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•Review•

Different processing methods and pharmacological effects of Atractylodis Rhizoma

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[ABSTRACT] Atractylodis Rhizoma, a traditional Chinese medicine with an extensive history of treating gastrointestinal disorders and other diseases, undergoes various processing methods in China to enhance its therapeutic efficacy for specific conditions. However, a comprehensive report detailing the changes in chemical composition and pharmacological effects due to these processing methods is currently lacking. This article provides a systematic review of the commonly employed processing techniques for Atractylodis Rhizoma, including raw Atractylodis Rhizoma (SCZ), bran-fried Atractylodis Rhizoma (FCZ), deep-fried Atractylodis Rhizoma (JCZ), and rice water-processed Atractylodis Rhizoma (MCZ). It examines the alterations in chemical constituents and pharmacological activities resulting from these processes and elucidates the mechanisms of action of the primary components in the various processed forms of Atractylodis Rhizoma in the treatment of gastrointestinal diseases.

[KEY WORDS] Atractylodis Rhizoma; Processing method; Pharmacological effect; Change in chemical composition; Gastrointestinal disease

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Introduction

Atractylodis Rhizoma, derived from *Atractylodes lancea* (Thunb.) DC. or *A. chinensis* (DC.) Koidz., is a traditional Chinese medicine first documented in the "*Shennong's Herbal Classic*", where it is esteemed as a top-grade herb. According to the *Chinese Pharmacopoeia*, Atractylodis Rhizoma has been traditionally employed to treat rheumatic diseases, digestive disorders, night blindness, and influenza [1-4]. It continues to be widely utilized in China and Southeast Asia for managing gastrointestinal and rheumatic conditions. Notably, ancient formulations such as Ermiao Pill and Ping Wei San prominently feature Atractylodis Rhizoma as a primary ingredient [5, 6]. Atractylodis Rhizoma preparations such as Furthermore, contemporary preparations like Xuanfei Paidu Tang and Huashi Baidu Decoction have demonstrated efficacy in the prevention and treatment of COVID-19 [7, 8].

The extensive history of Atractylodis Rhizoma in traditional Chinese medicine includes a wealth of knowledge regarding its processing. Historical records reveal that the clinical efficacy of Atractylodis Rhizoma varies significantly depending on the processing method. For example, unprocessed Atractylodis Rhizoma was traditionally used to treat cold and rheumatic diseases, whereas processed Atractylodis Rhizoma was preferred for treating diarrhea and other conditions [2]. These processing techniques, documented across different dynasties and regions, remain relevant today.

Modern research has shown significant differences in the chemical composition and pharmacological effects of Atractylodis Rhizoma processed by various methods, highlighting distinct biochemical pathways and therapeutic targets. However, current studies are fragmented and lack a systematic approach, limiting their utility in guiding clinical practice and further research and development.

Our research group has been investigating Atractylodis Rhizoma for over 20 years, focusing on different processing methods, chemical composition changes, and alterations in pharmacological effects. This extensive research has

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provided us with valuable first-hand data and insights [9, 10]. In this study, we aim to systematically compile existing research on Atractylodis Rhizoma, encompassing its processing techniques, changes in chemical constituents, pharmacological variations, and therapeutic efficacy in treating gastrointestinal diseases. Our objective is to provide a comprehensive reference for the rational selection of processed Atractylodis Rhizoma products in clinical practice and to identify future directions for experimental research.

Processing Method of Raw Atractylodis Rhizoma (SCZ)

Atractylodis Rhizoma has a rich history of processing methods, many of which are detailed in ancient texts. These methods can be divided into two categories: those without auxiliary materials, such as frying and steaming, and those involving auxiliary materials, such as bran, salt water, vinegar, oil, and wine [11, 12] (Table 1).

Table 1 History of Atractylodis Rhizoma concoction through the age

Dynasty	Processing method	Ingredients	Literature sources
Tang (618-907)	Cook it using vinegar	Vinegar	"Rational Injury Discontinuity Formula"
Song (960-1276)	Soak it in rice water and fry	Rice water	"Production and Breeding of Bao Qing Set"
	Steam it with water	/	"Theory of Three Causes and One Disease Syndrome"
	Stir-fry it with bran	Bran	"Prescriptions of Taiping Pharmaceutical Bureau For Benevolence"
Yuan (1271-1368)	Soak it in rice water	Rice water	"Treatise on the Spleen and Stomach"
Ming (1368-1644)	Stir-fry it with salt water	Salt water	"Miscellaneous Records of Ming Medicine"
	Stir-fry it with wine	Wine	"Compendium of Medicine"
	Soak it in rice water or child's urine and fry	Rice water Child's urine	"Introduction to Medicine"
Qing (1636-1912)	Deep-fry	/	"The Golden Mirror of Medicine"
	Soak it in oil	Oil	"Collection of Medical Prescriptions with Notes"

SCZ tablets

To process SCZ tablets, impurities are first removed from the herbs. The cleaned herbs are then thoroughly soaked and washed in water before being sliced into thick pieces. After drying, the slices are sieved to remove any remaining debris [13].

Bran-fried Atractylodis Rhizoma (FCZ)

First, a pot is heated, and wheat bran is sprinkled in, heating it over medium heat until it starts to smoke. Clean Atractylodis Rhizoma slices are then added and stir-fried continuously until their surface turns dark yellow. The wheat bran is then removed, the slices are sieved to remove debris, and they are allowed to cool [13].

The optimum processing conditions for FCZ are 1 kg of SCZ with 100 g of wheat bran, heated to 200 °C, and fried for 80 s [14].

Deep-fried Atractylodis Rhizoma (JCZ)

Atractylodis Rhizoma slices are placed in a hot pot and heated over medium heat, stir-frying until they turn brown. Water is then sprinkled on the slices, and they are stir-fried on low heat until dry. The slices are subsequently removed, cooled, and sieved to eliminate any debris [12].

The optimal processing conditions for JCZ involve heating SCZ to 220−230 °C and stir-frying for 6 min at a frequency of 50 times per minute [15].

Rice water processing of Atractylodis Rhizoma

Rice is crushed into a fine powder, with 98% passing through a No. 4 sieve. The rice powder is mixed with water to create rice water, which is then used to soak SCZ. After soaking, the rice water is discarded, and the Atractylodis Rhizoma slices are washed and air-dried [12].

