

# *Advancements in the Research Status of the Application of Polygonatum Sibiricum Granules*

Yuqing Shu<sup>1,a</sup>, Jiahao Cheng<sup>2</sup>, Bochao Yan<sup>2</sup>, Lihan Zheng<sup>2</sup>, Anqi Jiang<sup>2</sup>, Haiyin Jiang<sup>3,b,\*</sup>

<sup>1</sup> School of Public Health, Hangzhou Medical College, Hangzhou, Zhejiang, 311399, China

<sup>2</sup> Hangzhou Medical College, Hangzhou, Zhejiang, 311300, China

<sup>3</sup> College of Pharmacy, Hangzhou Medical College, Hangzhou, Zhejiang, 311300, China

<sup>a</sup>2173962741@qq.com, <sup>b</sup>2020000298@hmc.edu.cn

\*Corresponding author

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**Abstract:** Polygonatum sibiricum, a traditional Chinese medicine with food-medicine homology, contains various bioactive components beneficial to human health, such as polysaccharides, saponins, anthraquinones, alkaloids, cardenolides, lignans, vitamins, etc. Polygonatum sibiricum granules are a Chinese patent medicine prepared from the dried rhizomes of Polygonatum sibiricum. They exhibit extensive pharmacological activities, including nourishing Yin, benefiting the kidney, tranquilizing the mind, and modulating the immune system. In recent years, there has been growing attention to the research on Polygonatum sibiricum granules. Clinically, they have been used as an adjuvant therapy for various diseases involving the urinary, endocrine, cardiovascular, and digestive systems. Current research focuses on three main areas: pharmacological effects, drug-drug interactions, and clinical applications of Polygonatum sibiricum granules. This paper reviews the research progress on the compatibility of Polygonatum sibiricum granules and their clinical applications, aiming to provide references for researchers involved in the development of Polygonatum sibiricum granules.

## 1. Introduction

Polygonatum sibiricum (PS) is a commonly used medicinal herb. Its extracts possess many beneficial pharmacological activities and have been widely used for treating diseases such as diabetes, cancer, hypercholesterolemia, and inflammation. Among the major bioactive components in Polygonatum sibiricum, Polygonatum sibiricum polysaccharide (PSP) stands out, exhibiting various pharmacological activities, including immunomodulation, antioxidant, antimicrobial, and anti-inflammatory effects. Clinically, PSP has been used for diseases like diabetes, osteoporosis, and atherosclerosis. The bioactivities of polysaccharides are closely related to their complex structures, including molecular weight, monosaccharide composition, glycosidic bonds, substituents, and degree of branching. Polygonatum sibiricum granules are a novel dosage form developed based on traditional decoctions and syrups. They overcome the shortcomings of traditional formulations, such as inconvenience in administration, portability, dispensing, and inaccurate dosing. As a result, they are

suitable for a wider population, especially children who prefer meat and high-calorie processed food. As an adjuvant therapy, *Polygonatum sibiricum* granules can moisten the lungs, invigorate the spleen, and enhance immunity in children, thereby reducing the recurrence of respiratory infections. Currently, there is no published review on the prescription compatibility and clinical application of *Polygonatum sibiricum* granules. Therefore, conducting a review in this field is innovative and valuable.

## **2. Pharmacological Action**

### **2.1 Antioxidation**

Various reactive oxygen species, including superoxide anion radicals, hydroxyl radicals, hydrogen peroxide, and singlet oxygen, are generated during oxidative metabolism in organisms. Among them, lipid peroxidation is particularly detrimental to cells. To counteract these harmful effects, the human body possesses a sophisticated antioxidant system that eliminates free radicals through both enzyme and non-enzyme reactions. A study on the effects of *Polygonatum sibiricum* polysaccharide (PSP) on antioxidant indexes in rat serum and skeletal muscle[1] showed that PSP could significantly decrease malondialdehyde content and increase the activities of endogenous superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in rat serum, as well as SOD activity in skeletal muscle. These results demonstrate the antioxidant capacity of polysaccharides in *P. sibiricum*, enabling them to scavenge free radicals, inhibit lipid peroxidation, and reduce tissue damage, thereby contributing to overall health maintenance.

