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Review

# Traditional Uses, Phytochemistry, Pharmacology and Toxicology of *Rhizoma phragmitis*: A Narrative Review

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**ABSTRACT** ***Rhizoma phragmitis*** **is a common Chinese herbal medicine whose effects are defined as 'clearing heat and fire, promoting fluid production to quench thirst, eliminating irritability, stopping vomiting, and disinhibiting urine'. During the Novel Coronavirus epidemic in 2020, the Weijing Decoction and Wuye Lugen Decoction, with *Rhizoma phragmitis* as the main herbal component, were included in The Pneumonia Treatment Protocol for Novel Coronavirus Infection (Trial Version 5) due to remarkable antiviral effects. Modern pharmacological studies have shown that *Rhizoma phragmitis* has antiviral, antioxidative, anti-inflammatory, analgesic, and hypoglycemic functions, lowers blood lipids and protects the liver and kidney. This review aims to provide a systematic summary of the botany, traditional applications, phytochemistry, pharmacology and toxicology of *Rhizoma phragmitis*.**

**KEYWORDS** ***Rhizoma phragmitis*****, pharmacology, phytochemistry, Chinese medicine**

*Rhizoma phragmitis* is the fresh or dried rhizome of the perennial grass *Phragmites communis* Trin. *Phragmites* can degrade drug residues such as carbamazepine, ibuprofen, benoxaprofen, diquat and nalidixim-methyl in wastewater and plays an important role in maintaining the ecological balance in wetlands.[1-4] It is a very important Chinese medicine (CM), and its effects are defined as clearing heat and fire, promoting fluid production to quench thirst, eliminating irritability, stopping vomiting, and disinhibiting urine. Therefore, it is often used to treat diseases such as wasting thirst, vomiting, and cough, and has a history of clinical application in China for more than 2,000 years. Modern research has shown the main components of *Rhizoma phragmitis* have anti-inflammatory, analgesic, hypoglycemic, hypolipidemic, antioxidant, antitumor and others pharmacological activities.[5,6]

The medicinal value of *Rhizoma phragmitis* has been indicated throughout the history of CM. Unfortunately, current research efforts on *Phragmites* have focused on the ecological balance of wetlands, and less research has been conducted on the pharmacological effects of its rhizome and aerial parts. More importantly, none of the literature has comprehensively evaluated this important and abundant CM resource. Therefore, to further explore and promote the medicinal value of *Rhizoma phragmitis*, we present the narrative review of the research progress of this CM with regard to botany, traditional applications, phytochemistry, pharmacology and toxicology for providing a detailed and reliable reference for the further development and utilization of *Rhizoma phragmitis*.

## Literature Research

*Rhizoma phragmitis*, *Phragmites*, active ingredient, pharmacology, botany, safety and molecular mechanism were used as keywords to collect all references related to *Rhizoma phragmitis* in Web of Science, SciFinder, Google Scholar, Baidu Scholar, PubMed, VIP, China Biomedical Database (CBM), Wanfang, China National Knowledge Infrastructure (CNKI) and other databases. All references included in this study were published in Chinese or English before 1st November 2021.

## Botany

*Phragmites* are widely distributed throughout



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temperate regions of the world, including China, southern Europe, the western coastal regions of the United States, South Africa, and Australia, particularly in wetlands, marshes, and lakes.[7] *Phragmites* is a typical perennial water-supported plant that is well suited for growing in wetland environments. The leaves are green, about 25 cm in length and 3.5 cm in width. The height of plant is 1–3 m and the diameter of stem is 1–4 cm. Its stem is extremely tough with a high content of fiber and is an important raw material in the paper industry. The florescence of *Phragmites* is September to October. Its flowers are conical and made up of purple spikelets about 20 cm in length. *Phragmites* has an extremely well-developed cylindrical rhizome that is approximately 1.5 cm in diameter and up to 1 m in length with nodes and resembles bamboo shoots. *Rhizoma phragmitis* is a common medicinal herb in China. It can be dug and harvested throughout the year and used fresh or dried after removing the buds and membranous leaves.

