

Research progress of traditional Chinese medicine and its monomer compounds and extracts on alcoholic gastric injury

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Abstract: Alcoholic gastric injury is a gastric disease caused by excessive intake of alcohol directly stimulating the gastric mucosa or alcohol entering the gastric wall after the dissolution of lipids. Traditional Chinese medicine has a long history in the treatment of alcoholic gastric injury, and has the characteristics of high cure rate, low recurrence rate and small adverse reactions. This article reviews the experimental research and clinical application of traditional Chinese medicine, single compounds of Chinese herbs, traditional Chinese medicine extracts and traditional Chinese medicine compounds in preventing and treating alcoholic gastric injury. This article reviews the effectiveness of herbal medicines for the treatment of alcoholic gastric injury, and their mechanisms of action is presented to provide a reference for further research on anti-alcoholic gastric injury herbal medicines.

1. Introduction

Alcoholic gastric injury is a disease in which the gastric mucosa becomes congested, edematous, erosive, and hemorrhagic as a result of excessive alcohol consumption and absorption of ethanol by the gastric mucosa through different mechanisms [1]. Alcoholic intoxication has always been one of the risk factors for human health, and every year about 200,000-300,000 people die from alcohol-related diseases or accidents caused by it. In China, the total percentage of acute alcoholism among different poisoning types is about 38.81% [2]. Therefore, it is significant to study alcoholic gastric injury. The current therapeutic drugs for alcoholic gastric injury are gastric acid inhibitors, gastric mucosal protectants and digestive enzyme preparations, which relieve stomach pain and protect the gastrointestinal mucosa by reducing gastric acid secretion. However, patients often have serious adverse reactions, such as atrophic gastritis, tachycardia, and reversible or non-reversible autonomic dyskinesia. [2]. Traditional Chinese medicine has a long history in the treatment of alcoholic gastric injury. Traditional Chinese medicine (TCM) treats the disease by combining and matching blood-activating medicines, damp elimination medicines, correction medicines and detoxification medicines to realize clearing heat and dampness, strengthening the spleen and harmonizing the middle, this scheme has the characteristics of a high curing rate, low recurrence rate, and small adverse reactions [3]. Modern pharmacological studies have also found that herbal medicines and their monomer compounds and extracts, compared to gastric acid drugs, gastric mucosal protective agents, and digestive enzyme preparations, have high efficacy and safe therapeutic effects.

This paper mainly outlines the pathogenesis of alcoholic gastric mucosal injury and the related studies of traditional Chinese medicine (TCM) and its monomer compounds and extracts in alcoholic gastric mucosal injury and comprehensively discusses the therapeutic effects of TCM on alcoholic gastric injury and its mechanism of action, to provide a basis for the subsequent studies of TCM in alcoholic gastric mucosal injury.

2. Pathogenesis of Alcoholic Gastric Injury

Alcoholic gastric injury is due to the entry of alcohol into the gastric wall through total dissolution in lipids, and the infiltration of hydrogen ions from gastric juice into the mucosal epithelium, which causes the release of histamine, 5-hydroxytryptamine, and heparin, and increases the pressure and permeability of the mucosal capillaries triggering mucosal congestion, erythrocyte exudation, and other symptoms. Inflammation and oxidation are the main pathogenic mechanisms leading to alcoholic gastric injury. The inflammatory response is mainly associated with the release of inflammatory factors and inhibition of signaling pathways, for example cyclooxygenase 2 (COX2) and nuclear factor-activated B cell κ -light chain enhancement (NF- κ B) signaling pathways leading to gastric inflammation [4]; Oxidation is caused by the entry of alcohol into the stomach leading to high expression of oxidizing factors such as ROS, MDA, SOD, T-AOC, NO and ultimately alcoholic gastric injury [5].

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3. The Mechanism of Traditional Chinese Medicine on Alcoholic Gastric Injury

3.1 Inhibiting inflammatory response

The inflammatory response resulting from alcoholic gastric injury is primarily associated with the release of multiple cytokines and inflammatory mediators, these inflammatory responses are generated by the activation of multiple inflammatory signaling pathways, among which, are the most representative COX2 and NF- κ B signaling pathways.

