

A Comprehensive Review of Coptidis Rhizoma and Magnoliae Officinalis Cortex Drug Pair and Their Chemical Composition, Pharmacological Effects and Pharmacokinetics Analysis

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Abstract: Herbal pairs are unique combinations of two relatively fixed herbs that are used in clinical practice. This is the most fundamental and straightforward form of multiple herbal treatment that aims to attain specific efficacy through unique methods. Coptidis Rhizoma (“Huanglian” in Chinese) and Magnoliae Officinalis Cortex (“Houpo” in Chinese) which are commonly used in combination and could also be used as important components of other prescriptions to treat damp-heat dysentery, splenic and stomach disorders, and qi stagnation in clinical practice. However, there is currently no summary on the compatibility of Huanglian and Houpo about traditional use, phytochemistry, and pharmacological activity. It was found the combination or separate extraction of the two drugs may affect the main active components, and new components may be produced after the combined extraction. At the same time, Huanglian and Houpo herb pair exhibited antiviral, anti-inflammatory, antibacterial and other pharmacological effects. At present, research mainly focuses on the indicator components of Huanglian and Houpo, such as berberine, magnolol, and magnolol. The models used for pharmacological validation are limited, mainly including ulcerative colitis, pneumonia, bacterial infections, etc. In order to verify the pharmacological activity of the combination of Huanglian and Houpo, it is necessary to try more in vitro and in vivo models. It's still need to study the compatibility mechanism of the Huanglian and Houpo drug pair, including but not limited to the interactions between different components and the impact of compatibility on efficacy, bioequivalence studies, and the impact of different dosage forms on pharmacokinetics in the future. It's believed that the systematic review provided comprehensive information for the study of Huanglian-Houpo drug pair, which will help highlight the importance of the Huanglian-Houpo herb pair and provide some clues for future research on this herb pair.

Keywords: Coptidis Rhizoma, Magnoliae Officinalis Cortex, drug pair, chemical constituents, pharmacological effects

Introduction

Over thousands of years of development, traditional Chinese medicine (TCM) has continually absorbed and integrated advanced scientific knowledge, technological advancements, and humanistic ideas from various periods, leading to consistent innovation and development. Consequently, its theoretical framework has become increasingly refined, and its technical methods have diversified, resulting in distinct characteristics. As an indigenous medical science of the Chinese nation, traditional Chinese medicine is not only widely practiced in China but is also gradually gaining recognition in other countries, offering modern treatment options for critically ill patients worldwide. Multi-herb therapy continues to play a significant role in traditional medical systems. TCM compounds represent the primary form of clinical medication, guided by the principles of TCM compatibility theory. Herbal pair, usually refers to the combination of two Chinese medicines used in combination with high frequency, consists of a distinctive combination of two relatively fixed herbs utilized in clinical practice. This pairing constitutes the most fundamental and straightforward form of multiple herbal treatment, achieving specific therapeutic effects through unique methodologies.¹ In the clinical application of TCM, there

are 686 prescriptions that include *Coptidis Rhizoma* (“Huanglian” in Chinese) and *Magnoliae Officinalis Cortex* (“Houpo” in Chinese). These prescriptions primarily focus on heat-clearing and dampness-drying effects and are widely employed to treat conditions such as damp-heat dysentery, spleen-stomach disharmony, and qi stagnation in clinical practice. According to TCM property theory, Huanglian is characterized as bitter and cold, whereas Houpo is described as bitter, pungent, and warm. The combination of Huanglian and Houpo signifies the use of both cold and heat properties to balance each other’s medicinal effects, thereby promoting qi and facilitating dampness drying. Furthermore, modern pharmacological studies have demonstrated that the Huanglian-Houpo herb pair exhibits antiviral, anti-inflammatory, and various other pharmacological activities.^{2,3} However, there is currently no comprehensive summary on the compatibility of Huanglian and Houpo. To better develop and utilize the Huanglian-Houpo drug pair, this paper reviews the traditional use, chemical composition, pharmacological activity and other aspects of the compatibility between Huanglian and Houpo. This study also provides support for follow-up studies on Chinese herbal medicines.

Traditional Application of Compatibility of *Coptidis rhizoma* and *Magnoliae officinalis Cortex*

Pursuant to the authoritative 2020 edition of the Chinese Pharmacopoeia, Huanglian is formally designated as the dried rhizome derived from three specific plant species: *Coptis chinensis* Franch, *Coptis deltoidea* C. Y. Cheng et Hsiao, and *Coptis teeta* Wall. The flowering season occurred from February to April, with the harvest of fruits taking place from April to June. Huanglian is widely distributed across various regions in China, including Sichuan, Guizhou, Yunnan, and Hunan, among others. It grows in mountainous forests or valleys.⁴ It was first recorded in Shennong’s Herbal Classic and is listed as a top grade. The Huanglians possess bitter and cold properties, and are associated with the meridians of the stomach, spleen, heart, gallbladder, liver, and large intestine. They have the therapeutic actions of clearing heat, drying dampness, purging fire, and detoxifying. Their primary applications encompass the treatment of diabetes, gastrointestinal diseases, skin damage, and other diseases. Pharmacological studies have shown that Huanglians demonstrated hypoglycemic, antibacterial, antioxidant, anti-inflammatory, and anti-tumor effects.⁵ Houpo comes from the dried bark, root bark, and branch bark of *Magnolia officinalis* Rehd. et Wils. or *Magnolia officinalis* Rehd.

The utilization of Houpo in China can be traced back to the period spanning from the late Western Han Dynasty to the early Eastern Han Dynasty (1st century BC to 1st century AD), and even earlier. It is mentioned in Shennong’s Herbal Classic and is classified as an intermediate product, commonly implying either non-toxic or containing minimal toxins. Houpo, primarily distributed in East and Southeast Asia, has been found to thrive predominantly in subtropical and humid environments. Houpo stands as a geographically significant product originating from Dujiangyan and Nanjiang in Sichuan Province, and Enshi in Hubei Province. Contemporary pharmacological research has demonstrated that Houpo had antibacterial, anti-tumor, analgesic, anti-inflammatory and antioxidant effects.⁶ Discovered from ancient books, many prescriptions contained Huanglian-Houpo drug pairs, for example, Niujiao (Jiaosi) Powder in the fifteenth volume of “Qianjin Fang”, Muxiang Huazhi Decoction in the thirty-sixth volume of “Yitong”, Muxiang Daoqi Decoction in the third volume of “Gujin Yijian”, Mugua Yin, Baizhi Huanglian Decoction and Muxiang Decoction in “Shengji Zonglu”, Huazhi Decoction in the twenty-fifth volume of “Yilue Liushu” and so on. Houpo can relieve stagnation, Huanglian could clear heat and dry dampness, and Huanglian-Houpo drug pairs are mainly used to treat dysentery, abdominal distension, and abdominal pain. The Huanglian Houpo Decoction, derived from “Puji Prescription”, contains only the Huanglian and Houpo these two drugs. The Huanglian Houpo Decoction serves as an effective prescription for the treatment of damp-heat diarrhea, as it is capable of energizing the middle region and promoting the flow of qi to eliminate dampness and heat. Similarly, Houpo Pill in “Taiping Shenghui Fang” incorporates both Huanglian and Houpo. Huanglian possesses bitter and cold properties, which contribute to its ability to clear heat, detoxify, purge fire, and dry dampness.⁷ Whereas Houpo possesses bitter, pungent, and warm properties, which contribute to promote qi and dry dampness, reduce adverse qi, and alleviate asthma.⁷ When combined, Huanglian and Houpo harness the opposing medicinal properties of cold and heat, respectively, to restrain each other’s effects while enhancing the overall promotion of qi and the drying of dampness. Therefore, the combination of Huanglian and Houpo is the basic formula for clinical use in traditional Chinese medicine, used to treat various diseases.

