

Therapeutic Effects of Traditional Chinese Medicine on Glioma: A Case Study of Phlegm-removing and Phlegm-resolving Herbs

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Abstract—Glioma is the most prevalent and aggressive primary malignant tumor of the central nervous system, with a dismal clinical prognosis. Current standard treatments, including surgical resection, radiotherapy, and chemotherapy, have long been limited, severely constrained by the blood-brain barrier, drug resistance, and unavoidable systemic adverse effects. However, in Traditional Chinese Medicine (TCM), the accumulation of the phlegm-dampness pathogen is identified as a core pathogenetic mechanism of glioma. This paper systematically elucidates the anti-glioma effects and pharmacological mechanisms of Chinese medicinal herbs that expel phlegm, such as centipede and radish seed, among others. This paper summarizes their main ingredients, key therapeutic targets, and signaling pathways, and accordingly provides theoretical support for TCM clinical application in glioma treatment. The results of this study confirm that phlegm-resolving and phlegm-dissipating Chinese medicines have definite therapeutic effects on glioma, and their anti-tumor activities are mainly mediated by various active substances acting on multiple molecular targets and signaling pathways.

Keywords—glioma, expectorant, phlegm-resolving drug, traditional Chinese medicine, Chinese material medica

I. INTRODUCTION

As a life-threatening tumor, glioma is a challenge of clinical treatment due to its complex pathological characteristics, high recurrence rate and high fatality rate. Clinical practice has shown that existing therapeutic strategies are unlikely to achieve radical cure, and long-term use often brings severe side effects; furthermore, this reduces the quality of life of patients. Traditional Chinese medicine (TCM) has been proven to provide a unique theoretical system for the prevention and treatment of tumors. Among phlegm-dissipating herbs, for example, Semen Lepidii has been widely used in the treatment of glioma due to its mild efficacy and low toxicity. In recent years, relevant basic and clinical studies have gradually increased, but there is still a lack of in-depth exploration of the multi-target and

multi-pathway regulatory effects of these herbs, and the correlation between their efficacy and TCM syndrome differentiation has not been fully elaborated [1].

This paper mainly adopts the method of literature collation and mechanism analysis, focusing on the representative phlegm-resolving and phlegm-dissipating herbs. The core research question is to explore the specific regulatory mechanisms of these herbs on glioma cells and the tumor microenvironment, and clarify the material basis of their therapeutic effects.

This paper is expected to enrich the theoretical system of TCM in treating glioma, to provide more targeted theoretical support for clinical application, and to lay a foundation for the development of new TCM preparations against glioma.

II. ACTIVE SUBSTANCES AND ACTION MECHANISMS OF PHEGDM-DISSIPATING TCM FOR GLIOMA

A. Main Anti-Glioma Active Components of Representative Phlegm-Expelling and Resolving Herbs

Modern pharmacological studies have confirmed that the core mechanism of phlegm-expelling and resolving herbs against glioma lies in their various natural active components, which serve as the material basis of their therapeutic effects. The following are representative phlegm-expelling and resolving herbs that have been studied in depth, along with their active components.

As a representative herb for calming wind and relieving convulsion and dissipating phlegm and resolving masses, Scolopendra has core anti-glioma active components that mainly include Scolopendra polypeptides, Scolopendra venom proteins, and fatty acid compounds. Among them, Scolopendra polypeptides can inhibit the malignant biological behaviors of glioma cells through multiple pathways and are the most extensively studied active components [2]. The core active component of *Raphani Semen* is sulforaphane, an isothiocyanate compound, which is the key substance for its effects of resolving phlegm and descending qi and resisting tumors. The main active components of *Lepidii Semen* include flavonoids, cardiac glycosides, and volatile oils; among them, flavonoids such as quercetin and isorhamnetin have been proven to exert significant

anti-glioma effects [3]. In addition, alkaloids in *Arisaematis Rhizoma*, pinellia protein in *Pinelliae Rhizoma*, peimine/peiminine in *Fritillariae Thunbergii Bulbus*, and triterpenoid saponins in *Trichosanthis Fructus* have all been confirmed to possess anti-glioma activities to varying degrees [4, 5].

