### III Simiao San

Simiao San, a classic TCM prescription, composed of CPC, *Achyranthis Bidentatae Radix*, *Coptidis Rhizoma* and *Atractylodis Rhizoma*, was first registered in 1904 in <Cheng Fang Bian Du>. The recipe was extensively employed in the treatment of down flow of damp-heat syndrome complex [58]. Currently, its application has been extended to the treatment of general infections and inflammatory diseases. In modern clinical practice, this recipe is usually modified by substituting *Achyranthis Bidentatae Radix* with *Rhizoma Coptidis* in order to enhance the anti-inflammatory effect, which is known as the modified Simiao San [59-61].

Liu et al. made a series of studies on the mechanism of modified Simiao San. For the treatment of inflammatory diseases, the underlying

<table>
<thead>
<tr>
<th>Cortex Phellodendri Chinensis</th>
<th>Relieving internal heat or fever, removing necrotic tissue and promoting granulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Rhei Radix et Rhizoma</em></td>
<td></td>
</tr>
<tr>
<td><em>Lonicerae Japonicae Flos</em></td>
<td></td>
</tr>
<tr>
<td><em>Anemarrhenae Rhizoma</em></td>
<td></td>
</tr>
<tr>
<td><em>Trichosanthis Radix</em></td>
<td></td>
</tr>
<tr>
<td><em>Margaritaria</em></td>
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<tr>
<td><em>Bovis Calculus Artificius</em></td>
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<tr>
<td><em>Borax</em></td>
<td></td>
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<tr>
<td><em>Mirabililium Praeparatum</em></td>
<td></td>
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<tr>
<td><em>Realgar</em></td>
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<tr>
<td><em>Catechu</em></td>
<td></td>
</tr>
<tr>
<td><em>Coptidis Rhizoma</em></td>
<td></td>
</tr>
<tr>
<td><em>Cortex Phellodendri Chinensis</em></td>
<td></td>
</tr>
<tr>
<td><em>Borneolum Syntheticicum</em></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:** The ingredients of Ermiao San and Ermiao Wan.
mechanism of modified Simioa San may be caused by the inhibition of ERK and NF-κB pathway, thereby suppressing the production of inflammatory mediators, such as IL-6, NO, TNF-α [62]. Modified Simioa San can also enhance inflammation-related glucose tolerance, thus improving hepatocyte insulin sensitivity by means of the inhibitor of NF-κB kinase-β (IKKβ)/ insulin receptor substrates-1 (IRS-1)/ serine/threonine kinase (Akt)-dependent pathway [58]. Advanced glycation end products-induced pancreatic B cell dysfunction can be ameliorated by modified Simioa San via inhibiting ROS-associated inflammation, which was associated with the regulation of AMPK activity [63].

IV Huanglian Jiedu Decotion

Huanglian Jiedu Decotion (HLJDD), also known as Oren-gedoku-to in Japan, is a famous ancient recipe composed of Rhizoma Coptidis, Scutellaria Radix, CPC and Gardeniae Fructus the proportion of 3:2:2:3 with a dry weight ratio. This formula was first recorded in the treatise <Wai Tai Mi Yao> by Wang Tao in Tang Dynasty. It has been used to treat various clinical symptoms, such as inflammation Alzheimer's disease stroke gastrointestinal disorders hypertension and cerebrovascular diseases etc. [64-69]. In this prescription, Rhizoma Coptidis serves on the chief ingredient with the main therapeutic effect of balance the disorder of the body. Scutellaria Radix performs as the minister drug to assist the therapeutic effect of chief ingredient.

CPC here acts as the adjuvant component and Fructus Gardeniae plays both roles as adjuvant and messenger components. In this recipe, berberine is the main active ingredient of Rhizoma Coptidis and CPC [64, 22]. It was reported berberine could lessen Aβ accumulation in Alzheimer's disease mouse model [70]. With the further research, the modified HLJDD (free of Scutellaria Radix) exhibited more significant Aβ precursor protein- and Aβ- reducing functions than berberine treatment alone [66]. The aqueous extracts of HLJDD can effectively improve collagen type II (CII)-induced arthritis, and dramatically inhibit immune response against CII with the analogical pharmacological effects, which demonstrated HLJDD has the potential to treat arthritis [71].