COX-2 is one of the important members of the COX family and plays an important role in inflammation and cell signal transduction [6]. The study found that COX-2 can induce the production of inflammatory mediators, promote cell proliferation, inhibit apoptosis and facilitate neovascularization by catalyzing the synthesis of prostaglandin E2. In gastric mucosal injury, inflammatory conditions, and gastritis gastric cancer due to *Helicobacter pylori* infection, COX-2 expression levels were all significantly upregulated [7].

NF- κ B is a eukaryotic transcription factor that plays an important role in maintaining the balance of peptic ulcer and anti-inflammatory responses. In the context of ulcer injury, activation of NF- κ B induces the expression and release of downstream signaling pathway-related inflammatory factors TNF- α , IL6, IL-1 β , and IL-18, which in turn exacerbates ulcer injury. Studies have found that NF- κ B participates in the occurrence, development and outcome of gastritis through various pathways such as oxidation, stress, proliferation, and apoptosis. The degree of activation is positively correlated with the progression of chronic gastritis [8]. The inflammatory factors TNF- α and IL6 produced by NF- κ B activation can induce the occurrence of chronic gastritis, and their levels are positively correlated with the degree of chronic gastritis. Meanwhile, in chronic gastritis, highly expressed TNF- α and IL-6 further activate the NF- κ B signaling pathway by activating the relevant receptors on the cell surface, leading to an inflammatory waterfall reaction that results in the continued progression of chronic inflammation [9].

3.2. Antioxidant

The oxidative reaction in alcoholic gastric injury is mainly related to the expression levels of ROS, MDA, SOD and NO in gastric tissue. Alcohol induces the liver to produce large amounts of reactive oxygen species, which, together with alcohol, trigger lipid peroxidation, the end product of which is MDA. Highly expressed MDA can severely damage biofilms and their functions; at the same time, the catabolism of alcohol promotes the production of reactive oxygen species (ROS), resulting in elevated ROS levels, which in turn can damage hepatocytes. While SOD can prevent ROS from damaging the gastric mucosa and reduce cellular damage caused by free radicals; NO, as an antioxidant, can react with superoxide anion to ameliorate gastric damage.

4. Treatment of ALCLHOLIC Gastric Injury with Herbal Monomer Compounds

Chinese medicine monomer compounds are the main active ingredients extracted and isolated from Chinese medicines, which have been shown to exert therapeutic effects on alcoholic gastric injury by modulating multiple signaling pathways, and we will introduce Chinese medicine monomer compounds in the following sections.

4.1. Curcumin

Curcumin is the main active ingredient of the Asian spice turmeric, which belongs to polyphenolic compounds. Studies have shown that curcumin can reduce ethanol-induced gastric inflammation in rats by inhibiting the NF- κ B signaling pathway [10]; It can inhibit CYP2E1 activity, increase AMPK expression, promote alcohol metabolism and enhance antioxidant activity, inhibit HIF-1 α and Cdx-2, activate HO-1 and SOD-2, reduce the release of endogenous PG, NO, gastrin and CGRP, reduce gastric injury caused by ethanol, and play a protective role [11].

4.2. Baicalin [12] and Astragaloside IV [13]

In clinical practice, *Scutellaria baicalensis* is widely used in the treatment of gastritis, ulcerative colitis, dysentery, hepatitis and other diseases. Its main bioactive components are baicalin and astragaloside IV, both of which are flavonoids. Modern pharmacological studies have shown that both astragaloside IV and baicalin have significant anti-inflammatory and antioxidant effects. Astragaloside IV can attenuate gastric mucosal injury and inhibit gastritis caused by the rat ethanol gastritis model by inhibiting the expression of MPO, TNF- α , NF- κ Bp65 and TRAF2, and up-regulating the level of anti-inflammatory factor IL-10; Baicalin exerts therapeutic effects on alcoholic gastric injury by inhibiting the expression levels of Akt, p-Akt, NF- κ Bp65, and down-regulating the expression of TNF- α , IL-8, and IL-1 β in a mouse model of ethanol gastritis.