The optimal processing conditions for rice water-processed Atractylodis Rhizoma (MCZ) involve using rice flour and water in a ratio of 1∶50. The volume ratio of rice water to SCZ is 10∶1. The SCZ is soaked in rice water for 12 h, followed by washing with water for 2 h [16] (Fig. 1).

Changes in the Composition of Atractylodis Rhizoma by Different Processing Methods

Main chemical components of SCZ

SCZ contains a diverse array of compounds, including sesquiterpenes, triterpenes, polyacetylenes, polysaccharides, coumarins, phenylpropanoids, flavonoids, xanthone glycosides, benzoquinones, and steroids. Among these, sesquiterpenes and polyacetylenes are the primary active ingredients [17-19] (Table 2).

Effect of stir-frying with bran on the chemical components of Atractylodis Rhizoma

The polysaccharide content in Atractylodis Rhizoma significantly decreases after processing due to the Maillard reaction that occurs during the heating of bran [54]. The level of 5-hydroxymethylfurfural (5-HMF) in FCZ is higher than in SCZ, which may be attributed to the conversion of fructose and glucose to 5-HMF during the frying process [55]. A com-

Fig. 1 Different processing methods of Atractylodis Rhizoma. SCZ is developed by cleaning and slicing herbs. FCZ is prepared using stir-frying wheat bran with SCZ at the right ratio, temperature, and time. MCZ (rice water processing of Atractylodis Rhizoma) is made by washing with 10 times the amount of rice water for 12 h, then washing with water for 2 h and finally drying. JCZ is created by stir-frying SCZ at 220−230 °C for 5 min.

parative analysis of the volatile oil components between SCZ and FCZ revealed a decrease in the content of seven components, including *β*-eudesmol, *α*-pinene, atractylone, atractylenol, and *α*-styryl pyridazine, following frying [56].

Additionally, studies have shown that the contents of atractylenolide-II (AT-II) and atractylenolide-III (AT-III) increase significantly after frying with bran, along with a notable rise in atractylenolide-I (AT-I) content [57]. After processing, the content of atractyloside A (AA) also increases, while the content of atractylodin (ATL) decreases [58].

Effects of deep-frying on the chemical composition of Atractylodis Rhizoma

The content of AA content in Atractylodis Rhizoma increases significantly after deep-frying, making it a primary incremental component. A comparison of AA content in 10 batches of SCZ and FCZ showed an increase from 58.44% to 87.00% after processing [59].

Gas chromatography fingerprint analysis of SCZ and JCZ revealed that the contents of *β*-eudesmol and AT-I, II, and III, as well as other volatile constituents, decreased after deep-frying [60]. In contrast, the content of 5-HMF increased [51].

Effects of rice water processing on the chemical composition of Atractylodis Rhizoma

After processing, the volatile oil of *Atractylodes chinensis* (DC.) Koidz. exhibited an increase in palmitic acid and a decrease in *β*-elemene and *α*-eudesmol components while retaining *γ*-eudesmol. Conversely, the volatile oil of *Atractylodes lancea* (Thunb.) DC. showed an increase in *α*-eudesmol and a decrease in 3-methylbiphenyl components, with the presence of geranyl acetate [61]. Furthermore, a study found that components such as hinokiene, 3-carene, pinene, (+)-limonene, *β*-terpinene, basilene, *γ*-pinene, terpinolene, and 4-isopropyltoluene decreased after processing [46].

Effects of Different Processing Methods on the Pharmacological Action of Atractylodis Rhizoma

Pharmacological effects of SCZ

SCZ possesses various pharmacological effects and is primarily used to treat gastric ulcers, intestinal diseases, acute lung injury (ALI), and arthritis [4].

Therapeutic effects in treating acute gastric ulcers

The volatile oil of SCZ has been demonstrated to alleviate gastric spasms in rats with diabetic gastroparesis and hypoglycemia while enhancing gastrointestinal motility. Its mechanism of action may involve increasing serum insulin-like growth factor-1 (IGF-1), upregulating IGF-1 receptor, acetylcholine transferase, and stem cell factor (SCF) expression, and restoring Cajal-positive interstitial cells in gastric tissues [62]. *In vivo* and in *vitro* studies have shown that the ethanol extract of SCZ treats lipopolysaccharide (LPS)-induced gastritis by inhibiting the production of nitric oxide (NO) and prostaglandin E2 (PGE2) in LPS-induced RAW264.7 macrophages. It also reduces the expression of in-