## Traditional Uses

As early as the pre-Qin period, *Phragmites* were widely used for purposes such as weaving mats, building houses, and making clothes. In 220–450 A.D., *Phragmites* was first recorded as a medicinal herb in the *Miscellaneous Records of Famous Physicians* (Ming Yi Bie Lu). In 659 A.D., *Newly Revised Materia Medica* (Xin Xiu Ben Cao) recorded the effects of *Rhizoma phragmitis* in clearing Wei (Stomach) heat and stopping vomiting. In the Tang Dynasty, *Invaluable Prescriptions for Emergencies* (Bei Ji Qian Jin Yao Fang) documented the efficacy of *Rhizoma phragmitis* in clearing Fei (Lung) heat, dispelling phlegm and draining pus. In addition, the other pharmacological effects of *Rhizoma phragmitis* have also been recorded in ancient books such as the *Yu Qiu's Exegesis for Materia Medica* (Yu Qiu Yao Jie) and *Preparation of Materia Medica* (Ben Cao Bei Yao). In 1953, the first edition of the Chinese Pharmacopoeia detailed the pharmacological effects, harvesting, preparation and dosage of *Rhizoma phragmitis*. In 2002, the Chinese Ministry of Health defined fresh *Rhizoma phragmitis* as a medicinal and food product. *Rhizoma phragmitis* exists in many classical prescriptions, some of which are shown in Appendix 1.

## Phytochemistry

To date, more than 83 compounds have been isolated and identified from *Rhizoma phragmitis*. Phytochemical studies have shown that the main components present in *Rhizoma phragmitis* include p-coumaric acid, *Rhizoma phragmitis* polysaccharides, vitamin C, vitamin B1, vitamin B2, fatty acids, amino acids, sterols, and polyphenols (Appendix 2).[4,6,8-21] Further details are discussed below.

### Phenylpropanoids

According to the collected literature, 9 phenylpropanoid compounds are present in *Rhizoma phragmitis*, including p-hydroxycinnamic acid, 2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone, caffeic acid, ferulic acid, eugenol, anethole, 4'-hydroxy-3'-methoxycinnamaldehyde, coniferyl aldehyde, and n-propylbenzene.

### Steroids

Four steroid compounds are present in *Rhizoma phragmitis*, including stigmasta-3,5-dien-7-one, β-sitosterol, stigmasterol, and daucosterol.

### Organic Acids

A total of 12 organic acids from *Rhizoma phragmitis* are summarized in this paper, in the order of vanillic acid, p-coumaric acid, syringic acid, p-hydroxy benzoic acid, palmitic acid, heptadecanoic acid, gentisic acid, pelargonic acid, 2,5-dihydroxybenzoic acid, crystal Ⅵ, L-ascorbic acid, and L-proline.

### Alkaloids

Ten alkaloids are present in *Rhizoma phragmitis*, including phranisines B, phranisines A, moschamindole, N-p-coumaroyl serotonin, N-p-coumaroyl-tryptamine, aurantiamide acetate, N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-p-coumaramide, riboflavin, coixol, and (-)-democolcine.

### Carbohydrates

Five carbohydrates are present in *Rhizoma phragmitis*, which mainly include alpha-D-glucose, beta-D-glucose, DL-xylose, L-(+)-arabinose, and n-butyl-beta-D-fructopyranoside.

### Quinones

To date, 2 quinones, physcion and 2,5-dimethoxybenzoquinone, have been isolated from *Rhizoma phragmitis*.

### Terpenoids

There are 14 terpenoids in *Rhizoma phragmitis*,

including simiarenol, β-caryophyllene, linalool, (1R)-(+)-camphor, (R)-linalool, alpha-humulene, oleanic acid, b-AMYRIN, widdrene, cedrol, β-amyrin, taraxerol, 2-ethylbutyl methacrylate, and taraxerone.

### Flavonoids

In addition, 2 flavonoids, tricin 7-O-glucopyranoside and tricin, are found in *Rhizoma phragmitis*.