4.3. Cinnamaldehyde [1]

Cinnamaldehyde is the main component of the volatile oil of traditional Chinese medicine *Ramulus Cinnamomi* or *Cortex Cinnamomi*. The hot water extract of *Cortex Cinnamomi* is used in the treatment of gastric ulcer in a clinic. The main component of cinnamon hot water extract is cinnamaldehyde, which can down-regulate the mRNA and protein expression levels of TLR2, TLR4, MyD88, NF- κ B, TRIF and other genes, block the TLRs / MyD88 signaling pathway, reduce the production of inflammatory factors such as IL-1 β and TNF- α , and inhibit the inflammatory response. In addition, in vitro experiments also proved that cinnamaldehyde can inhibit the secretion of PGE2, NO and TNF- α in cells, down-regulate the mRNA expression levels of mPGES-1 and COX-2, and play a role in the treatment of alcoholic gastric injury by inhibiting inflammation.

4.4. δ -amyrone [14]

δ -amyrone is an active ingredient extracted and isolated from *Sedum lineare* Thunb. δ -amyrone resisted alcohol-induced gastric injury by inhibiting the production of COX-2 and PGE2 and suppressing the NF- κ B signaling pathway, reducing the overproduction of inducible nitric oxide synthase (iNOS) and the release of the inflammatory factors TNF- α , IL-6, and NO in a mouse model of alcoholic gastric injury.

4.5. Aucubin [15]

Aucubin is the main active ingredient of traditional Chinese medicine *Eucommia ulmoides*, *Plantago asiatica* L. and *Rehmannia glutinosa*. It is a cyclic iridoid glycoside compound. Aucubin reduced MPO activity and MDA level to exert antioxidant effects and inhibited the expression of inflammatory factors TNF- α and IL-6, increasing the levels of glutathione (GSH), heat shock protein 70 (HSP-70) and epidermal growth factor (EGF), and enhancing the activity of Superoxide dismutase (SOD), the gastric ulcer index of mice was improved, which played a role in inhibiting alcohol-induced gastric injury.

4.6. Other Chinese medicines

In addition to the above-described herbal monomer compounds that are useful in the treatment of alcoholic gastric injury, there are other types of. Such as the Tea Saponins [16], thymol [17], geraniol [18], Andrographolide [19] etc, can also play a role in the treatment of alcoholic gastric injury through anti-inflammatory and antioxidant effects.

5. Chinese Herb Extracts

Chinese medicine extract refers to the compound obtained from Chinese medicine by decoction, extraction, etc. with water or ethanol and other solvents.

5.1. *Tetradium ruticarpum* aqueous extract

Tetradium ruticarpum belongs to the *tetradium* in the family of *rutaceae*, and has the effect of dispersing cold and relieving pain, warming and stopping vomiting, and assisting Yang to stop diarrhea. Studies have shown that *Tetradium ruticarpum* aqueous extract can promote the release of NO in gastric mucosa by increasing the expression of eNOS in gastric mucosa of mice, play an antioxidant role, enhance gastric mucosal barrier function, and protect gastric mucosal injury [20]. *Tetradium ruticarpum* combined with *Rhizoma Coptidis* in the treatment of acute gastric injury in rats, Experiments have shown that the water extract obtained from *Coptidis Rhizoma* and *Tetradium ruticarpum* at a ratio of 1 : 6 can improve the blood circulation of gastric mucosa in rats with acute gastric injury caused by 50 % ethanol, inhibit the decrease of mucus-HCO₃-barrier and reduce acid reverse osmosis, and alleviate alcoholic gastric injury [21].

5.2. Tea extraction

Polyphenols are the main extracts of tea, and their main components include catechins (flavanols), flavonoids, flavonols, anthocyanins, phenolic acids, phenolic acids and polymeric phenols. Among them, catechins are the main components of tea polyphenols, accounting for about 65 % -80 % of the total tea polyphenols. Studies have found that tea polyphenols [22], Wushan tea polyphenols [23], and small-leaf kuding tea polyphenols [24, 25] have a good protective effect on alcoholic gastric injury. For example, tea polyphenols extracted from Pu'er tea and small-leaf kuding tea can activate and increase the activity of many antioxidant enzymes (SOD, GSH, CAT, etc.) in the body, reduce the content of MDA, up-regulate the mRNA expression levels of eNOS and nNOS in gastric tissue at the gene level, down-regulate the expression of COX-2, and protect gastric tissue from ethanol-induced gastric mucosal injury; Another study found that tea polyphenols extracted from Wushan tea can also reduce the release of pro-inflammatory factors TNF- α , IL-6, IL-12 and IFN- γ in gastric tissue of mice, and reduce the inflammatory response in gastric tissue of mice.