### **2.2 Antibacterial**

*Polygonatum sibiricum* polysaccharides have exhibited potent antibacterial properties, effectively inhibiting various bacteria, including *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Staphylococcus aureus aureus* [2]. Su et al.[3] used the paper disc diffusion method to investigate the inhibitory effects of *Polygonatum sibiricum* polysaccharides on common bacteria. The results showed that *P. sibiricum* polysaccharides exhibited significant inhibitory effects on *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus* and *Salmonella typhimurium*. Peng et al.[4] established models of keratoconjunctivitis and corneal inflammation in rabbits, and utilized various acute and subacute inflammatory models to study the anti-inflammatory pharmacology of *P. sibiricum* polysaccharides. Their results validated the remarkable anti-inflammatory effects of *P. sibiricum* polysaccharides.

### **2.3 Anti-tumor or Anti-cancer**

Studies on the effects of *P. sibiricum* granules in eliminating "low calcium and high phosphorus" status and treating kidney Yin-Yang deficiency[5] showed that miR-142-3p exists in thyroid cancer cells, and the thyroid gland is involved in regulating calcium and phosphorus levels. After taking *P. sibiricum* granules, miR-142-3p was downregulated, while the highly expressed inhibitory cytokines D1 and G0/G1 phase cells were upregulated, effectively inhibiting the proliferative ability of thyroid cancer cells. Therefore, miR-142-3p acts as a tumor suppressor in thyroid cancer cells. The mechanism involves the transfection of NC mimics, miR-142-3p mimics, and miR-142-3p inhibitors into cells for MTT and colony formation assays. High expression of miR-142-3p significantly inhibited cell proliferation and clone formation, while inhibition of miR-142-3p increased cell proliferation and clone formation. Cell cycle analysis and cyclin D1 western blot analysis revealed that upregulated expression of miR-142-3p inhibited the expression of cyclin D1, leading to cell cycle

arrest at the G0/G1 phase. MiR-142-3p inhibits cell division by suppressing cyclin D1 expression, thereby restraining cell proliferation. Consequently, miR-142-3p acts as a tumor suppressor in thyroid cancer.

### 3. Drug Interaction Research

Several studies have focused on the interactions between *P. sibiricum* and various co-administered drugs. *P. sibiricum* supplements Qi, nourishes Yin, invigorates the spleen and moistens the lungs[6]. *P. sibiricum* and wolfberry prepared as granules using dry paste and microcrystalline cellulose at 2:1 ratio significantly antagonized blood glucose levels in vivo[7]. Additionally, *P. sibiricum* combined with several drugs can exert synergistic effects and improve therapeutic efficacy. For example, when *Vaccinium vitis idaea* and *P. sibiricum* are used together at a 5:1 ratio, they can increase calcium and phosphorus ion levels and show good effects for patients with kidney Yin-Yang deficiency (manifested as aversion to cold, cold limbs, weakness, and emaciation)[8]. Furthermore, the combination of *P. sibiricum* polysaccharide and *Tripterygium wilfordii* glycoside in granule form enhances the effects of dispelling rheumatism-heat, activating blood circulation, eliminating swelling, and alleviating pain. It regulates the imbalance of Yin and Yang in the kidney, and promotes the repair of reproductive tissue damage caused by diseases in females[9].