### Phenols

Six phenolic compounds are present in *Rhizoma phragmitis*, including guasol, vanillin, syringaldehyde, apocynin, tocopherol, and 4-hydroxybenzaldehyde homopolymer.

### Other Constituents

In addition, 19 other compounds are found in *Rhizoma phragmitis* such as 5-hydroxymethylfurfural, 7-chloroarctinone B, widdrene, dioctyl phthalate, furfural phenylacetaldehyde, nonanal, 13-methyl-pentadecanoic acid methyl ester, ethyl hexadecanoate, 11-methyl-nonadecanoic acid methyl ester, 6,9,12,15-octadecatetraenoic acid, methyl ester, thiarrubrine A, arctinal, vitamin B1, fmoc-Asn(Trt)-OPfp, bis(2-ethylhexyl) phthalate, methyl linoleate, 3-butylphthalide, and phenylethyl alcohol.

## Pharmacological Activities

Studies have reported that *Rhizoma phragmitis* has pharmacological activities such as antibacterial, anti-inflammatory, antiviral, antitumor, hypoglycemic, hepatic and renal protective, skin protective, and immunomodulatory activities. These pharmacological activities are recorded in Appendix 3,[4,22-41] and further details are discussed below.

### Anti-inflammatory Activity

During the inflammatory response, macrophages are the main cells that express proinflammatory factors such as nitric oxide (NO), prostaglandin 2 ($PGE_2$), tumor necrosis factor (TNF-α), and interleukin (IL-6).[42] Therefore, inhibition of macrophage activation is of great importance for the treatment of inflammatory diseases. A cellular assay showed that stigmasta-3,5-dien-7-one from *Rhizoma phragmitis* could significantly reduce the levels of proinflammatory factors such as NO, $PGE_2$, TNF-α, IL-1β and IL-6 expressed by RAW246.7 macrophages through inhibiting nuclear factor kappa-B (NF-κB) signaling pathway in dose-dependent manner in the range of 50–100 μg/mL.[4] More importantly, stigmasta-3,5-dien-7-one did not decrease the physiological expression of $PGE_2$ or cell viability in the absence of lipopolysaccharide stimulation, suggesting that 50–100 μg/mL stigmasta-3,5-dien-7-one was not toxic to RAW246.7 macrophages. In addition, stigmasta-3,5-dien-7-one was shown to alleviate the joint inflammatory response by decreasing IL-1β, IL-6, TNF-α and interferon-gamma (IFN-γ) in systemic lupus erythematosus mice.[22] Another study showed that acidic polysaccharides from *Rhizoma phragmitis* were also a major component in inhibiting NO expression by RAW246.7 macrophages. When the concentration of acidic polysaccharides reached 25 μg/mL, the NO expression level was significantly reduced compared with that in the model group. When the concentration of acidic polysaccharide reached 200 μg/mL, the expression of NO was close to that of the healthy control group.[23]

### Antioxidant Activity

Excess free radicals are the major cause of many diseases such as aging and diabetes. Study has shown that alcohol extracts of *Phragmites* roots, stems, leaves and flowers all have antioxidant capacity but with different scavenging abilities for different free radicals.[43] Under the same conditions, the scavenging ability for hydroxyl radical (•OH) was ranked in the following order: *Phragmites* leaves > *Phragmites* flowers > *Phragmites* roots > *Phragmites* stems. The scavenging ability for superoxide anion radical ($O2^{\bullet-}$) was ranked in the following order: *Phragmites* flowers > *Phragmites* leaves > *Phragmites* roots > *Phragmites* stems. The scavenging ability for 1,1-diphenyl-2-picrylhydrazyl radical (DPPH•) was ranked in the following order: *Phragmites* flowers > *Phragmites* leaves > *Phragmites* stems > *Phragmites* roots. The antioxidant effect of *Rhizoma* phragmitis is related to polyphenols, flavonoids and polysaccharides.[44,45] The scavenging ability of the *Rhizoma phragmitis* polysaccharide for free radicals is slightly inferior to that of vitamin C.[46,47] Study has shown that both oral and injected *Rhizoma phragmitis* polysaccharide can significantly prolong swimming time, reduce plasma creatine kinase levels and accelerate lactate metabolism in mice by reducing hypothalamic–pituitary–adrenal axis hyperactivation and oxidative stress-induced damage.[24] Moreover, injected *Rhizoma phragmitis* polysaccharide can also reverse swimming-induced weight loss. In addition,