5.3. *Momordica charantia* extract

Momordica charantia is the fruit of *Momordica charantia* of the *Cucurbitaceae* family. *Momordica charantia* polysaccharide is an important active ingredient in bitter melon extract, which has pharmacological activities such as enhancing immunity, scavenging free radicals, and inhibiting bacteria. *Momordica charantia* polysaccharide can prevent gastric oxidative stress by reducing MPO, TNF- α and IL-6 in mice, inhibiting lipid peroxide, enhancing glutathione and catalase activity. On the one hand, *Angelica dahurica* polysaccharide can inhibit the activity of Bax and caspase-3, enhance the anti-apoptotic protein Bcl-2, which is beneficial to cell survival; On the other hand, *momordica charantia* polysaccharides reduce the degradation of I κ B α by down-regulating NF- κ B, and bitter melon polysaccharides play a role in protecting alcoholic gastric injury through these two.

5.4. Raspberry extract

Raspberry ketone, the main active ingredient in raspberry extract, found primarily in blackberries, raspberries and cranberries, is a natural phenolic compound with antioxidant and anti-inflammatory properties. Raspberry ketone can play a protective role against alcoholic gastric injury by elevating the levels of GSH, CAT, GPx, Bcl-2 and other proteins, decreasing NF- κ B, TNF- α , Bax, Bcl-2, activating the Nrf2 antioxidant defense system, resisting apoptosis, and inhibiting the NF- κ B signaling pathway.

5.5. Water Extract of *Acrostichum aureum*

Acrostichum aureum is a medicinal pteridophyte. Its main chemical components are steroids, triterpenes, flavonoids, glycosides, monosaccharides, amino acids and sulfonic

acidester. These compounds have antibacterial, anti-inflammatory, anti-tumor, antioxidant and other biological activities. The results showed that the Water Extract of *Acrostichum aureum* reduced the ulcer area of gastric tissue in rats and improved the pathological damage caused by alcohol by increasing the levels of GSH, SOD, CAT and MDA, reducing the secretion of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6, and reducing the expression of I κ B α and p65 phosphorylated proteins.

5.6. *Hericium erinaceus* extract

As a medicinal fungus, *Herichium erinaceus* has a good effect on chronic gastritis, duodenal ulcer and other digestive tract diseases. *Herichium erinaceus* polysaccharide is an effective active ingredient extracted from the fruiting body of *Herichium erinaceus*. It can reduce the levels of TNF- α and IL-1 β in serum, reduce the decrease of POD activity in gastric tissue, enhance the antioxidant capacity of gastric tissue, enhance the defense factors (NO, PGE2, EGF) in gastric tissue, and protect gastric mucosa.

5.7. Other Chinese herbal extracts

In exception to the herbal extracts described above that are known to be useful in the treatment of alcoholic gastric injury, there are other types, for instance Agarwood Alcohol Extract, Aqueous extract of quinoa , *Artemisia argyi* aqueous extract, *Myristica fragrans* ethanol extract have also been shown to have significant therapeutic effects on alcoholic gastric injury.

6. Chinese Herbal Compound

A Chinese medicine compound formula is a formula composed of two or more medicines, with prescribed processing procedures and methods of use, and is designed for a specific disease or condition. Herbal compounding has achieved excellent results and efficacy in the treatment of alcoholic liver and stomach injury.

6.1. Jin Zhao capsule

The ingredients of Jin Zhao capsule are mainly Radix *Puerariae*, *Hovenia acerba* Lindl, Cape Jasmine. Jin Zhao capsule inhibits the release of inflammatory factors such as IL-1, IL-6 and TNF- α by increasing intestinal mucosal permeability. It can also increase the levels of NO and PGE2 in the gastric tissues of mice to inhibit the oxidative reaction, which has a favorable protective effect on the gastric mucosa of mice with acute alcoholic gastric injury.