Chemical Constituents of the Compatibility of “Huanglian-Houpo”

Numerous literature has reported in detail the progress in research on the chemical constituents of Huanglian and Houpo.^{4,6} In this study, the active components of Huanglian and Houpo were searched in the TCMSP database. Furthermore, the oral bioavailability $\geq 30\%$ and drug-likeness ≥ 0.15 were selected as the conditions. The findings indicated the presence of 15 chemical components in Huanglian and 8 in Houpo, as illustrated in Figures 1 and 2. The compatibility of TCM possesses a characteristic that exerts influence on the drug's chemical composition, pharmacokinetics, and metabolism. This principle equally applies to the chemical compositions of varying compatibility ratios within the drug pair. According to the principle of compatibility of TCM, the formula's active ingredients may vary from quantitative to qualitative, potentially leading to differing degrees of efficacy or toxicity within the body.^{8–10} A summary of the impact of varying compatibility ratios and extraction techniques on the active components is detailed in Table 1. It's reported that there were discrepancies in the extraction efficiency of Huanglian and Houpo when utilizing water or alcohol as solvents. Furthermore, it has been observed that the extraction yield of berberine is optimized at a 1:1 compatibility ratio. Notably, a decrease in the proportion of Houpo corresponded to an increase in the extraction rate.¹¹ In the subsequent investigation, the extraction and paste rates of berberine and magnolol were employed as benchmarks to ascertain the optimal extraction methodology for the Huanglian-Houpo (1:2) herbal pair, utilizing orthogonal experimental design. The optimal extraction process for Huanglian-Houpo comprised a 10-fold water volume, 70% ethanol reflux, and an extraction duration of 60 minutes, with a single extraction cycle. Additionally, alcohol extraction was found to enhance the solubility of berberine, magnolol, and honokiol.¹² Regarding the chemical

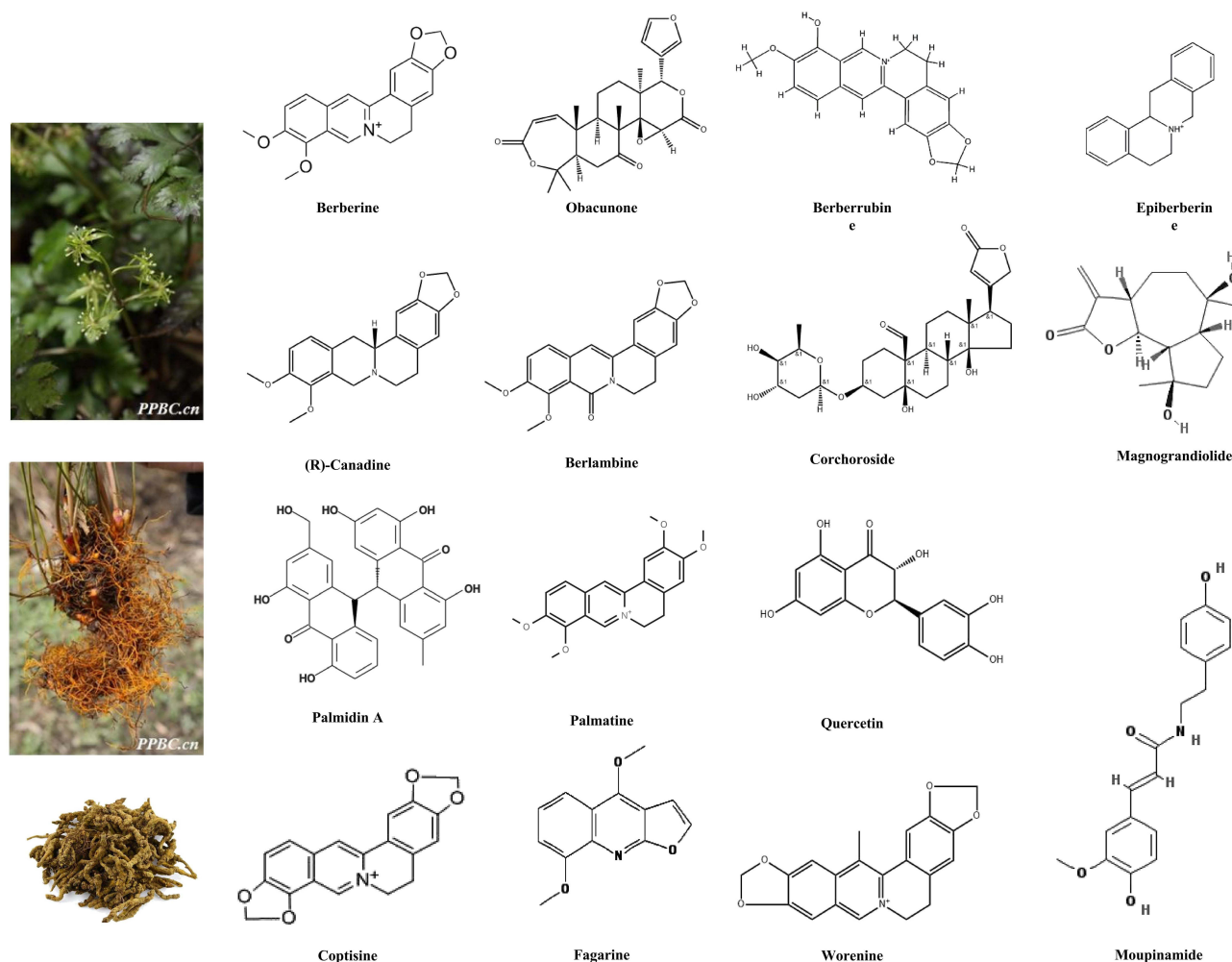


Figure 1 The Structural Formula of 15 Chemical Constituents in Huanglian (OB $\geq 30\%$, DL ≥ 0.15 through TCMSP).

Notes: The plant picture is reproduced with permission from www.iplant.cn.