Miao, et al[25] treated aging mice with *Rhizoma phragmitis* polysaccharide for 30 days and showed that *Rhizoma phragmitis* polysaccharide not only significantly increased the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) but also decreased the content of lipid peroxide in plasma, brain, and liver tissues of aging mice and alleviated the atrophy of thymus, spleen, and brain tissues induced by aging.

### Antibacterial Activity

The oligosaccharides in *Rhizoma phragmitis* had significant antibacterial effects with the greatest inhibition against *Staphylococcus aureus* when administered at a concentration of 100 μg/mL, followed by *Bacillus subtilis* and *Escherichia coli*.[26] Yu, et al[48] showed that extracts from *Rhizoma phragmitis* rich in flavonoids had obvious antibacterial and antioxidant properties.

### Antiviral Activity

MDBK cells infected with bovine herpes virus type 1 (BoHV-1) were treated with aqueous extracts of *Phragmites* leaves at different concentrations for 24 h. The results showed that the aqueous extracts of *Phragmites* leaves inhibited virus replication in a dose-dependent manner but only inhibited MDBK cell viability (12.03%) when the extracts concentration was higer than 200 μg/mL.[27] This experiment showed that low concentrations of *Phragmites* leaves extracts inhibited the virus without affecting cell physiological activity.

### Activity of Improving Glycolipid Metabolism

As society develops and living standards continue to improve, the morbidity rates of metabolic-related diseases such as obesity and diabetes mellitus (DM) are on the rise. Such metabolic diseases often have a chronic inflammatory response and an increase in free radicals. Therefore, the treatment of DM requires anti-inflammatory and antioxidant drugs in addition to improving glucolipid metabolism. However, most drugs contain only a single ingredient, and patients are at risk of taking more than one drug at the same time and exhibiting more severe toxic side effects. Therefore, the search for some multitargeted drugs with low toxicity has become critical.

A large number of polyphenols, polysaccharides, flavonoids, steroids and other compounds are present in *Rhizoma phragmitis*, which has anti-inflammatory, antioxidant, improving lipid metabolism and low toxicity characteristics.[49,50] Cui, et al[28] treated DM mice with 100 and 200 mg/kg *Rhizoma phragmitis* polysaccharide for 21 days and showed that both doses significantly reduced the levels of glycated serum protein, triglyceride (TG), total cholesterol (TC) and low-density lipoprotein (LDL) and increased the levels of liver glycogen and high-density lipoprotein (HDL). The mechanisms of *Rhizoma phragmitis* in treating DM may be related to peroxisome proliferators-activated receptor-gamma (PPAR-γ), which can reduce the inflammatory response by improving glucolipid metabolism and inhibiting the NF-κB signaling pathway. Rosiglitazone, an agonist of PPAR-γ, is often used in the treatment of DM.[51] Gao, et al[29] treated HeLa cells with different concentrations of extracts from *Rhizoma phragmitis* to observe its effect on PPAR-γ activation. The results showed that extracts of 100 μg/mL had the strongest activation of PPAR-γ up to 5.69-fold of the physiological state and 1.37-fold of 0.5 μg/mL rosiglitazone. In addition, the aerial part of *Phragmites australis* also significantly reduced the levels of fasting blood glucose, TC, LDL and TG in DM mice and improved diabetes-induced liver dysfunction by inhibiting α-amylase and restoring pancreatic β-cell function.[30]

### Analgesic Activity

Pain is a common symptom of many diseases and a major factor to reduce quality of life of patients. Sultan, et al[32] showed that the effective components of the aerial part of *Phragmites australis* extracted by methanol, petroleum ether and carbon tetrachloride, had good peripheral analgesic activity in Swiss albino mice in a dose-dependent manner. This is the first report of the analgesic activity of *Rhizoma phragmitis*. However, the mechanisms are not clear. Because most pain is caused by inflammatory response, we speculate that the analgesic effect of the aerial part of *Phragmites australis* may be related to anti-inflammatory and antioxidant activities, but this idea needs further experimental proof.