Table 2 The main chemical components of Atractylodis Rhizoma

Compounds	MW/(g·mol^{-1})	PubChem CID	After processing↑or↓	Pharmacological effects	Ref.
β-Eudesmol	222.4	91457	(FCZ) ↓ (JCZ) ↓	Diarrhea Anti-angiogenic Anticancer Anti- inflammatory Antitumor	[20-22]
β-Sitosterol	414.7	222284	Unknown	Anti-inflammatory Anticancer Liver protection Antioxidant	[20, 23]
Daucosterol	576.8	5742590	Unknown	Colitis Anti-inflammatory Anticancer	[20, 24, 25]
Stigmasterol	412.7	5280794	Unknown	Colitis Rheumatoid arthritis	[20, 26, 27]
Atractylenolide I	230.3	5321018	(FCZ)↑ (JCZ) ↓	UC Liver protection Anticancer Antitumor	[20, 22, 28, 29]
Atractylenolide II	232.3	14448070	(FCZ)↑ (JCZ) ↓	Anticancer	[20, 30]
Atractylenolide III	248.32	155948	(FCZ) ↑ (JCZ) ↓	UC Anticancer Anti-inflammatory	[20, 30, 31]
Atractylenolide IV	306.4	57509416	/	Unknown	[20]
Atractyloside A	448.5	71307451	(FCZ)↑ (JCZ) ↑	Diarrhea Antiviral effect	[7, 32]
Atractyloside B	450.5	71448952	Unknown	Unknown	[32]
Atractyloside C	400.5	71448953	Unknown	Unknown	[33]
Atractyloside D	562.6	71448954	Unknown	Unknown	[33]
Atractyloside E	694.8	71448955	Unknown	Unknown	[33]
Atractyloside G	416.5	71448957	Unknown	Unknown	[33]
Atractylodin	182.22	5321047	(FCZ) ↓	UC Anticancer Anti-inflammatory Anti-oxidant Anti-virulence	[34-36]
Atractylon	216.32	3080635	(FCZ)↓	Antiviral activities Antitumor	[34, 37, 38]
β-Selinene	204.35	519361	Unknown	Unknown	[39]
α-Selinene	204.35	10856614	Unknown	Unknown	[39]
Hinesol	222.37	10878761	Unknown	Antitumor Anticancer	[39, 40]
β-Guaiene	204.35	15560252	Unknown	Unknown	[33]
(1*R*,2*R*,4*S*)-2-hydroxy-1,8-cineole *β*-D-glucopyranoside	350	73815050	Unknown	Unknown	[33]
Icariside F2	402.4	14079045	Unknown	Unknown	[33]
Syringin	372.4	5316860	Unknown	Colitis Liver protection Anticancer	[33, 41-43]
Longifloroside B	568.6	14570952	Unknown	Unknown	[44]
Puerarin	146.4	5281807	Unknown	Antioxidant Anticancer Anti-inflammation Alleviating pain	[44, 45]
3′-Methoxy puerarin	446.4	5319485	Unknown	Unknown	[44]
α-Eudesmol	222.4	92762	(MCZ) ↑	Unknown	[46]
α-Pinene	136.23	6654	(FCZ) ↓	Anticancer Anti-inflammatory	[46-48]
3-Carene	136.23	26049	(MCZ) ↓	Unknown	[46]
4-Isopropyltoluene	134.22	7463	(MCZ) ↓	Unknown	[46]
Terpinolene	136.23	11463	(MCZ) ↓	Anti-inflammatory	[46, 49]
β-Elemene	204	6918391	(MCZ) ↑	Anticancer	[46, 50]
5-HMF	126.11	237332	(FCZ)↑ (JCZ) ↑	Anti-inflammatory Antioxidant	[51-53]

ducible NO synthase (iNOS), cyclooxygenase-2 (COX-2), and tumor necrosis factor-α (TNF-α) while lowering NF-κB–activated Akt/IκBα/NF-κB kinase activity. Additionally, it mitigates gastric tissue degeneration and inflammatory cell infiltration in rats with HCl/EtOH-induced gastric damage [63]. SCZ has also been found to downregulate TNF-α, interleukin-8 (IL-8), IL-6, and PGE2 levels in an acetic acid-induced mouse model of gastric ulcer while upregulating epidermal growth factor (EGF) and trefoil factor 2 (TFF2) levels, thereby exerting protective effects on the gastric lining [64]. Moreover, treatment with SCZ extract in mice restored levels of biomarkers such as hemolytic phosphatidylcholine (PC), L-glutamic acid, arachidonic acid, deoxycholic acid, and bile acids to normal. The SCZ extract also corrected antibiotic-induced metabolic abnormalities in mice, potentially by modulating arachidonic acid and phospholipid metabolism, which increases PGE2 levels in the stomach. This process helps inhibit gastric acid output, alleviate ulcers, and exert immunosuppressive, anti-inflammatory, and antidiarrheal effects while normalizing serum metabolite levels [65].

Therapeutic effects in treating intestinal diseases

Atractylode oil can inhibit the SCF/c-kit pathway, reducing inflammation and inflammatory factors such as MLCK/MLC2, TNF-α, IL-1β, and IL-6. This inhibition protects the intestinal barrier from damage and alleviates diarrhea symptoms in mice with irritable bowel syndrome (IBS) [66]. Additionally, treatment with the ethanol extract of SCZ inhibits the phosphorylation of the mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways. It ameliorated dextran sodium sulfate (DSS)-induced ulcerative colitis (UC) in mice by inhibiting inflammatory responses and maintaining intestinal barrier function by modulating the MAPK/NF-κB pathway [67]. Furthermore, the chloroform extract of SCZ significantly downregulates the expression of inflammatory factors and the TLR4/MyD88/NF-κB pathway in *Salmonella typhi* Typhimurium (STM)-infected cell models. It also restores the expression of intestinal barrier-related genes and proteins in intestinal cells damaged by STM infection, thereby attenuating the infection [68].

Therapeutic effect in treating ALI

Research has demonstrated that the ethanolic extract of SCZ has significant therapeutic effects on LPS-induced ALI. It markedly alleviates the pathological state by reducing pulmonary edema, enhancing lung barrier function, and effectively mitigating lung damage. SCZ achieves these effects by reducing oxidative stress and inflammatory responses through the TLR4/NF-κB and Keap1/Nrf2 signaling pathways. Specifically, it lowers the expression of inflammatory factors such as TNF-α, IL-1β, iNOS, and COX-2 while inhibiting the activation of the NF-κB signaling pathway [69]. Furthermore, ATL also plays a crucial role in managing LPS-induced ALI. ATL suppresses the activation of the TLR4-NF-κB and MAPK pathways, as well as the NLRP3 inflammasome, thereby contributing to the reduction of inflammation and lung injury [70].

Therapeutic effect in treating arthritis

Metabolomic analysis has shown that Atractylodes oil impacts rheumatoid arthritis by modulating nine metabolic pathways, including arginine and proline metabolism, alanine, aspartate, and glutamate metabolism, D-glutamine and D-glutamate metabolism, aminoacyl-tRNA biosynthesis, and the metabolism of galactose, taurine, and hypotaurine. Furthermore, Atractylodes oil significantly reduces the expression of inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-17, as well as matrix metalloproteinases MMP-2 and MMP-9 in rheumatoid arthritis rats. The anti-arthritic effects of Atractylodes oil may be attributed to its modulation of cytokine and chemokine levels and its interference with MMP expression. Its mechanism is likely linked to the regulation of intestinal microbiota and metabolites (Fig. 2) [71].