B. Core Action Targets of Active Components in Phlegm-Expelling and Resolving Herbs

Active components of phlegm-expelling and resolving herbs exert multi-target regulatory effects by acting on key targets in the occurrence and development of glioma, a notion that aligns with the theoretical characteristics of holism and syndrome differentiation-based treatment in TCM. The confirmed core action targets are mainly divided into the following categories:

First, targets related to cell cycle and apoptosis, including Bcl-2/Bax family proteins, Caspase family proteases, p53 gene, Cyclin family proteins, etc. Among them, sulforaphane can induce glioma cell apoptosis by upregulating the expression of the pro-apoptotic protein Bax, downregulating the expression of the anti-apoptotic protein Bcl-2, and activating the Caspase-3 and Caspase-9 apoptotic pathways [6]. Second, targets related to cell invasion and migration, including matrix metalloproteinases MMP-2/MMP-9, vascular endothelial growth factor VEGF, TGF- β /Smad pathway-related proteins, etc. Scolopendra polypeptides can significantly downregulate the expression of MMP-2 and MMP-9, inhibiting the invasion and migration of glioma cells [7]. Third, targets related to tumor immunity and inflammation, including the NF- κ B signaling pathway, TLR4 receptor, PD-1/PD-L1 immune checkpoints, and inflammatory factors such as IL-6/IL-1 β , etc. [8]. Quercetin in *Lepidii semen* can regulate the immune microenvironment of glioma by inhibiting the activation of the NF- κ B signaling pathway and reducing the release of pro-inflammatory factors. In addition, there are targets related to multidrug resistance, such as MDR1/P-glycoprotein, which are active components of a notion that aligns with the theoretical characteristics of holism and syndrome differentiation-based treatment in TCM. Phlegm-expelling and resolving herbs can reverse chemotherapy resistance in glioma cells by downregulating the expression of this target [9, 10].

In addition to the above-mentioned multi-target regulatory mechanisms, whether the active components of phlegm-expelling and resolving herbs can effectively cross the blood-brain barrier to reach intracranial lesions is another key prerequisite for their anti-glioma effects. The Blood-Brain Barrier (BBB) is a natural barrier composed of brain capillary endothelial cells, basement membrane, and astrocytic foot processes. While protecting the central nervous system, it also becomes the major obstacle for intracranial delivery of anti-glioma drugs—over 98% of small-molecule drugs and almost all macromolecular drugs cannot effectively penetrate the BBB. Therefore, the ability to effectively cross the BBB is a key prerequisite for active components of phlegm-expelling and resolving herbs to exert intracranial anti-glioma effects.

Existing studies have confirmed that many active components of phlegm-expelling and resolving herbs possess natural BBB-penetrating ability. As a small-molecule lipophilic compound with a molecular weight of only 177.29 Da, sulforaphane can effectively cross the BBB via passive diffusion and reach effective drug concentrations in brain tissue. Scolopendra polypeptides, which are small-molecule polypeptides, can cross the BBB through receptor-mediated transcellular transport; meanwhile, they can transiently open the BBB by regulating the expression of tight junction proteins, thereby improving the intracranial delivery efficiency of these peptides and co-administered chemotherapeutic drugs. In addition, components such as *Arisaema* alkaloids and pinellia polysaccharides have also been proven to have certain BBB-penetrating capacity, which is an important reason for the unique advantages of phlegm-expelling and resolving herbs in glioma treatment [11, 12].

Based on current basic research findings, phlegm-expelling and resolving herbs exert anti-glioma effects through multi-target and multi-pathway synergistic regulation in multiple dimensions: inhibiting malignant biological behaviors of tumor cells, regulating the tumor microenvironment, reversing drug resistance, and improving BBB permeability. Their core pharmacological mechanisms can be divided into four aspects.

C. Inhibiting Proliferation, Invasion and Migration of Glioma Cells, and Inducing Apoptosis

Unlimited proliferation, high invasiveness, and high migration are the core malignant biological characteristics of glioma cells, as well as the fundamental causes of high postoperative recurrence and poor prognosis. Active components of phlegm-expelling and resolving herbs can curb the malignant phenotype of glioma cells by regulating the cell cycle, activating intrinsic/extrinsic apoptotic pathways, and inhibiting Epithelial-Mesenchymal Transition (EMT).