### Liver Protection

With the improvement in living standards, liver diseases resulting from a high-fat diet are increasing. CM has a very long history of using *Rhizoma phragmitis* to treat liver diseases, mainly because *Rhizoma phragmitis* has significant anti-inflammatory and antioxidant activities as well as the functions of improving glycolipid

metabolism.[52,53] In 2013, Chen, et al[34] gavaged mice with 100, 200, and 500 mg/kg aqueous extracts from *Rhizoma phragmitis* for 5 days, and then induced liver injury via intraperitoneal injection of $CCl_4$. The results showed that the aqueous extracts of *Rhizoma phragmitis* alleviated transaminase elevation in a dose-dependent manner. More importantly, the mice treated with 500 mg/kg of extracts showed only a mild inflammatory response and almost normal liver structure. Furthermore, to investigate the safety of *Rhizoma phragmitis*, they treated mice with 2,000 mg/kg of aqueous extracts from *Rhizoma phragmitis* by gavage for 2 weeks and did not find any signs of toxicity or mortality. This experiment fully illustrates the hepatoprotective effect and low toxicity of the aqueous extracts of *Rhizoma phragmitis*. In 2017, Rehman, et al[33] showed that extracts from both *Phragmites* roots and leaves significantly improved $CCl_4$-induced hepatocyte injury.

After an extensive literature analysis, it is now largely established that the main component of *Rhizoma phragmitis* against liver fibrosis is *Rhizoma phragmitis* polysaccharide. Li, et al[54] showed that the protective effect of *Rhizoma phragmitis* polysaccharides on liver cells was mainly achieved by reducing hydroxyproline (HYP) and malondialdehyde (MDA) and increasing SOD and GSH-Px in the liver of rats with liver fibrosis. HYP, an amino acid unique to collagen, is involved in collagen deposition during liver fibrosis. MDA is an important lipid peroxidation indicator. GSH-Px and SOD are two important antioxidant enzymes. Therefore, the anti-hepatic fibrosis effect of *Rhizoma phragmitis* polysaccharides is related to antioxidation and inhibition of collagen deposition. More importantly, they proved that the anti-hepatic fibrosis effect of *Rhizoma phragmitis* polysaccharides can also be achieved by decreasing the expressions of transforming growth factor-beta1 (TGF-β1) and Smad3 and enhancing the expression of Smad7 in liver tissue.[55]

## Lung Protection

With the effect of clearing Fei heat, *Rhizoma phragmitis* is commonly used to treat respiratory diseases such as cough and sore throat.[56] In China, Weijing Decoction (苇茎汤) and Wuye Lugen Decoction (五叶芦根汤) have a long history of treating severe respiratory infection, and are herbal formulas in which *Rhizoma phragmitis* played an important role in the fight against Corona Virus Disease 2019 (COVID-19) in 2020. These decoctions were listed in The Pneumonia Treatment Protocol for Novel Coronavirus Infection (Trial Version 5). The treatment results of 52 cases of COVID-19 in Wuhan also proved that they could significantly improve the symptoms, shorten the course of the disease, and increase the cure rate in patients.[57]

Currently, smoking and air pollution are the main causes of chronic bronchitis, emphysema and chronic obstructive pulmonary disease. In 2008, a study by Wang[12] showed that the extracts from *Rhizoma phragmitis* could be used as an additive to cigarettes to reduce damage to the body as a result of smoking via improving the aroma and reducing irritation. Cao, et al[21] investigated the mechanisms of *Rhizoma phragmitis* in the treatment of chronic bronchitis through network pharmacology and showed that 31 chemical components were present in *Rhizoma phragmitis*, 4 of which inhibited the expression of IL-6, TNF-α, and prostaglandin-endoperoxide synthase 2 (PTGS2) by regulating 139 signaling pathways, such as advanced glycation endproducts-the receptor of advanced glycation endproducts (AGE-RAGE) signaling pathway. To validate further research on the specific mechanism of *Rhizoma phragmitis* for the treatment of chronic bronchitis, Cao, et al[35] conducted *in vitro* and *in vivo* experiments using 16HBE cells exposed to cigarette smoke and a rat model of chronic bronchitis, and showed that *Rhizoma phragmitis* significantly inhibited the expression of TGF-β and IL-6 in human bronchial epithelial cells, reduced the airway inflammatory response, and promoted cellular repair.