Pharmacological effects of FCZ

A comparison of the therapeutic effects of SCZ and FCZ in DSS-induced colitis revealed that both SCZ and FCZ alleviated the severity of colitis, reduced weight loss, and prevented the loss of goblet cells to varying extents. Additionally, both SCZ and FCZ inhibited the reduction of mucoglycoprotein 2 (MUC2) and the tight junction proteins zonula occludens-1 (ZO-1) and occludin. They also suppressed the production of colonic inflammatory factors TNF-α, IL-6, and IL-1β, as well as the activation of pro-inflammatory macrophages (Fig. 3). Notably, FCZ demonstrated a superior effect compared to SCZ. Both SCZ and FCZ improved the *α*- and *β*-diversity of the intestinal flora in mice with colitis. They increased the abundance of beneficial bacteria, such as *Lactobacillus*, and decreased harmful pathogenic bacteria, including *Bacteroides*, *Parabacteroides*, *Clostridium*, and *Turicibacter*. Additionally, they regulated the metabolism of disease-related metabolites, including amino acids and cholesterol. FCZ exhibited more potent modulating effects than SCZ. Specifically, FCZ enhanced the production of beneficial metabolites like alanine, L-proline, serine, L-threonine, glutamic acid, hypoxanthine, and anhydrous sorbitol while inhibiting cholesterol accumulation, which is harmful in intestinal diseases. *In vitro* experiments further revealed that AT-I, an active component in FCZ, significantly inhibited the protein expression levels of TNF-α, IL-6, and IL-1β [72].

Atractylodis Rhizoma, in both its raw (SCZ) and bran-fried (FCZ) forms, effectively treats SDS. The therapeutic mechanism involves enhancing digestive enzyme activity, thereby increasing the production of trypsin and amylase (AMS). Additionally, it boosts gastrointestinal hormone levels by upregulating the production of vasoactive intestinal peptide (VIP), somatostatin (SS), gastrin (GAS), and substance P (SP). It also enhances membrane protein activity through the upregulation of Na^+-K^+-ATPase and alters mitochondrial activity by increasing succinic dehydrogenase production. Comparative studies in rats with SDS indicate that FCZ has superior modulating effects on VIP, SS, GAS, SP, and Na^+-K^+-ATPase levels compared to SCZ, leading to more substantial alleviation of SDS symptoms [73]. Furthermore, FCZ outperformed SCZ in regulating intestinal microbiota,

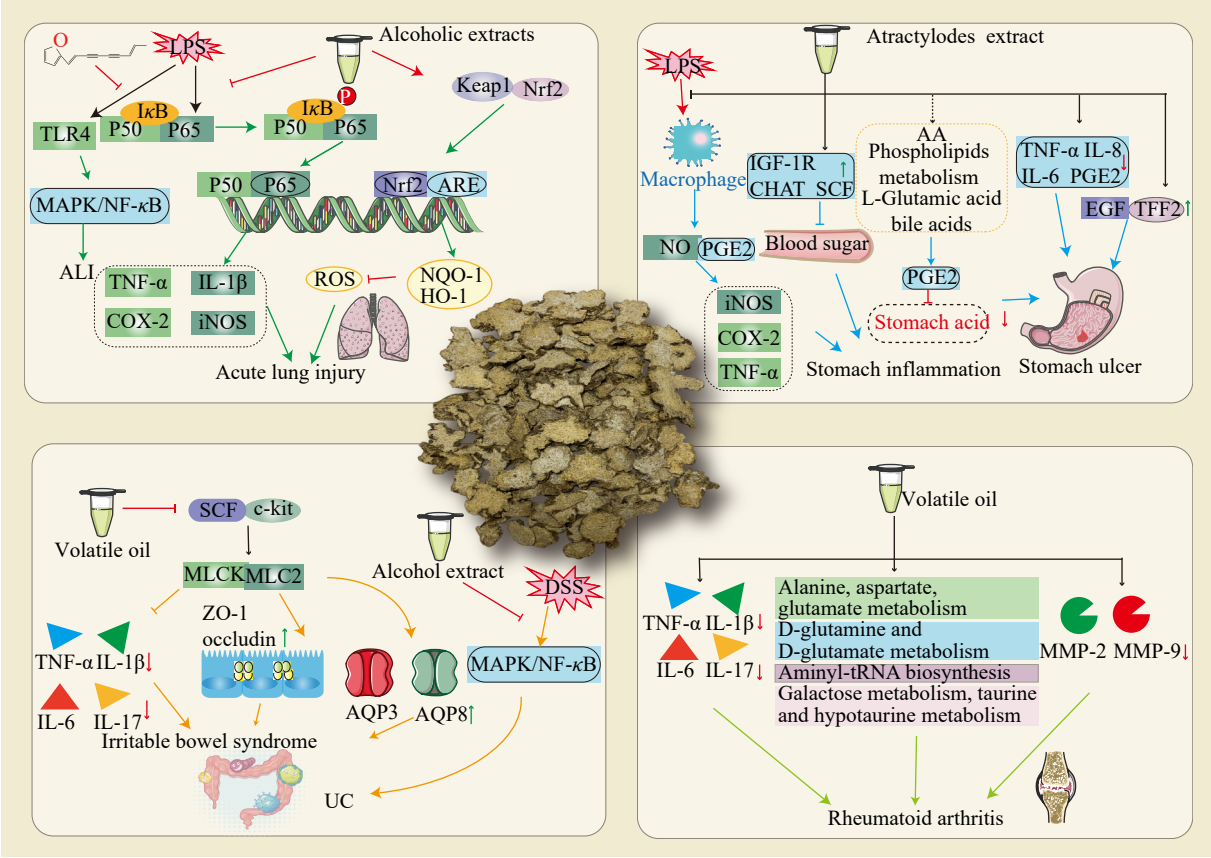

Fig. 2 The main effects of SCZ, which can treat stomach ulcers, UC, ALI, and arthritis. Ethanol extract and ATL can treat ALI. Atractylode extracts can treat stomach ulcers and inflammation. Moreover, the volatile oil can treat rheumatoid arthritis and IBS, while its alcohol extract can treat DSS-induced UC.

effectively controlling the abundance of *Bacteroides*, *Escherichia-Shigella*, and *Phascolarctobacterium* [74]. Both SCZ and FCZ significantly regulated the levels of nicotinic acid, dihydrofolic acid, pantetheine 4′-phosphate, and PC, as well as the niacin and nicotinamide metabolic pathways, with FCZ showing superior effects on these pathways [75].

Additionally, FCZ demonstrated a more potent anti-ulcer effect than SCZ in alleviating acetic acid-induced gastric ulcers. The mechanism of this anti-ulcer effect may involve the downregulation of inflammatory factors such as TNF-α, IL-8, IL-6, and PGE2, along with the gastroprotective effects of epidermal growth factor (EGF) and TFF2 [64].