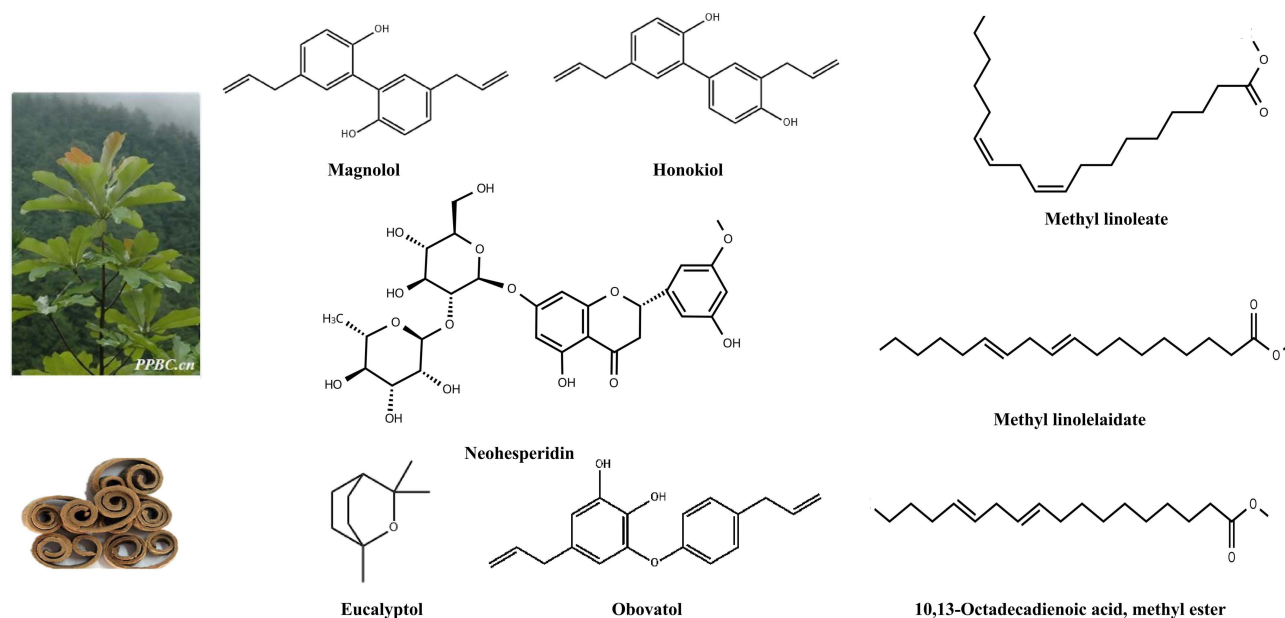


Figure 2 The Structural Formula of 8 Chemical Constituents in Houpo (OB $\geq$ 30%, DL $\geq$ 0.15 through TCMS).

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components present in the extracts of “Huanglian-Houpo” following either combined or separate extraction methods, the findings indicate that, under identical feed quantities, there are notable disparities in the chemical content among the extracts obtained via water extraction, alcohol extraction, and the combined extraction technique, which suggested that the combined

Table 1 Effects of Different Compatibility Ratios and Extraction Methods on the Active Components

Study	Extraction Method	Result
Niu 2011 ¹³	1. Water extraction respectively 2. Ethanol extraction respectively	1. After separate water extraction, the peak area of each component was higher than that of the two drugs co-extraction. 2. The peak area of most components separated by alcohol extraction was less than that of two drugs co-extraction. 3. The extraction efficiency of ethanol extract increased. 4. It was speculated that the combined extraction of the two drugs may cause the chemical synthesis of berberine hydrochloride and magnolol.
Meng and Zhang 2009 ¹⁴	1. Ethanol co-extraction 2. Ethanol extraction respectively, then co-extraction.	1. Some components of Huanglian and Houpo after Ethanol extraction respectively and then co-extraction were slightly higher than those of the direct combination of the two drugs 2. New components may be produced in the combined extraction.
Wu et al, 2012 ¹²	Ethanol co-extraction	The optimum extraction process was as follows: 10 times the amount of medicinal materials, 70% ethanol reflux, extraction for 60 min, extraction once.
Wu et al, 2011 ¹¹	Water co-extraction and alcohol co-extraction	1. The extraction rate of ethanol extraction process was better than that of water extraction. 2. The content of berberine in the water extraction process decreased by 40%, and only decreased by 1% in the alcohol extraction process. 3. The content of Houpo increased by about 2% in the co-extraction. 4. When the compatibility ratio was 1: 1, the extraction rate of berberine was higher, and the lower the proportion of Houpo, the higher the extraction rate.
Wang et al, 2011 ^{15,16}	Different proportions of water extraction	1. The decoction rate of berberine and total alkaloids increased with the increase of the compatibility dose of Huanglian in the drug pair. 2. When the compatibility dose of Huanglian began to be greater than the dose of Houpo, the increase trend of alkaloid decoction rate slowed down. Honokiol was most dissolved when Huanglian: Houpo = 1: 3, and magnolol was most dissolved when Huanglian: Houpo = 1: 1. 3. The total amount of honokiol and magnolol the highest when Huanglian: Houpo = 1: 1 and the lowest when Huanglian: Houpo = 2: 1.

extraction process of Huanglian and Houpo may lead to the chemical synthesis of berberine and magnolol.¹³ Another study demonstrated that there is a transformation among the chemical constituents during the co-extraction process of Huanglian and Houpo.¹⁴ The primary constituents in Huanglian Houpo decoction are alkaloids, honokiol, and magnolol. It has been reported that the extraction rate of berberine and total alkaloids in the decoction rises with an augmentation in the compatible dosage of Huanglian within the drug pair. Nevertheless, the compatible dosage of Huanglian surpasses that of Houpo, resulting in a deceleration in the upward trend of alkaloids. Specifically, honokiol achieved its maximum solubility when Huanglian: Houpo = 1:3, and magnolol achieved its maximum solubility when Huanglian: Houpo = 1:1. The total amounts of honokiol and magnolol were highest when Huanglian: Houpo = 1:1, and lowest at 2:1.^{15,16} In summary, the chemical components of Huanglian Houpo herb pair are mainly concentrated in berberine, magnolol, and magnolol, which were influenced by the different compatibility ratios of Huanglian and Houpo, suggesting that alkaloids may interact with magnolol and honokiol. Ethanol extraction should be performed to increase the efficiency of drug extraction. This was because honokiol and magnolol are insoluble in water. It is not sufficient to rely solely on chemical composition analysis to scientifically and reasonably evaluate the efficacy of a prescription. It's also found that there is very little research on other components. In fact, TCM is a multi-component medicine, and studying a single component is far from enough. It is necessary to study other components of Huanglian Houpo herb pair. In addition, studies have confirmed that new components are produced after co-decoction of Huanglian and Houpo. Given this situation, it is necessary to use new methods to accurately identify new compounds and verify their pharmacological effects and absorption of each component, laying the foundation for their pharmacological substance basis.

Pharmacological Effects of “Huanglian-Houpo” Compatibility

Modern pharmacological investigations have revealed that the active components of Huanglian and Houpo exhibited anti-inflammatory, antitumor, antibacterial, and other pharmacological effects. Furthermore, and that the compatibility of the two drugs has broad application prospects. The combination of the drug pair mainly includes anti-virus, anti-inflammatory, improvement of gastrointestinal disease symptoms, and antibacterial, etc., which are summarized in Table 2.