V Zishen Wan

Zishen Wan, a classic prescription of treating benign prostatic hyperplasia which was originated from <Secret Record of the Chamber of Orchids> by Li Gao in Yuan Dynasty, consists of Anemarrhenae Rhizoma, CPC and Cinnamomi Cortex with the quality ratio of 10:10:1. Modern clinical also commonly used it to treat prostatitis, urinary frequency, urinary system infection, and osteoporosis [72-74]. Anemarrhenae Rhizoma and CPC is a famous “herb pair”, which was first reported in <Ben Cao Gang Mu> and first include in Zishen Wan, as well as often involved in many other TCM prescriptions, such as Zhibai Dihuang Wan, Dabuyin Wan, Shengui Ziyin Wan, etc. In Zishen Wan, Anemarrhenae Rhizoma was the sovereign drug, having the effect of clearing heat and fire.

CPC was the ministerial drug with a good treatment of lower energizer’s damp-heat. Cinnamomi Cortex was the anti-adjuvant drug which can prevent and control the cold effect of Anemarrhenae Rhizoma and CPC. Sun et al. reported that Zishen Wan can restrain benign prostatic hyperplasia of the induced-testosterone castrated rat by down-regulating the expression of vascular endothelial growth factor and basic fibroblast growth factor, as well as up-regulating the expression of prostate transforming growth factor-β1 in prostate [74]. Although the above studies clarified the mechanism of CPC as a drug pair in Zishen Wan, there is no explanation of this compatibility rule in present study.

VI Other Prescriptions Including Cortex Phellodendri Chinensis

Dahuang Xiaoshi Decotion (DHXSD) consists of four herbs, Rhei Radix et Rhizoma, Miribilium, CPC and Gardeniae Fructus, with the mass ratio of 4:4:4:3. It was originally designed in <Jin Kui Yao Lue> to be used for treating jaundice caused by interior-heat syndrome. The constituents of CPC, such as tetrahydropalmatine, jatrorrhizine, and berberine exerted hepatoprotective activities in tert-butylhydroperoxide-injured BRL-3A cells [75]. Zhibai Dihuang Wan is an ancient formulation consist of eight kinds of herb, Rehmanniae Radix Praeparata, Corni Fructus, Dioscoreae Rhizoma, Moutan Cortex, Poria, Alismatis Rhizoma, Anemarrhenae Rhizoma and CPC. It was originated from <Yi Zong Jin Jian> and has been used for the treatment of chronic kidney inflammation and diabetes for thousands of years [76].

Rehmanniae Radix Praeparata as the principal drug can nourish Yin and strengthen kidney, Corni Fructus, CPC, Dioscoreae Rhizoma, and Anemarrhenae Rhizoma act as minister drug, Moutan Cortex, Pori, and Alismatis Rhizoma serve as adjuvant drug, these herbs act together to generate the effect of nourishing Yin and removing fire. Hsu et al. explored the effect of Zhibai Dihuang Wan on cell growth and gentamicin-induced apoptosis in renal tubular cells [76]. The results demonstrated that Zhibai Dihuang Wan generated the protective effect against gentamicin-induced apoptosis in cells via a dose-dependent form and can also decrease gentamicin-induced renal toxicity in vivo which indicated that Zhibai Dihuang Wan may have therapeutic potential for gentamicin-induced kidney injury patients. K-601 is a hospital-prepared prescription comprised of five herbs, Loniceræ Japonicae Flos, Isatidis Radix, Rhei Radix et Rhizoma, CPC, and Scutellariae Radix, which is usually used for relieving influenza symptoms and treating the cough caused by non-bacteria causes [77].

It is popular in China, especially for children and adults. Qianyu Decotion, as one of traditional Chinese recipe, was consisted by Astragali Radix, Epimediæ Washanensis Folium, Leonuri Herba, CPC, and Achyranthis Bidentatae Radix. Due to its anti-inflammatory and broad-spectrum antibacterial activity, Qianyu Decotion can be commonly used to treat chronic prostatitis/chronic pelvic pain syndrome [78, 79]. Ruyi Jinhuang San, an important prescription in surgery of TCM, was firstly described in <Wai Ke Zheng Zong> by Shigong Chen in Dynasty Ming. This prescription contains a variety of TCMs, Curcumæ Longæ Rhizoma, Rhei Radix et Rhizoma, CPC, Rhizoma Atractylodis, Magnoliæ Officinalis Cortex, Citri Reticulatae Periciarpium, Glycyrrhizæ Radix et Rhizoma, Arisaematis Rhizoma, Paeoniae Radix Alba, and Trichosanthis Radix. It’s well known for reducing swelling, relieving pain, and removing poisons [80]. At present, the study of prescriptions containing CPC mainly focuses on the evaluation of their effectiveness, followed by the
study of the effective ingredients. From ancient times to the present, CPC and other TCMs, such as Anemarrhenar Rhizoma, Paoniae Radix Rubra, usually form prescriptions in the form of "drug pairs". Future research can start with "CPC drug pairs", systematically study the analogous prescriptions containing CPC, and it is believed some breakthrough results will be obtained.