Pharmacological effects of deep-fried Atractylodis Rhizoma

Both SCZ and JCZ enhance the integrity of the intestinal barrier by increasing the expression of tight junction proteins ZO-1 and occludin. They also boost the expression of water channel proteins aquaporin 3 (AQP3) and AQP8, suppress the phosphorylation of p38 MAPK and MLC, and significantly reduce PAR-2 levels, thereby improving spleen deficiency diarrhea (SDD) (Fig. 4) [10].

The ethanolic extract of JCZ is particularly effective in alleviating SDD and improving intestinal pathology. It prevents the reduction of tight junction protein levels through the p38 MAPK signaling pathway, thus protecting intestinal barrier integrity. JCZ also regulates and improves the structure of the intestinal flora, significantly ameliorating SDD symptoms in mice. Its antidiarrheal effect is more potent than that of SCZ, as it inhibits pro-inflammatory factors TNF-α, IL-1β, and IL-6 and enhances the production of AQP3, AQP4, and AQP8. Additionally, JCZ promotes the production of tight junction proteins (ZO-1, occludin, and claudin-1), prevents the loss of colonic goblet cells, alleviates colitis, and increases the expression of AQPs and tight junction markers. JCZ also significantly enhances the content of short-chain fatty acids (SCFAs) in the feces of mice with SDD, a change closely associated with gut microbiota composition. It increases the abundance of probiotic bacteria, such as *Lactobacillus* and *Akkermansia*, while reducing pathogenic bacteria like *Escherichia-Shigella* and *Mucispirium*. Furthermore, JCZ is more effective than SCZ in improving gastrointestinal digestion and absorption functions. The mechanism by which JCZ alleviates SDS in rats may involve its enhanced regulatory effect on *Bacteroides*, *Shigella*, *Phascolarctobacterium*, Deferribacteres, and *Akkermansia* [76].

Pharmacological effects of rice water processing of Atractylodis Rhizoma

Studies have shown that MCZ exerts a potent spleen-strengthening effect by increasing the levels of AMS, D-xylulose, and GAS, as well as enhancing the small intestinal

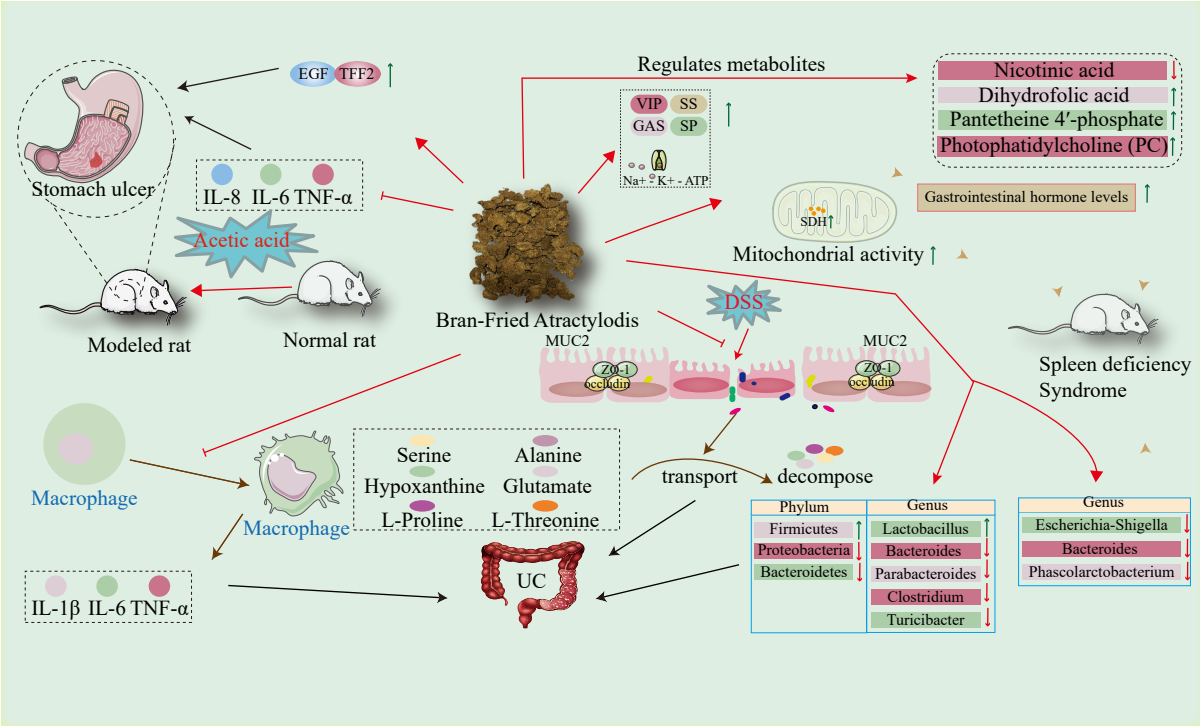

Fig. 3 The pharmacological effects of FCZ. FCZ can help treat UC, stomach ulcer, and spleen deficiency syndrome (SDS). FCZ treats UC by suppressing inflammatory factor expression, modulating the intestinal flora, and regulating disease-related products. FCZ can treat SDS by modifying the levels of VIP, SS, GAS, SP, and Na^+-K^+-ATPase. FCZ helps treat acetic acid-induced stomach ulcers by down-regulating inflammatory factors and EGF and TFF2 expression. FCZ showed more potent therapeutic effects than SCZ.