Antivirus

Neuraminidase possesses the ability to hydrolyze the glycosidic bond that exists between the influenza virus and host cells, ultimately leading to the release of the virus and the subsequent onset of influenza.³⁶ A study has been conducted to investigate the influence of nine different compatibility ratios (0:1, 1:5, 2:5, 2:3, 1:1, 3:2, 5:2, 5:1, and 1:0) of Huanglian:

Table 2 Pharmacological Activities of Huanglian and Houpo Drug Pair

Pharmacologic Action	Research Object/Model	Pharmacological Activity	Study
Anti-virus	H1N1 infected MDCK cells	Huanglian and Houpo drug pair had the strongest inhibitory effect on H1N1 influenza virus.	Yu and Wu 2021 ¹⁷
	H1N1 induced pneumonia model mice	Huanglian and Houpo drug pair significantly reduced the lung index of H1N1 infected mice, increased the spleen and thymus index, reduced the levels of cytokines interleukin 6 (IL6), tumor necrosis factor- α (TNF- α), interferon- γ , nitric oxide, and increased the levels of IL-2. Huanglian and Houpo drug pair inhibited the levels of TLR / MyD88 / NF- κ B pathway-related proteins or mRNA in lung tissue. Huanglian and Houpo drug pair also regulated antioxidant factors superoxide dismutase and glutathione.	Zhang et al, 2021 ²
	Normal rats	Each compatibility ratio had an inhibitory effect on neuraminidase activity, and the inhibitory effect was the strongest when the compatibility ratio was 1: 1.	Chen et al, 2017 ¹⁸
	Normal rats	Different compatibility ratios of Huanglian and Houpo drug pair had different effects on the inhibition of neuraminidase activity. The optimal compatibility ratio was 1:1.	Li et al, 2019 ¹⁹
	H3N2 infected MDCK cells.	Different processes had different inhibition rates on the virus. The best process was to add 9 times the amount of water to the medicinal materials, extract 3 times at 72 °C, 54 min each time.	Wu et al, 2022 ²⁰
	H1N1 infected MDCK cells.	Huanglian and Houpo drug pair had anti-influenza virus effect, which is related to the improvement of IFN- β secretion.	Zhang et al, 2022 ²¹

(Continued)

Table 2 (Continued).

Pharmacologic Action	Research Object/Model	Pharmacological Activity	Study
Antibiosis	Bacillus anthracis	Huanglian and Houpo drug pair has inhibitory effect on Bacillus anthracis in vitro and in vivo.	Liao et al., 1954 ^{22,23}
	Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus	Huanglian and Houpo drug pair had antibacterial effects.	Meng et al, 2009 ²⁴
Promote gastric motility, anti-diarrheal	Normal mice, senna induced diarrhea in mice	Huanglian and Houpo exacted respectively then co-exaction was stronger than that of the co-extraction.	Meng et al, 2009 ²⁴
	Normal mice, diarrhea model mice	The combined extract after ethanol extraction of Huanglian and Houpo drug pair could significantly inhibit the propulsion rate of carbon powder in the small intestine of mice.	Zheng et al, 2014 ²⁵
	Normal mice, glacial acetic acid induced pain, senna induced diarrhea	Huanglian and Houpo drug pair also alleviated the diarrhea caused by senna in mice.	Qiu et al, 2012 ²⁶
		Huanglian: Houpo 1: 1 significantly alleviated the side effects of gastrointestinal motility inhibition caused by Huanglian, and had good antidiarrheal effect.	
		The effective parts and main components of Huanglian and Houpo drug pair had antidiarrheal and analgesic effects	
		The compatibility effect of effective components is not as good as that of raw medicinal herbs or effective parts from raw medicinal herbs.	
		The best ratio of Huanglian and Houpo is 1: 2.	
Chronic gastritis	Experimental gastric mucosal injury, diarrhea and vomiting model	Different doses of Huanglian Houpo Pill can resist gastric mucosal injury, promote intestinal absorption, antidiarrheal, antiemetic and other effects to varying degrees.	Pan et al 2004 ²⁷
	Chronic gastritis rats	Huanglian and Houpo drug pair reduced the inflammatory response and apoptosis of gastric mucosal tissue.	Song et al, 2023 ²⁸
		The mechanism is related to ribosome and NF-κB signaling pathways, which can play a role by regulating key genes TPT1 and RPL37.	
	Network pharmacology	It is also predicted that Huanglian and Houpo herb pair may mainly regulate PI3K / AKT / P53 signaling pathway.	Xiang and Lv 2021 ²⁹
Anti-ulcerative colitis (UC) activity	TNBS-induced UC rats	Huanglian and Houpo drug pair can improve the activity of model rats, the pathological damage of colon tissue, and the depth and scope of tissue necrosis.	Yang et al, 2020; Yang et al, 2021 ^{5,30}
		The mechanism is related to down-regulating the expression of Bax and Caspase-3 protein, inhibiting the release of inflammatory cytokines TNF-α, IL-6 and MPO, and promoting the release of anti-inflammatory factor IL-10.	
		It may be achieved by inhibiting the PI3K / Akt signaling pathway.	
	DSS-induced UC mice	Huanglian and Houpo drug pair could inhibit NLRP3 inflammasome activation.	Zhu et al, 2023 ³¹
	DSS-induced UC mice	Huanglian Houpo decoction could inhibit the expression of inflammatory factors TNF α - and IL-1β, reduce the content of apoptotic protein, regulate the expression of ROS.	Wang et al, 2022 ^{15,32}
		Huanglian Houpo decoction regulated the activity of brain-gut peptide and its receptor to reduce the inflammatory response and pathological damage of colon tissue.	
	TNBS-induced UC rats	Huanglian and Houpo drug pair could decreased serum TNF-α and increased TGF-β1, also decreased COX2 positive cells in colon tissue.	Li et al, 2021 ³³
	DSS-induced UC mice	Huanglian and Houpo drug pair could protect intestinal mucosal barrier and regulate macrophage polarization.	Cheng et al, 2023 ³
	DSS-induced UC mice	Huanglian and Houpo drug pair significantly restored the reduced colon tissue length, body weight and DAI, improved colon histopathology, and reduced the inflammatory factors.	Wang et al, 2023 ³⁴
	TNBS-induced UC rats	Huanglian: Houpo 1:1 could regulate the intestinal flora in UC rats, inhibit the inflammatory response of colon, and repair the mucosal barrier.	Xie et al, 2022 ³⁵

Houpo on neuraminidase activity in rats. The findings of this study indicated that each compatibility ratio demonstrated an inhibitory effect, and the strongest inhibitory effect was observed at the 1:1 ratio.¹⁸ Another study has further corroborated that Huanglian: Houpo = 1:1 exhibited marked inhibitory effects on neuraminidase activity.¹⁹ Utilizing an Apriori association rule analysis, Yu et al screened seven pairs of cold and heat medications, notably Huanglian-Houpo, Huanglian-Banxia, and Huanglian-Zisuye, which exhibited a high prevalence of usage. These medications were subsequently compared in terms of their anti-influenza virus efficacy. Ultimately, the study revealed that Huanglian-Houpo exhibited the most potent inhibitory effect against the H1N1 influenza virus.¹⁷ In addition, the Huanglian-Houpo herb pair could suppress inflammation and oxidative stress through the Toll-like receptor (TLR)4/myeloid differentiation primary response 88 (MyD88)/nuclear factor (NF)-κB signaling cascade in the lung tissue of a mouse model induced by AH1N1 influenza (H1N1) - induced pneumonia.² A additional study yet found that berberine and magnolol, the main

bioactive constituents derived from Huanglian and Houpo respectively, could resist H1N1 - induced pneumonia due to the improvement in interferon- β (IFN- β) secretion.²¹ Furthermore, it has been discovered that various processes of Huanglian-Houpo decoction could diminish the rates of virus replication in H3N2-infected Madin-Darby canine kidney (MDCK) cells. The optimal process involved the addition of nine times the quantity of water to the medicinal material, followed by extraction three times at a temperature of 72 °C for a duration of 54 minutes each time.²⁰ The mechanism of action of the Huanglian-Houpo drug pair is summarized in Figure 3.