Conclusion

Through the above review, as a high-grade herbal medicine in ancient codes and records, a large number of significant researches have been made into the phytochemistry and pharmacology of CPC in cells and animals. In these studies, we have not only seen the great prospect of CPC clinical application, but also found some aspects need to be strengthened.

Benefitting from the rapid progresses of analytical technology, chemical compositions of CPC have been continuously identified. Although there are many studies on the chemical compositions of CPC, most of them are extracted with mixed solvents, such as different proportions of methanol and water. Most of these researches aim at obtaining as many compounds as possible in one extraction. While, water is the most commonly used traditional extraction solvent. At present, there are few studies on CPC water extractions, and some components may be ignored. The use of herbal medicine in clinic is usually soaked in water firstly and then decocted to form decoction for administration. From the perspective of clinical application, more attention should be paid on the water extractions and its biological function in the future research to serve the clinical.

Furthermore, a variety of analytical techniques can be used together to expand the coverage of chemical components in order to discovering more chemical components. And novel extraction methods can be established, such as the use of various SPE columns and selective enrichment components. Due to the diversity pharmacological properties and efficacy of TCM, its active ingredients have the characteristics of multi-pathway, multi-target, multi-link and multi-effect. Different compatibility of TCM or combination of active ingredients can often achieve synergistic effect. In the light of CPC can be prepared with other herbs into prescriptions for clinical uses, it will be valuable to study the effective components and compatibility laws in different compatibility environments and corresponding disease status.

At present, the research on prescriptions containing CPC mainly focuses on pharmacological effects and screening of active ingredients. It is necessary to further determine the appropriate dosage of these prescriptions in human body, as well as the side effects, adverse effects and toxicity characteristics. Although the chemical composition has been well elucidated, few studies have been done on CPC active components except berberine. Most of the studies lacked the necessary pharmacological data, such as the value of IC50, long-term chronic toxicity studies and acute toxicity, the data of pharmacokinetic were also not be well understood. Thus, there is a broad space to be explored for pharmacological research of CPC.

As a traditional and valuable herbal medicine, pharmacological research of CPC should be more in-depth and meticulous, such as the determination of the active components and their mechanisms of action, the repeated verification of in vivo and in vitro studies, and so on, to form a series of complete research, which is of great help to the discovery of new drugs. Despite the “Chuan HuangBai” and “Guan HuangBai” has the same function according to pharmacopoeia records, with the progress of science and technology, it has been known that the components in particular the contents of two herbs exist differences, therefore, the pharmacology and biological activity may have different focuses.

While, the researchs concerned on the differences between the two herbs were relatively few, it is recommended to reinforce the investigation and development of pharmacology and pharmacological effects between “Chuan HuangBai” and “Guan HuangBai” to better facilitate their clinical applications for human health. Additionally, because of the wide distributions of CPC, the maturity time, time of harvesting, the climate and age can all affect the quality of CPC. In order to ensure the safety of the drug and the reliability of the experimental results, it is supposed to speed up the study of the CPC quality markers to ensure the safety and effectiveness of the CPC.

This review gathered the information of all-important aspects of CPC, including botanical description, phytochemical constituents, pharmacological activities, common clinical prescriptions. As discussed above, CPC has several potential uses for certain therapeutic activities, and how to solve the issues put forward in this review is also the key to the follow-up study of CPC. It is expected that this review will provide researchers with information, cornerstone and research directions for further in vitro, in vivo and clinical researches on CPC.

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Conflicts of Interest

None.
Abbreviation

AJβ: amyloid-β
Akt: serine/threonine kinase
AMPK: AMP-activated protein kinase
CII: collagen type II
COX: cyclooxygenase
CPC: Cortex Phellodendri Chinensis
DHXSD: Dahuang Xiaoshi Decoction
ERK: extracellular signal regulated kinase
GSH: glutathione
HLJDD: Huanglian Jiedu Decoction
IC₅₀: half maximal inhibitory concentration
IκKB: inhibitor of NF-κB kinase-β
IxB: inhibitor of NF-xB
IL: interleukin
Inos: inducible nitric oxide synthase
IRS-1: insulin receptor substrates-1
LPS: lipopolysaccharide
MAPK: mitogen-activated protein kinases
MRSA: methicillin-resistant Staphylococcus aureus
MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazenium bromide
NF: nuclear factor
PEEK: poly ether ether ketone
ROS: Reactive oxygen species
TCM: traditional Chinese medicines
TNF: tumor necrosis factor

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