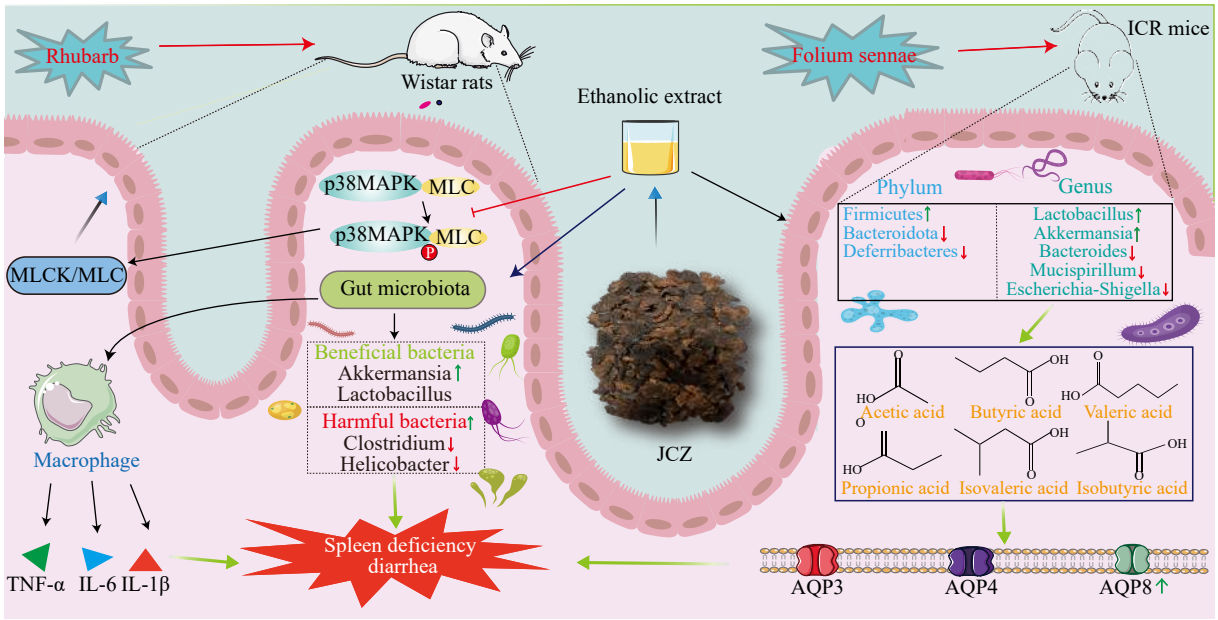

Fig. 4 The pharmacological effects of JCZ. JCZ can treat SDD *via* the p38MAPK pathway while improving intestinal flora. It can treat senna-induced SDD among mice by modulating SCFAs and intestinal flora. JCZ showed more potent therapeutic effects than SCZ.

propulsive rate. Additionally, MCZ helps restore body weight in rats with SDS, demonstrating a stronger effect than SCZ [77].

MCZ also exhibits significant spleen-strengthening and antidiarrheal effects by reducing fecal water content and serum levels of motilin (MTL), D-lactate, and IL-1β. Furthermore, MCZ increases the relative abundance of beneficial microbes, such as *Lactobacillus*, *Prevotella*, *Bacteroidetes Mortierella, Filobasidium,* and *Chaetomium*, while reducing the

relative abundance of potentially harmful bacteria such as *Alloprevotella*, *Ruminococcaceae*, *Phascolarctobacterium*, *Lachnospiraceae*, *Alloprevotella*, and *Aspergillus*. This results in a significant elevation in the overall abundance and diversity of the intestinal flora [78, 79].

Unique Advantages of Atractylodis Rhizoma and Its Extracts in Protecting the Gastrointestinal Tract

Atractylodis Rhizoma offers distinct advantages in the clinical treatment of gastrointestinal diseases. Various studies have revealed that its components, including ATL, *β*-eudesmol, AT-I, AT-II, AT-III, and AA, exhibit significant protective effects on the gastrointestinal tract. The mechanisms of action of these components are gradually being elucidated, highlighting the therapeutic potential of Atractylodis Rhizoma in managing gastrointestinal disorders.

Effects of Atractylodin on the gastrointestinal tract

ATL has demonstrated significant potential in preventing and treating colitis by reversing key symptoms such as weight loss, diarrhea, blood in stool, colon shortening, and damage to the pathological structure of colon tissue, including the loss of goblet cells. Additionally, ATL helps maintain MUC2 and tight junction protein (ZO-1) levels in colon tissues. It inhibits the MAPK pathway, macrophage activity, and the secretion of pro-inflammatory factors in mice with DSS-induced colitis [80]. ATL exerts its anti-inflammatory effects by reducing the levels of TNF-α, IL-1β, and IL-6, which also alleviates movement disorders in rats with constipation and diarrhea. Furthermore, ATL can regulate jejunal segment contraction in these rats, demonstrating state-dependent effects [81]. Docking simulation analysis, luciferase assays, and *in vitro* binding assays have shown that ATL has a high affinity for peroxisome proliferator-activated receptor alpha (PPARα). By reducing NF-*κ*B p65 phosphorylation in TNF-α-treated HCT116 cells, ATL activates PPARα, contributing to its anti-inflammatory effects on colon epithelial cells [82].

Effect of β-eudesmol in treating gastrointestinal disorders

A pharmacodynamic study observed that *β*-eudesmol exhibits a bidirectional effect on intestinal motility. It promotes gastrointestinal motility but also has an inhibitory effect in conditions such as spleen deficiency, diarrhea, or hyperactive gastrointestinal function. This dual action may be related to the anticholinergic properties of *β*-eudesmol, or it may act directly on the smooth muscle of the gastrointestinal tract. Furthermore, *β*-eudesmol enhances gastric emptying and small intestinal motility by interfering with the functions of dopamine D2 and 5-HT3 receptors [83].