Antibacterial

In 20st, it was confirmed that Huanglian and Houpo were confirmed to have inhibitory effects on *Bacillus anthracis* in vitro and in vivo.^{22,23} There are two ways to obtain medication. Huanglian and Houpo were individually extracted, and subsequently, a co-extraction was conducted with the extracts of these two drugs, constituting one approach for acquiring mixtures. Another method involved the direct combination of Huanglian and Houpo to obtain a mixture. Furthermore, a study has reported that when Huanglian and Houpo are extracted separately and then subjected to co-extraction, the resulting mixture had stronger inhibitory effects against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* than when Huanglian and Houpo are co-extracted directly.²⁴ Therefore, we were able to accurately determine the antibacterial effects of Huanglian and Houpo. In real-world scenarios, numerous bacteria significantly impact human life. Presently, the investigation into the antibacterial properties of Huanglian Houpo herb pair primarily centers around *E. coli*, *P. aeruginosa*, and *S. aureus*. To broaden the applicability of Huanglian Houpo herb pair, it is imperative to intensify our understanding of the antibacterial mechanisms exhibited towards other bacterial strains. Additionally, enhancing research on the antibacterial mechanism and the underlying pharmacological substances within the body, while elucidating its precise antibacterial modus operandi, is of paramount importance.

Promote Gastrointestinal Motility, Anti-Diarrheal

As mentioned above, The Huanglian Houpo herb pair serves as an effective prescription for the treatment of damp-heat diarrhea, as it is capable of energizing the middle region and promoting the flow of qi to eliminate dampness and heat. Similarly, the effects of the two methods on the small intestinal function of mice were compared. The findings indicated that the mixture after ethanol separate extraction of the Huanglian and Houpo drug pair significantly inhibited the

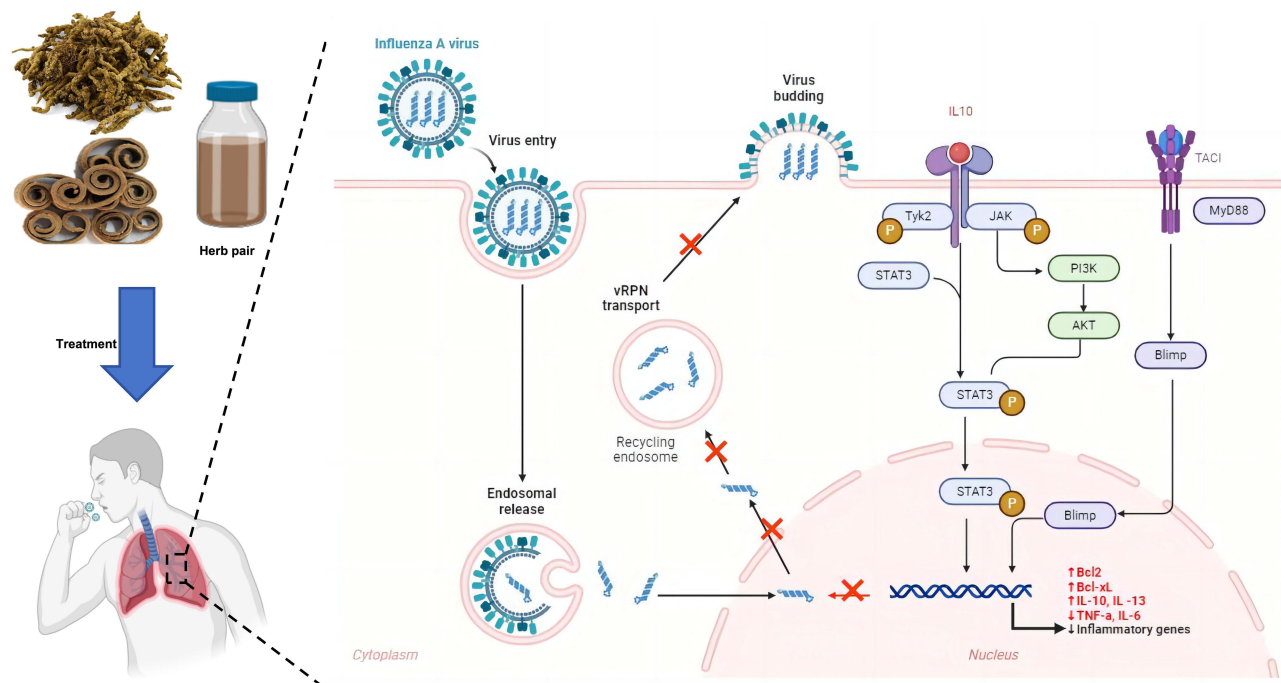


Figure 3 The mechanism of Huanglian Houpo herb pair in anti-virus.

Notes: Created in BioRender. Xie, Q. (2024) BioRender.com/n12p793.

propulsion rate of carbon powder in the small intestine of mice and alleviated diarrhea caused by senna leaves in mice.²⁴ Huanglian possesses a pronounced bitterness, which can easily damage the spleen and stomach. Notably, Huanglian: Houpo = 1:1 significantly alleviated the side effects of gastrointestinal motility inhibition caused by Huanglian, while also demonstrating a favorable anti-diarrheal effect.²⁵ Berberine and magnolol are the main compounds of Huanglian and Houpo drug pairs, which were also combined to evaluate their efficacy. It's reported that the different proportions of Huanglian and Houpo drug pairs, as well as their active fractions and berberine-magnolol pairs, exhibited antidiarrheal and analgesic properties. However, it was observed that the synergistic effect of these active components was inferior to that achieved using the raw medicinal materials and their respective active fractions. Notably, the optimal ratio identified was 1:2.²⁶ Another study also demonstrated that Huanglian Houpo Pill possesses the ability to effectively resist gastric mucosal injury, enhance intestinal absorption, and exhibit antidiarrheal and antiemetic properties.²⁷ As a result, numerous scholarly reports existed on the enhancement of gastrointestinal motility and anti-diarrheal properties of Huanglian Houpo herb pair. These reports demonstrated its capacity to mitigate gastrointestinal motility disorders or diarrhea models that stemmed from a diverse array of causes. The above effects are closely related to their traditional efficacy.