6.2. Wang 's Baochi Pill

Wang's Baochi Pills consists of Rhei Radix Et Rhizoma and *Coptis chinensis* Franch, *Arisaema heterophyllum* Blume and *Fritillaria cirrhosa* as the ingredients of the

formula. Wang 's Baochi Pill can enhance the activity of alcohol dehydrogenase (ADH) in mice and the content of ADH in liver, and shorten the relieving alcoholism time of mice with acute alcoholic injury.

6.3. Weishusan

Weishusan is a compound powder of integrated traditional Chinese and Western medicine containing basic bismuth carbonate. The main components include *Aucklandia costus* Falc, *Citri Reticulatae* Pericarpium, *Acori Tatarinowii* Rhizoma, and Rhei Radix Et Rhizoma. It has the effects of regulating qi and relieving pain, convergence and acid production. In previous clinical studies, it was found that Weishusan has a good effect on peptic ulcer, chronic gastritis and other diseases. Animal experiments showed that Weishusan inhibited alcoholic gastric injury in mice by increasing SOD activity in gastric tissue and plasma NO level.

6.4. Xiao Chaihu Decoction

Xiao Chaihu Decoction consists of *Bupleuri Radix*, *Scutellariae Radix*, *Ginseng Radix Et Rhizoma*, *Pinellia ternata*, *Glycyrrhizae*, *Zingiber officinale* Roscoe, *Ziziphus jujuba* Mill. Studies have shown that Xiao Chaihu Decoction exerts its protective effects on ethanol-induced gastric ulcer in a mouse model mainly by decreasing the secretion of the pro-inflammatory factor TNF- α , increasing the anti-inflammatory factors NO and PGE2, and activating EGF and up-regulating the expression of HSP-70, p-AKT and PCNA.

7. Prospect and Discussion

Excessive consumption of alcohol may cause a variety of diseases, such as liver disease, high blood pressure, stroke, diabetes, and cancer. In terms of alcohol as a neurological depressant, it may lead to mood swings, depression, anxiety, insomnia and other problems. Excessive alcohol consumption can lead to immediate and rapid damage to the human body, which may lead to serious life-threatening diseases such as gastric perforation and gastrointestinal hemorrhage[24]. Herbal monomer compounds, herbal extracts, and herbal compounds have good therapeutic effects on alcoholic gastric injury, which mainly exert their therapeutic effects through the mechanisms of promoting alcohol catabolism and metabolism, anti-inflammatory, and antioxidant effects. For instance, it improves oxidative stress and inflammatory responses by modulating the NF- κ B signaling pathway, affects the levels of factors related to apoptosis pathway, and enhances the gastric mucosal defense factor capacity [8]. However, throughout the studies on the mechanisms of herbal medicines on alcoholic gastric injury, it has been found that different herbal medicines have dual effects on certain factors. For example, NO, in curcumin [11] and Cinnamaldehyde [1] alcoholic gastric injury, plays the role of pro-inflammatory factors, inhibition of its content can significantly enhance the therapeutic effect; In the

treatment of alcoholic gastric injury with Jinzhao capsule and Xiao Chaihu Decoction, the content of NO increased, which played an antioxidant role to enhance the therapeutic effect. It can be seen that the mechanism of traditional Chinese medicine in the treatment of alcoholic gastric injury is complex.

Overall, the efficacy of single compounds and extracts of Chinese herbal medicines is not as good as that of Chinese herbal compounds in clinical practice. Nevertheless, due to the complexity of the components of TCM compounding, the functioning is often composed of many aspects, a complex network system in joint action, leading to the great difficulty in studying its mechanism of action. Moreover, studies on the mechanism of action of traditional Chinese medicine in the treatment of alcoholic gastric injury have involved relatively simple animal models. Target knockout using the gene editing technology Crisp-Cas9 can be considered in subsequent studies to form corresponding knockout mice to validate specific targets, making the results more reliable. In the hope of future research and screening of Chinese herbal medicine compounding with better efficacy on alcoholic gastric injury through the combination of various active ingredients. Besides, some herbs have dual-use medicinal and food properties, such as propolis, which can also be developed as a health drink for people who drink alcohol to make it more useful.

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