## Kidney Protection

The kidney, an important metabolic organ of the human body, is mainly responsible for the elimination of metabolites and certain toxins, most of which can cause kidney damage by inducing overexpression of free radicals.

Jia, et al[36] used different doses of extracts from *Rhizoma phragmitis* to treat rats with kidney stones. The results showed that extracts from *Rhizoma phragmitis* could inhibit the formation of kidney stones by increasing the excretion of calcium oxalate and inhibiting the expression of osteopontin in renal tissue. Interestingly, in this experiment, they found that the serum creatinine of rats with kidney stones that were

treated with *Rhizoma phragmitis* aqueous extracts was significantly reduced and was accompanied by increased SOD expression and decreased MDA expression. In addition, cadmium, a toxic substance, has obvious liver and kidney toxicity. A study conducted by Wang, et al[37] showed that different concentrations of *Rhizoma phragmitis* polysaccharide (120, 240 and 480 mg/kg) had protective effects on cadmium-induced liver and kidney injury in mice. The strongest protective effect was observed at higher doses and was achieved by reducing the expression of MDA and increasing the expression of GSH-Px in the kidney. Therefore, its renal protective effect is also related to antioxidation.

In addition, hyperlipidemia is also an important reason to induce oxidative stress in renal cells. *Rhizoma phragmitis* polysaccharide has the functions of antioxidation, improving lipid metabolism, alleviating urinary protein and reducing glomerular diameter. Therefore, it has certain protective effects against kidney damage of rats caused by a high-fat diet.[58]

## Skin Protection

Aging is natural, and the organ that changes most dramatically during aging is the skin. Studies have shown that aging is mainly the result of oxidative damage to cells.[59] This process results in the gradual dehydration of skin tissues, reduced collagen, and increased pigmentation. Water is an important factor that affects the appearance and function of the skin. The dehydration of skin tissues causes the stratum corneum to lose elasticity and become rough and flaky. Therefore, skin moisture can be used as an indicator to detect skin aging, and retaining skin moisture is important for the treatment of skin diseases.

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease in which subcutaneous hydration is usually less than 10%. Dehydration-induced skin dryness and itchiness are its main features.[60] During the development of AD, Th2 cells induce increased IgE synthesis in B cells by expressing high levels of IL-4 and IFN-γ, ultimately resulting in the host allergic response. A study has shown that topical application of *Rhizoma phragmitis* polysaccharide ointment can significantly improve skin dryness, decrease the number of mast cells, multinucleated leukocytes, and nerve fibers as well as lower the activation of IgE and the expression of cytokines IFN-γ and IL-4 in AD mice.[38] In addition, the mechanisms of action of *Rhizoma phragmitis* polysaccharide in relieving dry skin are related not only to its anti-inflammatory and antioxidant properties but also to its moisturizing effect. Barua, et al[39] mixed *Rhizoma phragmitis* polysaccharide with serine and applied them to the surface of dry skin. The results showed that *Rhizoma phragmitis* polysaccharide could effectively deliver serine into the skin and improve skin hydration. Furthermore, the extracts from *Rhizoma phragmitis* significantly alleviated UV damage to human dermal fibroblasts, and 200 μg/mL extracts showed no significant cytotoxicity.[40] In addition to the skin-protective effects of *Rhizoma phragmitis*, *Phragmites* leaves also have the potential to treat skin diseases and whiten skin. Moreover, study has shown that the extracts from *Phragmites* leaves mainly reduce the intracellular melanin content by inhibiting the cAMP-response element binding protein (CREB)/melanocyte inducing transcription factor (MITF)/tyrosinase signaling pathway in a dose-dependent manner to whiten skin.[61] In addition, polysaccharides, flavonoids and polyphenols in *Rhizoma phragmitis* can also exhibit antiaging effects on the skin by scavenging free radicals such as DPPH• and 2,2'-azinobis-(3-ethylbenzthiazoline-6-sulphonate) ($ABTS^{\bullet+}$).