Anti-Gastritis

Chronic gastritis is a chronic inflammatory reaction in the gastric mucosa. This condition is prevalent in the clinical digestive system and has a high incidence. A network pharmacology prediction found that Huanglian and Houpo may potentially contribute to the prevention and treatment of inflammation-cancer transformation in chronic gastritis, primarily through the modulation of the phosphatidylinositol - 3 - kinase (PI3K)/AKT/P53 signaling pathway.²⁹ It's demonstrated that Huanglian and Houpo drug pairs could alleviate the symptoms of chronic gastritis, accompanied by a reduction in inflammatory reactions and apoptotic processes within the gastric mucosa. The pharmacological basis of this effect has been identified as coptisine. The underlying mechanism is related to the ribosomal and NF- κ B signaling pathways, which can play a role in regulating key genes such as tumor proteins, translationally controlled 1 (TPT1), and ribosomal protein L37 (RPL37).²⁸

Anti-Ulcerative Colitis

Ulcerative colitis (UC) is a type of refractory bowel disease, which is treated without effective strategy. Several studies have reported the effects of Huanglian and Houpo drug pairs on UC. The utilization of 2,4,6-trinitrobenzenesulfonic acid solution (TNBS) and dextran sulfate sodium (DSS) as inducers for UC models are prevalent in scientific research. Inflammatory response plays an important role in the occurrence and development of UC. The combination of Huanglian and Houpo has been demonstrated to effectively mitigate UC induced by TNBS, potentially through modulation of the PI3K/Akt signaling pathway, suppression of inflammatory reactions, and regulation of apoptosis.^{30,37} It was also reported that the administration of Huanglian and Houpo drug pair to UC rats could decrease serum tumor necrosis factor- α (TNF- α) and colon cyclooxygenase-2 (COX2) protein levels, while increase transforming growth factor- β (TGF- β) levels.³³ Huanglian Houpo decoction could also inhibit the activation of NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome and regulate the expression of reactive oxygen species (ROS) and brain-gut peptide to alleviate DSS-induced UC in mice.^{31,32,38} In addition, the extracts of the Huanglian and Houpo drug pair, as well as their nano-preparations, could improve colon length and body weight in a DSS-induced UC model to alleviate colonic mucosal injury, which is achieved through multiple mechanisms including the suppression of the inflammatory responses, safeguarding the integrity of the intestinal mucosal barrier, and modulating macrophage polarization.^{3,34} Intestinal flora plays an important role in both physiological and pathological conditions.³⁹⁻⁴¹ Lianpoyin is a TCM prescription only with Huanglian and Houpo. It's reported that Lianpoyin possesses antibacterial properties in the abundance and diversity of intestinal flora.⁴² Our previous study has further validated that Huanglian and Houpo 1:1 compatibility could effectively regulate the intestinal flora of UC rats, thereby inhibiting inflammatory responses within the colon and facilitating the restoration of the mucosal barrier.³⁵ The brain-gut axis is considered as a pivotal and essential center.⁴³ Huanglian Houpo decoction could reduce DSS-induced colonic inflammatory responses and histopathological damage in mice by regulating the activity of brain-gut peptides and their receptors.³⁸ These above results suggest that the Huanglian and Houpo drug pair can alleviate UC injury in a variety of ways, such as suppressing the inflammatory response and apoptotic processes, exhibiting antioxidant properties, modulating intestinal microbiota and

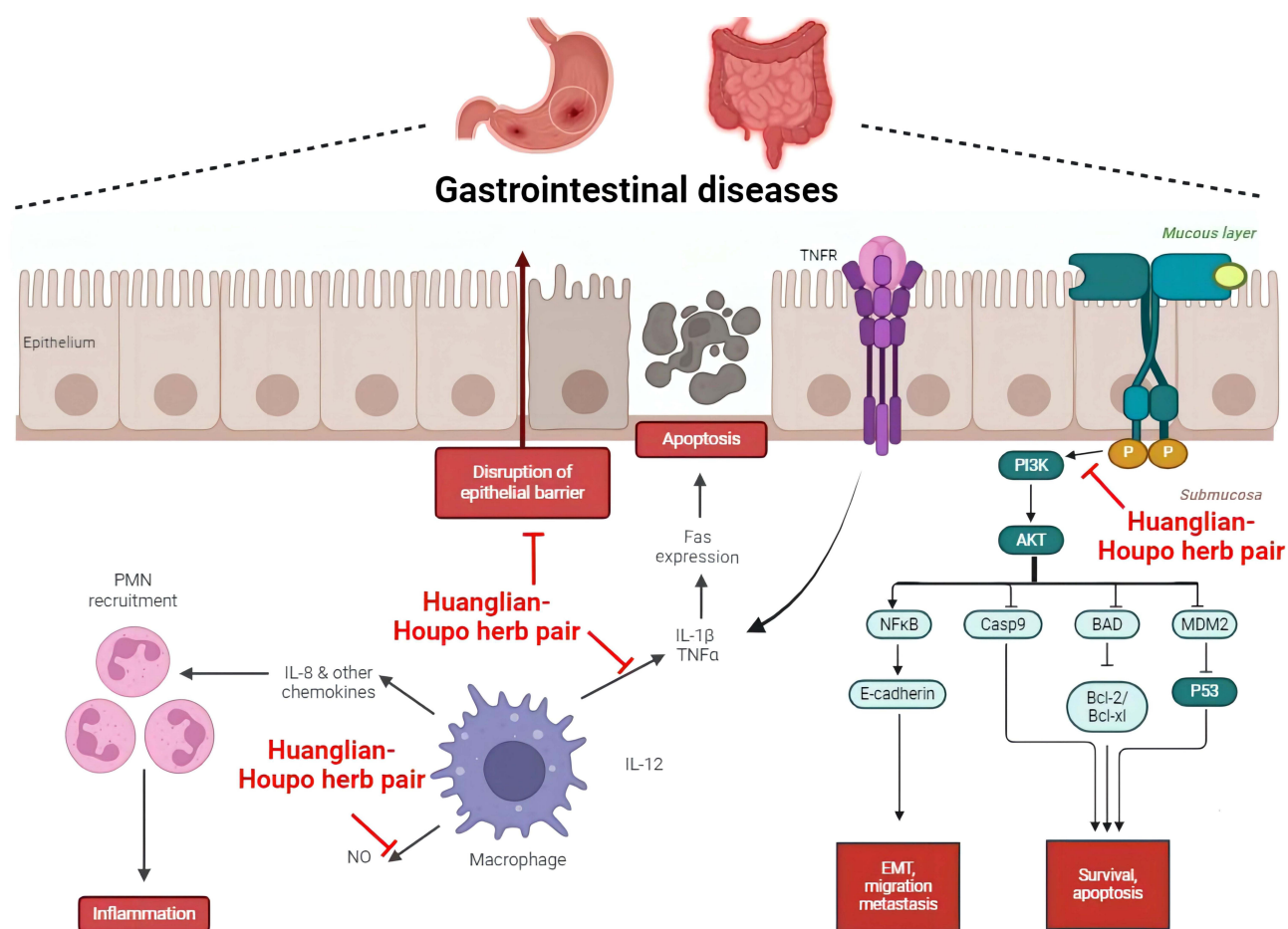


Figure 4 The mechanism of Huanglian-Houpo herb pair in gastrointestinal diseases.