Effects of Atractylenolide in treating gastrointestinal disorders

AT-I has demonstrated significant efficacy in treating gastrointestinal disorders. Studies have shown that AT-I can prevent and treat colitis in mice by inhibiting the abnormal elevation of colonic sphingosine kinase 1 (SPHK1) and *β*-1,4-galactosyltransferase 2 (B4GALT2), and by suppressing the activation of the PI3K-AKT pathway. AT-I's anti-inflammatory effect is more potent than those of AT-II, AA, and 5-hydroxymethylfurfural at equivalent doses. Metabolomic studies have indicated that AT-I primarily affects the metabolism and absorption of fructose and galactose in mice with colitis, thereby inhibiting intestinal flora disorders. AT-I may also suppress SPHK1 expression by reducing D-fructose uptake, thus inhibiting PI3K-AKT pathway activation and the production of inflammatory factors [84]. Intestinal epithelial cells (IEC-6) are crucial in gastrointestinal diseases as they promote the healing of mucosal ulcers and wounds. AT-I enhances therapeutic effects in the gastrointestinal tract by increasing transient receptor potential canonical type 1 (TRPC1) and phospholipase C gamma 1 (PLC-γ1) expression in IEC-6 cells. AT-I-treated intestinal epithelial cells show increased migration and proliferation *via* polyamine-mediated Ca^{2+} signaling, elevated polyamine content, increased cytoplasmic free Ca^{2+} concentration, and enhanced TRPC1 and PLC-γ1 mRNA and protein expression, all of which stimulate cell migration and proliferation. Thus, AT-I can treat conditions such as inflammatory bowel disease and peptic ulcers associated with gastrointestinal mucosal damage. Moreover, AT-I significantly inhibits the viability of colorectal cancer (CRC) cell lines, suppresses colony formation, induces apoptosis, increases cleavage of Caspase-3 and PARP-1, enhances BCL2-associated X protein (BAX) expression, and decreases B-cell lymphoma-2 (BCL-2) expression. Additionally, AT-I blocks cellular glycolysis by inhibiting glucose uptake and lactate production in CRC lines, suggesting its anticancer activity is related to apoptosis induction and glycolysis inhibition [85]. AT-I reduces inflammation by targeting the SPHK1/PI3K/AKT pathway and regulating fructose- and galactose-related metabolism, which helps control the composition of intestinal flora and treat DSS-induced UC [84]. It also prevents the onset of IBS by modulating the miR-34a-5p-LDHA pathway, reversing miR-34a-5p-inhibited glucose metabolism under oxidative stress, and mitigating IBS-induced intestinal mucosal dysfunction [86].

AT-II significantly inhibits the growth and migration of human gastric cancer cells HGC-27 and AGS, exerting a potent antitumor effect by regulating the Akt/ERK signaling pathway in a dose-dependent manner [87].

AT-III is effective in treating gastrointestinal diseases by controlling oxidative stress through the FPR1 and Nrf2 pathways and modulating the development of intestinal flora. It alleviates 2,4,6-trinitrobenzene sulfonic acid-induced acute colitis by reducing inflammation, specifically by inhibiting pro-inflammatory factors IL-1β and TNF-α. AT-III also significantly suppresses the expression of pro-oxidant markers, reactive oxygen species, and malondialdehyde while increasing the expression of antioxidant enzymes, including catalase, superoxide dismutase, and glutathione peroxidase [88]. Furthermore, AT-III reduces precancerous gastric lesions and inhibits angiogenesis in rats, potentially by downregulating

hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor A (VEGF-A), which are linked to angiogenesis, as well as delta like canonical Notch ligand 4 (DLL4) [89]. AT-III also significantly inhibits the growth of human colorectal cancer HCT-116 cells and induces apoptosis *in vitro* in a concentration-dependent manner. This mechanism involves upregulating the expressions of BCL-2-associated X, cleaved Caspase-3, and p53, while downregulating Bcl-2 in HCT-116 tumor tissues. As a result, AT-III induces apoptosis and inhibits the growth of HCT-116-transplanted tumors in nude mice [90].

Effect of AA in treating gastrointestinal diseases

Research on the therapeutic effects and mechanisms of AA in improving diarrhea due to spleen deficiency has identified several potential mechanisms: 1) Modulation of gut microbiota: AA enhances intestinal health by increasing the abundance of beneficial bacteria and reducing harmful bacteria. The alteration of gut microbiota is a crucial factor in AA's therapeutic effects. Gut microbiota is the critical factor for AA to exert a therapeutic effect. 2) Anti-inflammatory action: AA decreases the secretion of intestinal pro-inflammatory factors by inhibiting gene expression linked to the TLR4/NF-*κ*B signaling pathway. This inhibition results in increased synthesis of aquaporins (AQPs) and tight junction proteins on cell membranes, as well as an increase in the number of goblet cells and mucins. By inhibiting the TLR4/MyD88/NF-*κ*B signaling pathway, AA mitigates the intestinal inflammatory response, reverses mucin synthesis damage, and alleviates pathological diarrhea symptoms associated with spleen deficiency [59]. 3) Enhancement of intestinal barrier function: AA intervention leads to increased body weight and intestinal motility, along with elevated levels of MTL, GAS, c-Kit, ZO-1, and occludin in mice with SDD. AA also reduces gastric residues and mitigates intestinal tissue damage. The levels of AQP1, AQP3, and fibroblast growth factor 2 (FGF-2) are elevated, which positively impacts the epidermal growth factor receptor (EGFR) and proliferating cell nuclear antigen (PCNA). Additionally, AA improves intestinal mucosal barrier function by suppressing the activation of the p38 MAPK signaling pathway in rat models of SDS [91].

Effect of Atractylodis Rhizoma polysaccharide in alleviating gastrointestinal diseases

Polysaccharides from Atractylodes have been shown to enhance the immune organ index and increase levels of TNF-α, IL-1β, IL-6, IL-10, DAO, and sIgA. They also promote the expression of ZO-1 and occludin, thereby regulating intestinal microbiota disorders and treating cyclophosphamide-induced immune deficiency (Fig. 5) [92]. The crude polysaccharide fraction (ALR-5lla-1) from the aqueous extract of Atractylodis Rhizoma, when digested with *exo*-*β*-D-(1→3)-galactanase, suggested that the arabino-3,6-galactan moiety plays a vital role in modulating the intestinal immune system [93].

Additionally, the combination of *A. chinensis* (DC.) Koidz. polysaccharides and apatinib has demonstrated a synergistic effect in the gastric cancer cell line SGC-7901 [94].

Discussion

Different processing methods result in distinct chemical compositions and pharmacological effects in Atractylodis Rhizoma. Methods, such as FCZ, JCZ, and MCZ, reduce the content of volatile components, including ATL in SCZ. The ATL content ranges from low to high in the order of JCZ, FCZ, MCZ, and SCZ [95]. These processing methods also increase the levels of certain components such as atractyloside and atractylenolides (AA, AT-I, AT-II, and AT-III). SCZ possesses various pharmacological effects, including the treatment of gastric ulcers, intestinal diseases, ALI, and arthritis. Processing enhances its efficacy in treating gastrointestinal diseases. FCZ, JCZ, and MCZ exhibit promising therapeutic effects on the gastrointestinal tract, each with specific focuses: FCZ and MCZ are particularly effective in strengthening the spleen, while JCZ excels in stopping diarrhea [76, 77]. In clinical practice, SCZ is recommended for treating lung diseases such as colds and coughs, as well as water-dampness disorders like rheumatism (e.g., arthritis). For gastrointestinal diseases such as spleen deficiency, gastric ulcer, and colitis, FCZ and MCZ are preferable. JCZ is particularly suitable for treating symptoms like diarrhea and persistent dysentery induced by spleen deficiency.