Sulforaphane can arrest glioma cells in the G2/M phase, inhibiting mitosis and proliferation, and simultaneously induce glioma cell apoptosis through the mitochondrial apoptotic pathway by activating the Caspase cascade. Scolopendra polypeptides can significantly inhibit the EMT process of glioma cells, downregulate the expression of mesenchymal markers such as N-cadherin and vimentin, and upregulate the expression of epithelial markers such as E-cadherin, thereby inhibiting cell invasion and migration. Flavonoids in *Lepidii Semen* can block proliferation signal transduction in glioma cells by inhibiting the activation of PI3K/Akt/mTOR signaling pathway, and induce autophagic cell death. In addition, active components of *Pinelliae Rhizoma* and *Arisaematis Rhizoma* have also been confirmed to inhibit glioma cell proliferation and induce apoptosis by regulating the MAPK signaling pathway [11, 12].

D. Regulating the Tumor Immune Microenvironment of Glioma and Exerting Anti-Tumor Immune Effects

The tumor immune microenvironment of glioma is characterized by significant immunosuppression, with

massive infiltration of immunosuppressive cells such as Tumor-Associated Macrophages (TAMs) and regulatory T cells (Tregs) and high expression of immune checkpoint molecules, which prevents the body from effectively initiating anti-tumor immune responses—this is the core reason for the poor efficacy of glioma immunotherapy. Phlegm-expelling and resolving herbs can reverse the immunosuppressive state and exert anti-tumor immune effects by multidimensionally regulating the immune microenvironment of glioma.

Quercetin in *Lepidii semen* can inhibit the polarization of M2-type TAMs, promote their transformation to M1-type anti-tumor phenotype, reduce the infiltration of Tregs in tumor tissues, increase the infiltration ratio of CD8⁺ cytotoxic T cells, and restore the body's anti-tumor immune response. Sulforaphane can significantly downregulate the expression of PD-L1 in glioma cells, block the PD-1/PD-L1 immune checkpoint pathway, relieve the immunosuppressive state of T cells, and enhance their killing effect on glioma cells. Scolopendra polypeptides can improve the chronic inflammatory state of the tumor microenvironment and block inflammation-mediated tumor progression by inhibiting the NF- κ B signaling pathway and reducing the release of pro-inflammatory factors such as IL-6, IL-1 β , and TNF- α [11–13].

Beyond these well-characterized anti-tumor immune mechanisms at the cellular and molecular levels, the clinical efficacy and safety of phlegm-expelling and resolving method in the comprehensive treatment of glioma have also been extensively verified in numerous clinical studies. A number of clinical studies have confirmed that TCM treatment centered on the phlegm-expelling and resolving method combined with conventional therapy can significantly improve clinical outcomes for glioma patients with a favorable safety profile. A randomized controlled trial including 120 postoperative patients with high-grade glioma showed that, based on temozolomide concurrent radio chemotherapy, patients treated with combined TCM decoction for dissipating phlegm and resolving masses, reinforcing healthy qi, and eliminating pathogenic factors had significantly higher 1-year progression-free survival rates and 2-year overall survival rates than those in the radio chemotherapy alone group. Meanwhile, patients' KPS functional status scores were significantly improved, and the incidence of gastrointestinal reactions, myelosuppression, and liver function injury induced by radio chemotherapy was significantly reduced [14].

Another clinical study on recurrent glioma patients showed that TCM compound prescriptions centered on phlegm-expelling and resolving herbs such as *Pinelliae Rhizoma*, *Arisaematis Rhizoma* and *Scolopendra*, combined with temozolomide chemotherapy, achieved significantly higher objective response rates and disease control rates than those the chemotherapy alone group. The median progression-free survival and median overall survival of patients were significantly prolonged without increasing adverse reactions [15]. In addition, multiple clinical observations have confirmed that

phlegm-expelling and resolving herbal prescriptions can effectively relieve clinical symptoms such as headache, dizziness, and epileptic seizures in glioma patients, improve neurological deficits, enhance the quality of life, and have good safety with no obvious liver or kidney function damage after long-term use.