## Antitumor Activity

Cancer is a major disease that endangers human life. At present, chemotherapy is one of the main methods of treating tumors. Doxorubicin, a paclitaxel antitumor drug, is widely used clinically to treat various malignant tumors, including breast, prostate, ovarian, and lung tumors, but it usually causes serious adverse effects such as myelosuppression-neutropenia.[62] There is now growing evidence that *Rhizoma phragmitis* can significantly enhance the efficacy and reduce the side effects of chemotherapy. Studies have shown that p-hydroxycinnamic acid, a phenylpropanoid compound in *Rhizoma phragmitis*, can significantly ameliorate doxorubicin-induced myelotoxicity such as the reduction in leukocytes, neutrophils, and erythrocytes.[8,63] More importantly, p-hydroxycinnamic acid could promote the proliferation of primary splenocytes and thymocytes with no obvious toxicity to normal human somatic cells (particularly liver cells), which is important for alleviating the immunosuppression of chemotherapy

drugs. In addition, *Rhizoma phragmitis* can effectively ameliorate radiotherapy and chemotherapy-induced vomiting.[64] Therefore, *Rhizoma phragmitis* is an effective complementary therapy for cancer patients undergoing radiotherapy and chemotherapy. More importantly, a recent study showed that hydrophilic AuPt bimetallic nanoparticles (AuPtNPs) prepared from *Phragmites* can significantly enhance the antitumor ability of doxorubicin by approximately thrice more than doxorubicin alone.[65] Interestingly, although previous studies have shown no significant toxicity to normal human cells, tumor cells such as A549 cells, HeLa cells and B16 cells were highly sensitive to the extracts from *Rhizoma phragmitis* and were strongly inhibited.[66] For example, phranisines A and N-p-coumaroyl-tryptamine from *Rhizoma phragmitis* showed significant cytotoxicity against the HeLa cell line, and the half maximal inhibitory concentration ($IC_{50}$) ranged from 13.2 to 18.6 μmol/L.[17] Moreover, moschamindole from *Rhizoma phragmitis* induced apoptosis in glioma cells by blocking mitochondrial oxidative respiration.[18] In addition, *Rhizoma phragmitis* polysaccharide can also induce apoptosis of A549 cells by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway to promote autophagy and the expression of the apoptosis proteins Bax and Caspase-3.[67]

### Immune Regulation

With the deepening understanding of the immune system, the maintenance of immune homeostasis has gradually become the main direction of treatment for most diseases. Therefore, natural medicines such as *Rhizoma phragmitis* with immunomodulatory functions have also become a medical focus. *Rhizoma phragmitis* significantly increased the activity of T cells and natural killer cells, improved the phagocytic function of the reticuloendothelial system in normal mice, and had a strong antagonistic effect on immunosuppression induced by cyclophosphamide.[68,69] In addition, a recent study showed that feeding cows with *Rhizoma phragmitis* can clearly enhance the immune function of cows, improve the activity of SOD in the serum, and significantly increase the levels of protein and fat in milk.[70] More importantly, Kim, et al[63] have determined that p-hydroxycinnamic acid in *Rhizoma phragmitis* can promote the proliferation of spleen cells and thymocytes and is the main active component in enhancing the immune function of the body.