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key receptors of the brain-gut axis, and repair of the mucosal barrier. A concise summary of the mechanisms underlying the Huanglian-Houpo drug pair's efficacy in gastrointestinal disorders is presented in Figure 4.

Pharmacokinetics Analysis

According to our previous statement, magnolol, honokiol, and berberine are the main chemical components in the Huanglian and Houpo drug pairs. The pharmacokinetic analysis has revealed a temporal increase in the transportation of these compounds. The transport modes of magnolol and honokiol are mainly passive and active, and they are susceptible to the efflux action of P-glycoprotein (P-gp) located on the apical (AP) side. The mode of transportation of berberine in the AP → basolateral (BL) direction is primarily passive, whereas that in the BL → AP direction is mainly active mediated by P-gp, which is inhibited by verapamil. Notably, these transport modes exhibit significant differences when administered individually. The combination of Huanglian and Houpo is beneficial for the absorption of the main components to prevent the development of drug resistance.⁴⁴ Other study showed that Huanglian and Houpo drug pair could enhance the absorption of berberine hydrochloride, delay its elimination and improve the bioavailability of berberine hydrochloride.⁴⁵ Through the analysis of drug metabolism research, it has been definitively established that the peak time T_{max} (h) of berberine hydrochloride in the plasma sample of rats was 1.0 h, with a peak concentration (C_{max}) of 0.1620 ± 0.0217 mg/L. Furthermore, the mean retention time (MRT) for this compound was 28.75 ± 16.28 h, and the area under curve (AUC) ($0 \rightarrow \infty$) was 2.088 ± 0.8225 . The peak time of berberine hydrochloride in the plasma sample of Huanglian was 3 h, accompanied by a peak concentration of 0.0670 ± 0.0108 , the MRT was 17.15 ± 4.459 h, and the AUC ($0 \rightarrow \infty$) was 0.9370 ± 0.2530 . Upon the compatibility of Huanglian and Houpo, Houpo has been found to

Table 3 Pharmacokinetics of Huanglian and Houpo Drug Pair

Object	Results
Transporting mode	The transport mode of magnolol and honokiol is mainly passive transport and active transport. It is vulnerable to the efflux of P-gp at the AP side. The transport mode of berberine in the AP → BL direction was mainly passive transport, while the transport mode in the BL → AP direction was mainly active transport mediated by P-gp.
Normal rats	Berberine hydrochloride: $C_{\max}=0.1620 \pm 0.0217$ mg/L; $AUC=2.088 \pm 0.8225$, $T_{\max}$ (h) = 1.0 h, $MRT=28.75 \pm 16.28$.
Normal rats	Berberine: $C_{\max}=0.9086$ µg/mL, $AUC=347.74$ µg · min/mL, $T_{\max}=64.69$ min. Magnolol: $C_{\max}=0.9843$ µg/mL, $AUC=450.64$ µg · min/mL, $T_{\max}=56.86$ min.

promote the absorption, retard the elimination, and improve the bioavailability of berberine, the active ingredient in Huanglian. In addition, concentration-time profiles of berberine and magnolol, the two main components of Huanglian Houpo decoction in rat plasma, were conducted utilizing an influenza virus model. The outcomes revealed that for berberine: $C_{\max}$ was 0.9086 µg/mL, AUC was 347.74 µg · min/mL, $T_{\max}$ was 64.69 min. Meanwhile, for magnolol, $C_{\max}$ was 0.9843 µg/mL, AUC was 450.64 µg · min/mL, $T_{\max}$ was 56.86 min. The findings are summarized in Table 3. It is noteworthy that the discrepancies observed in the absorption, distribution, metabolism, and excretion (ADME) parameters may stem from the analytical methodology employed. In term of pharmacokinetics analysis, the authors think that different dosage forms and administration routes will affect ADME. Therefore, we look forward to more dosage forms and targeted formulations of Huanglian Houpo herb pair to enrich pharmacokinetic parameters. What's more, bioequivalence studies are also very necessary.

Discussion and Prospect

The Huanglian - Houpo drug pair is a constituent of the Lianpoyin and Huanglian Houpo decoction. They are also the important component of many traditional Chinese medicine prescriptions. Based on the aforementioned data, it has been found that due to the insolubility of magnolol and honokiol in water, the method of alcohol extraction from Huanglian and Houpo has proven to be more effective than water extraction. Concurrently, there have been few studies on the chemical composition of Huanglian in conjunction with Houpo. The preponderance of studies has focused on the influence of combined or individual extraction of the two drugs on the concentration of berberine, magnolol, or honokiol, whereas investigations into other components remain limited. It has been reported that the combination of Huanglian and Houpo has the potential to yield novel constituents. Nevertheless, a comprehensive and systematic investigation into the existence of these potential new components has yet to be undertaken. Compatibility of traditional Chinese medicine is a characteristic of TCM. Research on the modernization of TCM shows that compatibility has a great influence on the chemical composition of the liquid system. The question of whether the compatibility of Huanglian and Houpo leads to the emergence of novel components necessitates further scientific investigation. The supramolecular system of TCM has gradually become familiar to researchers.⁴⁶ Therefore, the necessity of conducting further investigation into whether the compatibility of Huanglian and Houpo generates supramolecular chemical components remains to be determined. With the advancement of modern technology, methodologies such as high-performance liquid chromatography - mass spectrometry (HPLC-MS) and the identification of Q biomarkers serve as a robust cornerstone for elucidating the chemical constituents of Huanglian Houpo decoction.⁴⁷⁻⁴⁹ In the future, high-throughput biological affinity chromatography stands as a viable method for screening the material basis underpinning the pharmacological efficacy of the Huanglian Houpo decoction, which will significantly contribute to advancing the modernization efforts within TCM research.

The pharmacological activities of the Huanglian-Houpo drug pair included antiviral, anti-inflammatory, and antibacterial effects (Figure 5). According to the reports, the integration of Huanglian and Houpo has demonstrated potent antiviral properties. The research object was the H1N1 virus, possibly due to the maturity and reliability of the model in modern pharmacological methods. However, given the current reality, the COVID 19 pandemic continues to persist globally, and the potential anti-COVID-19 effect of Huanglian - Houpo drug pair necessitates further reinforcement and validation by researchers. Numerous experimental studies have been conducted on the gastrointestinal tract, and clinical observations