Atractylodis Rhizoma has a long history as a traditional Chinese medicine, with numerous processing methods employed from ancient times to the present. Bran-frying and deep-frying are the main methods used clinically, with raw and bran-fried products being the most widely utilized. However, studies on rice water-processed Atractylodis Rhizoma are relatively rare. Our research group has extensively investigated common processing methods, including the concoction processing method of FCZ, optimal temperature, frying time, and wheat-to-bran ratio. We have also analyzed the compositional differences in FCZ produced under various conditions. These studies, conducted over many years based on a series of quality control standards, include several pilot studies in factories and real-world settings [9]. Despite this, further research is needed to optimize current processing methods.

Our review indicates that the chemical composition of Atractylodis Rhizoma undergoes significant changes after processing due to high temperatures and interactions with excipients. For instance, volatile components significantly decrease, glycosides increase, and lactone components undergo transformation. Comparative studies of the chemical composition before and after processing provide a material basis for understanding altered pharmacological effects. However, existing research mainly focuses on common components with higher content, often neglecting less common and lower-content components [92]. Furthermore, advancements in analysis and detection technologies for polysaccharides and oligosaccharides suggest that future research should focus on how dif-

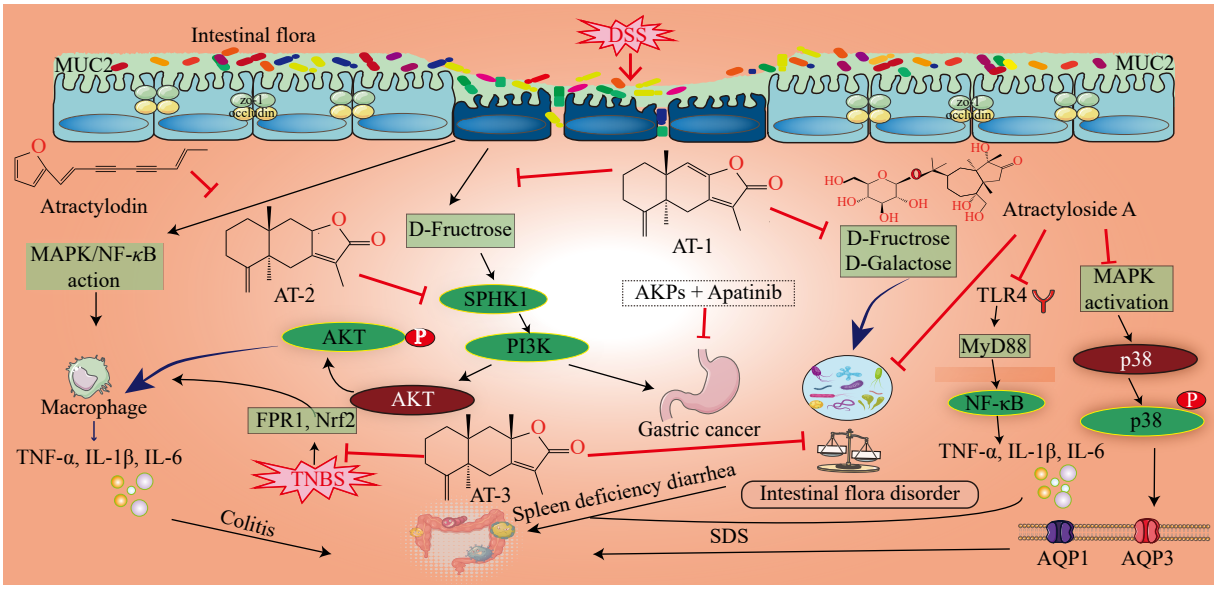

Fig. 5 The unique advantages of Atractylodis Rhizoma and its extracts to protect the gastrointestinal tract. AT-I (Atractylenolide I) can treat UC by suppressing the PI3K-AKT pathway activation and impacting the metabolism and absorption of fructose and galactose in UC-based mice, which suppresses intestinal flora disruption. AT-II (Atractylenolide II) regulates the Akt/ERK signaling pathway to exert anticancer effects on gastric cancer cells. AT-III (Atractylenolide III) modulates oxidative stress using the FPR1 and Nrf2 pathways, impacting intestinal flora and attenuating TNBS-induced UC. AA helps treat SDD by suppressing the genetic expression linked with the TLR4/NF-κB signaling pathway while curing intestinal flora disorder.

ferent processing methods affect these components in Atractylodis Rhizoma.

This review identified several studies on the pharmacological effects of unprocessed Atractylodis Rhizoma, including its use in treating ALI, gastric ulcers, and arthritis. These studies suggest that specific pharmacological effects may change with different processing methods [64, 71, 96]. For instance, bran- and deep-frying significantly enhance the gastroprotective effect of Atractylodis Rhizoma, likely due to the regulation and metabolism of gut microbiota [74]. The enhanced efficacy of processed Atractylodis Rhizoma is a common observation. Future research should explore the efficacy differences between processed and unprocessed Atractylodis Rhizoma using various models, such as liver injury models, to provide a scientific basis for its clinical applications. Although rice water processing enhances the spleen-strengthening effect of Atractylodis Rhizoma, the underlying mechanisms remain unclear.

Active components of Atractylodis Rhizoma, such as β-eudesmol, ATL, Atractylenolide, AA, and polysaccharides, show unique advantages in treating gastrointestinal diseases. These components provide a basis for treating gastric ulcers, gastritis, gastric cancer, UC, and SDS [64, 67, 74]. The pharmacological mechanisms of these active ingredients and processed products in alleviating gastrointestinal diseases may involve regulating gut microbiota and immune inflammation [10]. However, the specific bacteria with the most significant regulatory effects have yet to be identified, and the relationship between bacterial regulation and the human immune system remains unexplored. This review can serve as a starting point for further research on Atractylodis Rhizoma.

Recent research indicates that the structure and composition of polysaccharides change after bran-frying, improving their immune regulatory effects [92]. Future studies should investigate the structural and compositional changes of polysaccharides using different processing methods. Additionally, research should explore how various processing methods enhance pharmacological effects, focusing on process optimization, ingredient changes, and the identification of beneficial bacterial strains.

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