Although the phlegm-expelling and resolving method combined with conventional therapy exhibits definite therapeutic advantages and favorable safety in the clinical treatment of glioma, its clinical translation and standardized promotion still face numerous key problems that need to be urgently addressed. Although phlegm-expelling and resolving herbs have shown significant advantages and application prospects in the clinical treatment of glioma, many problems still exist in their clinical application. First, the quality of clinical research is uneven. Most studies are small-sample, single-center clinical observations, while high-quality large-sample, multi-center, randomized double-blind controlled studies are scarce, leading to an insufficient level of evidence-based medicine and difficulty in forming unified clinical diagnosis and treatment guidelines and medication norms. Second, there is a lack of unified standards for TCM syndrome differentiation. Different physicians vary greatly in syndrome differentiation, therapeutic principles and prescription selection for glioma, making clinical research results difficult to replicate and compare horizontally, which is not conducive to the promotion and standardized application of the phlegm-expelling and resolving therapy. In addition, the clinical application of phlegm-expelling and resolving herbs is mostly in the form of compound decoctions; the compatibility mechanism, dose-effect relationship, and in vivo metabolic process of compounds have not been fully clarified, hindering the realization of precise and individualized medication.

E. Reversing Chemotherapy Resistance of Glioma and Enhancing Radio Chemotherapy Sensitivity

Chemotherapy resistance is one of the core dilemmas in the clinical treatment of glioma. The incidence of primary and secondary resistance to first-line chemotherapeutic drugs such as temozolomide is extremely high in patients with high-grade glioma, and this resistance is the main cause of chemotherapy failure and tumor recurrence. Phlegm-expelling and resolving herbs can reverse chemotherapy resistance in glioma cells through multiple mechanisms and exert synergistic effects when combined with conventional radio chemotherapy.

The resistance of glioma cells to temozolomide is mainly related to high expression of O6-Methylguanine-DNA Methyltransferase (MGMT), enhanced DNA damage repair ability, and high expression of multidrug resistance protein P-gp. Sulforaphane can significantly downregulate the expression and activity of MGMT, inhibit the DNA damage repair ability of glioma cells, enhance the cytotoxicity of temozolomide against glioma cells, and reverse temozolomide resistance. Scolopendra polypeptides can downregulate the expression of P-gp protein, reduce the efflux of chemotherapeutic drugs,

increase the effective concentration of chemotherapeutic drugs in cells, and inhibit DNA damage repair in tumor cells, thereby enhancing radiosensitivity [16]. In addition, peimine and peiminine in *Fritillariae Thunbergii* Bulbus can act as inhibitors of P-gp protein, reverse multidrug resistance in glioma cells, and exert significant synergistic effects when combined with chemotherapeutic drugs [17].

F. Improving Blood-Brain Barrier Permeability and Enhancing Intracranial Drug Delivery Efficiency

The existence of the BBB not only restricts the intracranial delivery of chemotherapeutic drugs but also prevents targeted drugs and immunotherapeutic drugs from reaching effective therapeutic concentrations in the brain, thereby severely limiting the clinical efficacy of glioma treatment. Phlegm-expelling and resolving herbs can not only cross the BBB themselves but also improve its permeability by regulating the structure and function of the BBB, enhancing the intracranial delivery efficiency of combined drugs—this is their unique advantage in glioma treatment [11].

Scolopendra polypeptides can transiently and reversibly open the BBB by downregulating the expression of tight junction proteins Occludin and Claudin-5 in BBB endothelial cells, significantly increasing the concentration of combined temozolomide in brain tissue and enhancing its intracranial anti-tumor effect. Sulforaphane can regulate the cytoskeleton of BBB endothelial cells by inhibiting the RhoA/ROCK signaling pathway, reducing transendothelial electrical resistance, and improving BBB permeability without causing irreversible damage to the central nervous system. In addition, volatile oil components of *Arisaematis Rhizoma* and *Pinelliae Rhizoma* can promote drug transport across the BBB through liposome fusion, serving as ideal intracranial drug delivery carriers [12].

III. CLINICAL APPLICATION RESEARCH OF PHLEGM-EXPPELLING AND RESOLVING HERBS IN THE TREATMENT OF GLIOMA

At present, the routine clinical treatment regimen for glioma follows the Chinese Guidelines for the Diagnosis and Treatment of Central Nervous System Glioma (2022 Edition), adopting maximal safe surgical resection followed by concurrent radio chemotherapy plus adjuvant chemotherapy. However, this regimen cannot completely eradicate the tumor; moreover, adverse reactions such as myelosuppression, gastrointestinal reactions, and neurotoxicity caused by radio chemotherapy severely affect patients' quality of life, and the high recurrence rate remains the greatest clinical challenge. As an adjuvant therapy, traditional Chinese medicine has been widely used in the whole course of glioma treatment, among which prescriptions based on the phlegm-expelling and resolving method are the most applied.