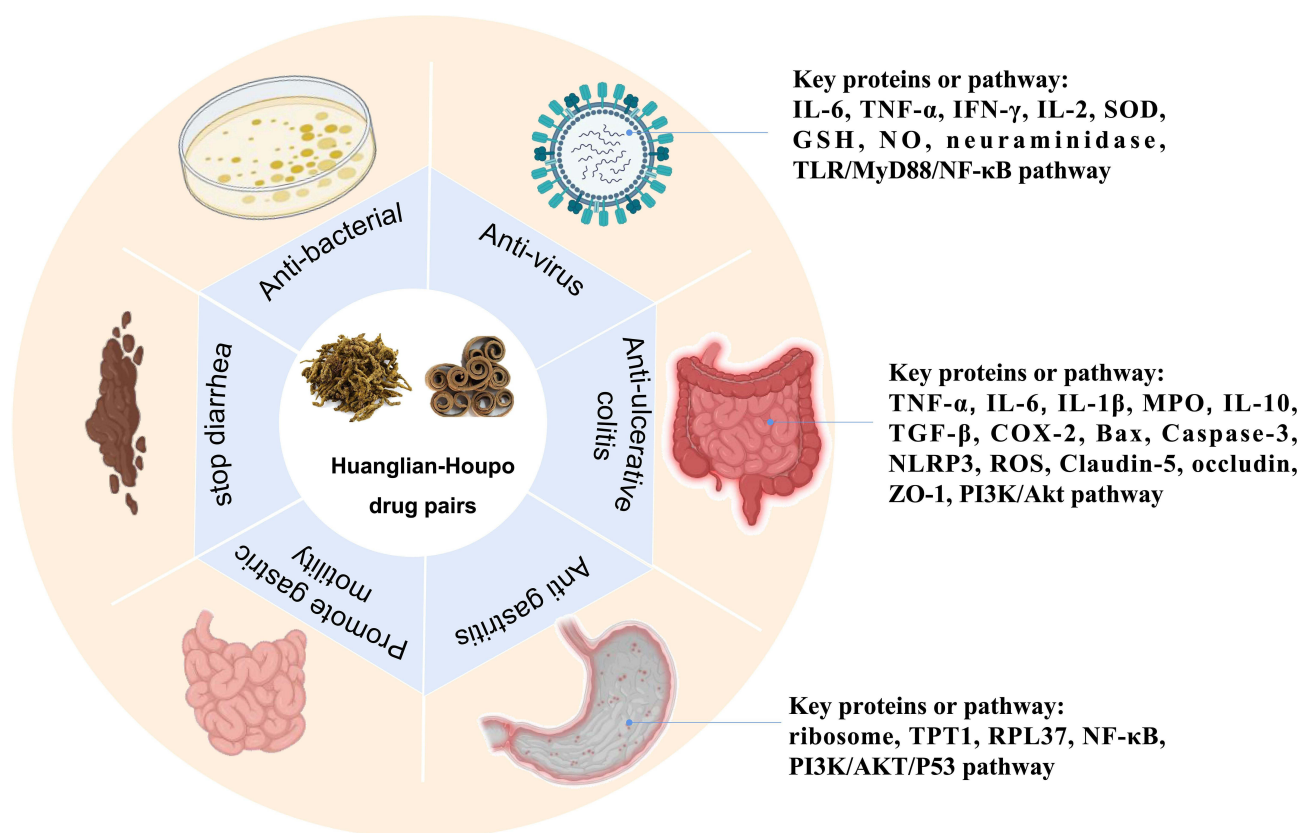


Figure 5 The pharmacological activities of Huanglian Houpo herb pair.

Notes: Created in BioRender. Xie, Q. (2024) BioRender.com/e29z738.

have confirmed that the Huanglian-Houpo drug pair is the core drug pair for the treatment of gastrointestinal diseases. This could potentially be attributed to its therapeutic effects of eliminating heat and drying dampness. In the realm of gastrointestinal diseases, UC has been extensively studied. Huanglian-Houpo drug pair could alleviate the symptoms of colitis, inhibit the inflammatory response, repair intestinal mucosal injury, and improve the intestinal flora. UC is a refractory and recurrent disease, and the precise mechanisms underlying the therapeutic effects of Huanglian-Houpo drug pair have not been fully elucidated. Therefore, its antiulcerative effects should be investigated in future studies. A noteworthy study reported that the superior therapeutic effect of the Huanglian-Houpo nano-preparation in the treatment of UC.³⁴ Nanomaterials possess excellent targeting properties, which may signify a promising trend for future research endeavors. It is evident that the Huanglian Houpo drug pair exhibited inhibitory effects on bacterial growth. However, no research has been conducted on its impact on bacterial biofilm formation. Bacterial biofilms are considered as significant contributors to the progression of various diseases.^{50,51} Our previous studies have also found that the Huanglian Houpo drug pair can improve the gut microbiota in UC models and inhibit the formation of biofilms in the colon. This could be a direction for future research. Our previous investigations have additionally revealed that the Huanglian Houpo drug pair was capable of enhancing the gut microbiota in UC models and suppressing the development of biofilms within the colon. This observation presents a potential avenue for future research endeavors. Apart from the TNBS and DSS-induced UC models, it is imperative to delve into additional models pertaining to gastritis and diarrhea. Furthermore, it is crucial to meticulously investigate the mechanism underlying the compatibility between Huanglian and Houpo, as well as the intricate interactions occurring among the various components within their extracts. This endeavor aims to elucidate the profound influence of compatibility on drugs efficacy, ascertain the material foundation of this efficacy, and ultimately, furnish invaluable insights for the precise and targeted treatment of disease. As reported, Huanglian and Houpo respectively process a significant effect on the treatment of cardiovascular and cerebrovascular diseases, and whether they are effective after compatibility can be used in the future. Finally, attention should be paid to the safety of the medicine. Huanglian has a strong bitter cold, and is prone to stomach damage. We can also design

a comparative study on the safety of Huanglian-Houpo drug pair, Huanglian, and Houpo based on the literature,⁵² laying the foundation for the rational use.

Conclusion

In general, the review provided comprehensive information for the study of Huanglian - Houpo drug pair, including traditional use, phytochemistry, and pharmacological activity. As known, Huanglian and Houpo are commonly used in combination to treat damp-heat dysentery, spleen and stomach disorders, and qi stagnation in clinical practice. Due to the limitation of chemical constituents of Huanglian Houpo drug pair, novel and modern methodologies should be used to conduct the further study. In addition, the pharmacological activity of Huanglian Houpo drug pair is wide, but the data are not extensive. In order to verify the pharmacological activity of the combination of Huanglian and Houpo, it is necessary to try more in vitro and in vivo models, develop and explore the effect of “composition-efficacy”. What’s more, it’s still need to study the compatibility mechanism of the Huanglian and Houpo drug pair, including but not limited to the interactions between different components and the impact of compatibility on efficacy, mechanism of action, bioequivalence studies, the impact of different dosage forms on pharmacokinetics, and clinical application research in the future. In addition, safety evaluations are required to discover any possible side effects of Huanglian Houpo herb pair for long-term usage in humans.

Abbreviations

AUC, area under curve; AP, apical; BL, basolateral; COX2, cyclooxygenase-2; DSS, dextran sulfate sodium; H1N1, AH1N1 influenza; H3N2, novel influenza A; IFN- β , interferon- β ; MDCK, Madin-Darby canine kidney; MRT, mean retention time; MyD88, myeloid differentiation primary response 88; NF- κ B, nuclear factor κ B; NLRP3, NOD-like receptor thermal protein domain associated protein 3; PI3K, phosphatidylinositol-3-kinase; P-gp, P-glycoprotein; ROS, reactive oxygen species; RPL37, ribosomal protein L37; TCM, traditional Chinese medicine; TLR, Toll-like receptor; TGF- β , transforming growth factor- β ; TNBS, 2,4,6-Trinitrobenzenesulfonic acid solution; TNF- α , tumor necrosis factor- α ; TPT1, tumor protein; translationally-controlled 1; UC, ulcerative colitis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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