### 4. Clinical Application

#### 4.1 Blood Glucose Lowering

Granules prepared from *P. sibiricum* and wolfberry in a 1:1 ratio significantly reduced blood glucose in type 2 diabetic patients[10]. By regulating the balance of Qi, blood, Yin, and Yang in the body, *P. sibiricum* granules effectively improve immune function, regulate lipid metabolism, and reduce serum inflammatory cytokine levels in children. They demonstrate significant therapeutic effects on lung, spleen, and kidney Qi deficiency, as well as blood weakness, wind, dampness, heat, and blood stasis in pediatric nephrotic syndrome, surpassing the use of glucocorticoids alone. This is particularly beneficial as children have low immunity, making them prone to disease recurrence and poor medication adherence. [11]. *P. sibiricum* granules can also reduce plasma viscosity, maximum platelet aggregation rate and fibrinogen levels, lower serum levels of C-reactive protein, improve clinical symptoms in children with allergic purpura, and alleviate kidney damage [12]. As an adjuvant therapy, *P. sibiricum* granules are used to treat multiple tics, systemic lupus erythematosus (by regulating B cell numbers and lowering serum levels of cell-activating factors and interleukin-10), as well as severe infectious myocarditis. Additionally, they improve left ventricular ejection fraction and enhance cardiac function in children.

#### 4.2 Treating Asthma

Granules prepared from *Polygonatum sibiricum*, *Lycium barbarum* and *Sophora alopecuroides* (*Sophora alopecuroides* and *Polygonatum Sibiricum* Granules)[13], Downregulate levels of IgE, IL-4 and IL-17, reduce Th0 cell differentiation into Th2 cells, promote Th1 cell differentiation and expression, and inhibit Th2 cell expression [14]. Simultaneously, *P. sibiricum* granules reduce eosinophil counts, alleviate respiratory mucosal injury, decrease secretions, improve intrapulmonary gas exchange, reduce airway permeability, enhance immunity, attenuate airway inflammatory responses, and ameliorate airway reactivity symptoms[15]. By reducing respiratory infections and asthma attacks in children, *Sophora alopecuroides* and *Polygonatum Sibiricum* Granules serve as an adjuvant therapy for asthma. Xu et al.[16] found that when this granule is combined with ICS

atomization treatment, it enhances lung function and relieves bronchial asthma in children. *P. sibiricum* exhibits effects of moistening the lungs, nourishing the kidneys, benefiting the liver, replenishing Qi, and strengthening bones and muscles. It is a sweet and mild herb. On the other hand, *S. alopecuroides* is acrid and mild, entering the lung, spleen, and kidney channels, and it is non-toxic. The combination of these two herbs complements each other, and the prepared granules have the effects of benefiting Qi and nourishing Yin, regulating Qi and Yin, invigorating the essence of the five zang organs, and moistening the organs and Yin fluid. Consequently, this granule relieves the adverse effects of ICS, including expanded bronchi in children, inhibited height growth due to bronchial smooth muscle spasms, pharyngitis, and oral fungal infections.

### 4.3 Therapeutic Efficacy and Reinfection Rate of *Mycoplasma pneumoniae* Pneumonia

*Sophora alopecuroides* and *Polygonatum Sibiricum* Granules have been widely used in pediatric clinical departments. They show good therapeutic effects on mycoplasma pneumonia, reduce inflammatory factors, and lower recurrence rate of infections[17]. They effectively alleviate symptoms of bronchiolitis (mainly manifested as dyspnea, cough, expectoration and low fever). The mechanisms are mainly four-fold:

- **Antibacterial activity:** *Sophora alopecuroides* and *Polygonatum sibiricum* granules contain active ingredients with antibacterial properties. These ingredients disrupt pathogen growth and reproduction while blocking their metabolic pathways, leading to a reduction in their numbers and activities. Consequently, the granules exert direct inhibitory effects on *mycoplasma pneumoniae*.
- **Inhibiting biofilm formation:** The biofilm formed on the surface of *mycoplasma pneumoniae* protects the bacteria from external environmental impacts, leading to increased drug resistance and survival. However, components in *Sophora alopecuroides* and *Polygonatum Sibiricum* Granules can interfere with biofilm formation and stability. These components disrupt bacterial aggregation and adhesion, thereby weakening bacterial viability.
- **Promoting immune responses:** *Sophora alopecuroides* and *Polygonatum Sibiricum* Granules have immunomodulatory effects, enhancing immune responsiveness. When *mycoplasma pneumoniae* invades the respiratory tract, these granules stimulate the activation and proliferation of immune cells, increase the production of immune factors, and heighten pathogen recognition and clearance by the body.
- **Interfering with pathogen metabolism:** The active ingredients in *Sophora alopecuroides* and *Polygonatum Sibiricum* Granules interfere with the metabolic pathways of *mycoplasma pneumoniae*, affecting its growth and replication. These ingredients disrupt bacteria's key steps like protein synthesis, nucleic acid metabolism and cell wall synthesis, thereby inhibiting pathogen growth. Clinical studies by Du et al.[18] , Li et al.[19] and Wang et al[20] found that this granule effectively improves clinical symptoms of respiratory syncytial virus bronchiolitis in children by increasing levels of immunoglobulin A, immunoglobulin G, immunoglobulin M and immunoglobulin E, and decreasing expression of interleukin G17 and interleukin G23.

*Sophora alopecuroides* and *Polygonatum Sibiricum* Granules combined with montelukast sodium prevent asthma bronchitis and reduce recurrence of the disease [21,22]. Scholars widely recognize that *Sophora alopecuroides* and *Polygonatum Sibiricum* Granules enhance humoral and cellular immune regulation, improve immune function in children, prevent recurrence of respiratory infections, and reduce disease relapse rates [23-27].

## 5. Conclusion

*Polygonatum sibiricum* possesses various medicinal values. Its rhizomes are rich in non-starch polysaccharides, oligosaccharides, steroidal compounds, triterpenoid saponins, flavonoids and other

nutritive and bioactive components, but devoid of starch. As medicine, the rhizomes have effects of invigorating and strengthening the body, clearing heat and nourishing Yin, treating anemia, invigorating the spleen and benefiting the lung, moistening the intestines and promoting defecation. *P. sibiricum* granules possess antioxidant, antimicrobial, antitumor, hypoglycemic and antiasthmatic pharmacological activities. The mechanisms involve the synergistic effects of antibacterial activity, inhibiting biofilm formation, immune regulation and metabolic interference. Hence, this granule is an effective drug choice for inhibiting mycoplasma pneumoniae infection.

Future studies should further investigate the pharmacokinetics and drug interactions of *P. sibiricum* granules to guide their clinical application and efficacy. Although some studies showed the potential of *P. sibiricum* granules to effectively address chronic diseases and chronic hunger caused by developmental disorders, mental illnesses, and overall poor health status[28], the specific mechanisms and ultimate therapeutic effects on diabetic patients remain unclear. Pharmacokinetic studies on the metabolic process of dynamic blood concentration changes after taking *P. sibiricum* granules can provide good guidance on clinical medication regimens, adjusting prescription compatibility, designing optimal administration routes and dosages, and optimizing the efficacy and safety of this drug. Additionally, pharmacokinetic studies on *P. sibiricum* granules can reveal metabolic differences in special populations including elderly, children and pregnant women, thereby better guiding its application in these groups. Studies on drug interactions can avoid adverse reactions and cost input. Existing studies showed interactions between *P. sibiricum* and drugs like warfarin, diazepam and fluoxetine. Hence, compatibility with drugs of similar mechanisms of action should be avoided in developing *P. sibiricum* granules.

In summary, the development of *P. sibiricum* granules is still in its early stages. Common clinical prescriptions often include other edible Chinese medicines, such as wolfberry, ginseng, and tangerine peel. The clinical applications of *P. sibiricum* granules are primarily focused on diabetes and pulmonary diseases.

## Author Contributions

Yuqing Shu designed the study, collected the data, analyzed and interpreted the data and wrote the manuscript. All authors contributed to this work equally. All authors read and approved the final manuscript.

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