Clinically, phlegm-expelling and resolving herbal prescriptions are mainly used in three stages: first, the

postoperative adjuvant therapy stage, in which patients present with deficient healthy qi and unresolved residual phlegm-stasis-toxin; the treatment focuses on dissipating phlegm and resolving masses as well as reinforcing healthy qi and consolidating the foundation, thereby reducing the risk of tumor recurrence and promoting postoperative recovery. Second, the concurrent radio chemotherapy stage, with a focus on resolving phlegm and harmonizing the stomach, as well as invigorating the spleen and replenishing qi, alleviating adverse reactions such as nausea, vomiting and myelosuppression caused by radio chemotherapy, and improving patients' treatment tolerance and compliance. Third, the advanced palliative care stage, for patients with recurrent high-grade glioma who are inoperable or have failed radio chemotherapy; treatment focuses on dissipating phlegm and resolving masses and removing toxicity and unblocking collaterals, relieving clinical symptoms such as headache and epilepsy, prolonging survival time, and improving quality of life.

IV. CONCLUSION

As the most common primary malignant tumor of the central nervous system, glioma has long been confronted with challenges including limited BBB penetration, chemotherapy resistance, high recurrence rate, and poor prognosis in clinical treatment, and existing conventional therapies have difficulty achieving fundamental breakthroughs. With its unique theoretical system and multi-target, multi-pathway advantages with low toxicity, TCM provides new ideas and directions for glioma treatment. This study systematically reviews and analyzes the TCM theoretical basis, active components, molecular pharmacological mechanisms and clinical application status of phlegm-expelling and resolving herbs in glioma treatment. It clarifies that "accumulation of turbid phlegm" is the core pathogenesis of glioma and that the phlegm-expelling and resolving method is the core therapeutic principle in TCM for glioma. It also elucidates the core mechanisms of these herbs against glioma from multiple aspects: inhibiting the malignant behaviors of tumor cells, regulating the tumor immune microenvironment, reversing chemotherapy resistance, and improving BBB permeability, thereby providing systematic theoretical support for their clinical application in glioma treatment.

This study finds that the anti-glioma effects of phlegm-expelling and resolving herbs have distinct characteristics: first, a clear material basis—many active components have been proven to exert significant anti-glioma effects, and most possess natural BBB-penetrating ability, solving the core problem of intracranial drug delivery in glioma treatment. Second, synergistic multi-target and multi-pathway mechanisms—these mechanisms act on multiple key links of glioma occurrence and development simultaneously, rendering them less prone to drug resistance compared with single-target targeted drugs. Third, a high clinical safety profile—with a long clinical application history, mild medicinal properties and low incidence of adverse

reactions, they can be combined with conventional therapy throughout the treatment course, possessing irreplaceable advantages in enhancing efficacy, reducing toxicity and improving patients' quality of life.

Meanwhile, this study also reveals obvious limitations in current research on phlegm-expelling and resolving herbs for glioma. In basic research, most studies focus on in vitro cell experiments of single active components, while research on the synergistic mechanisms of TCM compound compatibility, the in vivo pharmacokinetic characteristics of active components, and specific processes and regulatory mechanisms of crossing the BBB is still insufficient. In clinical research, high-level evidence is lacking, and there is a lack of unified standards for syndrome differentiation and medication norms, which hinders standardized and precise clinical application.

Future research can focus on three directions: first, conduct in-depth research on the synergistic mechanisms of phlegm-expelling and resolving herb compound compatibility, clarify the multi-component and multi-target synergistic rules in compounds based on TCM compatibility theory, and provide a scientific basis for clinical prescription. Second, carry out high-quality large-sample, multi-center, randomized double-blind controlled clinical studies, formulate unified TCM syndrome differentiation standards and clinical diagnosis and treatment norms, improve the level of evidence-based medical, and promote the standardized clinical application of the phlegm-expelling and resolving therapy. Third, develop new TCM preparations with high BBB permeability based on active components of phlegm-expelling and resolving herbs, such as nano-preparations, liposomes, and brain-targeted drug delivery systems, further improving intracranial drug delivery efficiency and therapeutic effects, and providing new drug options for glioma treatment.

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