## Toxic Side Effects

At present, few studies on *Rhizoma phragmitis* have reported toxic effects. To test the genotoxicity of *Rhizoma phragmitis*, Kim, et al[41] conducted a bacterial reverse mutation test with nutritionally deficient mutant strains of *Salmonella typhimurium* and *Escherichia coli*, and a chromosome aberration test with lung cells in Chinese hamsters. Meanwhile, a micronucleus test was performed with bone marrow cells from male mice that were orally treated with the extracts from *Rhizoma phragmitis*. The results showed no genotoxic phenomena in either the bacterial reverse mutation at concentrations up to 5,000 μg/plate of the extracts or the chromosomal aberration test at concentrations up to 500 μg/mL. In addition, oral administration of 5,000 mg/kg aqueous extracts of *Rhizoma phragmitis* for 2 days did not result in weight changes, mortality or bone marrow cell abnormalities in mice. Certainly, a high oral dose of 2 days may not be sufficient to cause a chronic toxic event. Unfortunately, there are no similar experiments on the extracts of *Rhizoma phragmitis* to study its toxic effects during long-term oral administration at high doses. However, Mazumder, et al[30] performed an animal toxicity study on high doses of extracts from the aerial part of *Phragmites australis*, in which they treated DM mice with high doses (2,000 and 5,000 mg/kg) by gavage for 28 days. The results showed that 2,000 mg/kg *Phragmites australis* did not damage the liver or kidney of mice, but when the dosage reached 5,000 mg/kg, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in the serum of mice increased significantly, and the liver, kidney and spleen showed inflammatory reactions, cell necrosis and even structural disorders. Interestingly, the mice in the experimental group did not die, although they showed obvious organ damage. In conclusion, the median lethal dose ($LD_{50}$) >5,000 mg/kg already proves that it is a very safe medicine. Moreover, the aerial part of *Phragmites australis* and *Rhizoma phragmitis* are two different parts of *Phragmites*, so the toxicity of the aerial part of *Phragmites australis* is not representative of the toxicity of *Rhizoma phragmitis*. In addition, Mazumder, et al[30] proved that high-dose extracts from the aerial part of *Phragmites australis* causes liver and kidney damage, but the protective effect of its low dose (150 and 300 mg/kg) on the liver and kidney was also demonstrated. Therefore, it may be necessary to further explore the safety of

*Rhizoma phragmitis*.

## Discussion

*Rhizoma phragmitis*, a common perennial grass plant, is distributed worldwide. It has a history of clinical application in China for thousands of years and is characterized by its wide distribution, broad pharmacological activity, low price and low toxicity. At present, more than 83 compounds have been isolated and identified from *Rhizoma phragmitis*. Among them, *Rhizoma phragmitis* polysaccharide is the most widely studied compound. The literature on pharmacological studies indicates that *Rhizoma phragmitis* has pharmacological activities such as anti-inflammatory, antibacterial, antiviral, hepatic and renal protective, skin protective and antitumor activity. However, there are still some problems in the development of new drugs related to *Rhizoma phragmitis* that need to be further studied and explored. First, all current studies have shown that *Rhizoma phragmitis* is a safe herbal medicine. As a natural herb, there is a high possibility that some unknown toxic components exist in *Rhizoma phragmitis*, so its potential toxicity needs to be further investigated in the future. Second, whether the active ingredients and pharmacological effects obtained from the above studies are reproducible and meaningful deserves further validation. Third, CM has multicomponent, multitarget and multichannel characteristics. In addition to the 83 compounds and various targets mentioned in this review, there are some new compounds and targets to be identified in follow-up studies. Although pharmacological activities, including anti-inflammatory, antioxidant, hypolipidemic, hypoglycemic, antiviral, and antitumor activities support its traditional uses in the treatment of diseases such as DM, tumors, and AD, modern pharmacology is needed to investigate other traditional uses such as antiemetic and diuretic. Finally, although Wuye Lugen Decoction and Weijing Decoction, which use *Rhizoma phragmitis* as the monarch medicine, have anti-novel coronavirus effects, the exact mechanisms remain to be investigated.

## Conflict of Interest

All the authors declare that there is no conflict of interest regarding the publication of this paper.

## Author Contributions

Ren Y drafted the manuscript. Cui GD was responsible for the literature screening and data extraction of this paper. Yao H and Zi CY were responsible for proofreading of the article. Gao YX and He LS revised and commented on the manuscript. All authors have read and approved the final version for publication.

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