Rhizoma polygonati from Mount Tai: nutritional value and usefulness as a traditional Chinese medicine, source of herbzyme, and potential remediating agent for COVID-19 and chronic and hidden hunger

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Abstract
Recently, traditional Chinese medicine-based treatment has succeeded in fighting coronavirus disease 2019 (COVID-19), and Rhizoma polygonati (Huangjing) has been one of the recommended components. Its processed products play antidiabetic, antiviral, antitumor, antioxidation, antifatigue, antiaging, and immune enhancement roles. The climate in Mount Tai is mild, and the dense forest is suitable for the growth of Rhizome polygonati, which has gradually evolved into a unique species. Considering the important medicinal value and pleasant taste of Mount Tai-Rhizoma polygonati, various healthy and functional food products, controlled by quality markers with anti-COVID-19 potential, as well as emergency foods can be developed. The study aimed to review current evidence on the nutritional value of Rhizoma polygonati from Mount Tai and its usefulness as a traditional Chinese medicine, source of herbzyme, and potential remediating agent for COVID-19 and food shortage. Most recent findings regarding herbal nanomedicine have revealed that nanoscale chemical compounds are potentially efficient in drug delivery or nanozyme catalysis upon bioprocessing. Nanoflower structure is found in processed Rhizoma polygonati by self-assembly and has wide application in enzymatic events, particularly nanoscale herbzyme. The novel findings regarding Mount Tai-Rhizoma polygonati could enhance its novel applications in chronic and hidden hunger, clinical nanomedicine, and as an anti-COVID-19 agent.

Keywords: Chemical composition, Coronavirus disease 2019, Pharmacology, Rhizome polygonati

1 Introduction
The recent outbreak of coronavirus disease 2019 (COVID-19) has culminated in a global pandemic, while traditional Chinese medicine, including Rhizome polygonati (Huangjing), has demonstrated efficacy in patient recovery. Over 60 varieties exist worldwide, with approximately half in China. There are different types of Huangjing, such as Rhizome polygonati, Many-flower polygonati, and Dian rhizome polygonati. Dian rhizome polygonati is distributed in Dali, Lijiang, and other areas in the western region of Yunnan Province. Many-flower polygonati is the dominant variety in the Jiuhua mountain area of Anhui and is related to named Jiuhua rhizome polygonati[1-2]. In the Shandong province of Mount Tai, it is predominantly distributed in the mountainous areas of Tai’an, Culai, and Yinteng; however, its classification remains unclear as far as phylogenetic analysis is concerned. Mount Tai-Rhizome polygonati has the effects of invigorating qi and nourishing yin, strengthening the spleen, moisturizing the lungs, and benefiting the kidneys. It is used to treat a weak spleen and stomach, fatigue, dry lungs, cough diseases due to insufficient blood, and internal heat and thirst.

Mount Tai-Rhizome polygonati grows in shady slopes, stone walls, weeds, or rock gaps under trees. When rhizomes are administered as medicine, they have the effect of nourishing the spleen, lungs, yin, and qi. It is well-known as one of Mount Tai’s four famous medicines with a long-recorded history[3-4]. Several legends and folktales

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stories exist regarding *Rhizome polygonati* use as an emergency and functional food due to its high content of polysaccharides and other nutrients. Moreover, recent nanotechnology has been applied to herbs, including *Rhizome polygonati*, in novel functional studies with the potential of wide application in future clinics. This study aimed to review current evidence on the nutritional value of *Rhizoma polygonati* from Mount Tai area, source of herbzyme its application as a traditional Chinese medicine, and potential remediating agent for COVID-19 and food shortage.

The literature review was performed by searching publications in PubMed, China National Knowledge Infrastructure, Google, Google scholar, Baidu. The most covered publications were from 2005 to 2020.

2 Cultivation of Mount Tai-Rhizome *polygonati*

*Rhizome polygonati* is a perennial herbaceous plant with the following characteristics: shade-loving, drought and cold resistance, poor adaptability, and strong habitat selectivity. Mount Tai-Rhizome *polygonati* is propagated using underground stems and seeds; however, the natural germination rate of its seeds is extremely low, which makes propagation under natural conditions mainly rely on underground stems[5]. The unique ecological habitat of Mount Tai-Rhizome *polygonati* renders the resource distribution sporadic, narrow, and scarce. Moreover, predatory mining and large-scale tourism cause the endangerment of wild resources and make resource recovery difficult. Sustained development brings heavy losses, and artificial cultivation techniques are required to increase production[6]. The flowering and fruiting periods of Mount Tai-Rhizome *polygonati*, *Many-flower polygonat*, and *Dian rhizome polygonati* are different[7].

The buds on the rhizome generally begin to germinate from October to November, and as the temperature decreases, the buds grow slowly and eventually stagnate[8-9]. In winter, Mount Tai-Rhizome *polygonati*’s underground part dies and then germinates in the spring of the following year[8-9]. Under natural conditions, the seed germination rate of Mount Tai-Rhizome *Polygonati* is considerably low. Mount Tai-Rhizome *polygonati* seeds first form small bulbs, which differentiate into adventitious roots and buds, subsequently stay dormant for 30 to 40 d, and finally form seedlings. It is speculated that there are secondary dormancy phenomena, namely, seed dormancy and small bulb dormancy[9-10]. Studies have shown that seed dormancy can be overcome by refrigeration followed by 100 mg/L gibberellin treatment for 24 h[10]. Spring planting is the optimal planting time; nevertheless, it can also be planted in autumn from September to October[11]. For seed propagation, when the berries turn black in August, wet sand stratification should be immediately carried out[12-14].

Recent experiments have shown that wild Mount Tai-Rhizome *polygonati* can be reproduced using tissue culture in a Murashige and Skoog plant growth medium containing 4.0 mg/L 6-benzylaminopurine, 1.5 mg/L thidiazuron, and 1.0 mg/L 2,4-dichlorophenoxyacetic acid for proliferation, and the survival rate of transplanted test-tube seedlings after rooting can reach 90%[9]. Moreover, wild Mount Tai-Rhizome *polygonati* reproduction can be carried out by domestication using optimized soil and other environmental conditions[13-19] because the climate of Mount Tai experiences a significant vertical change, with the temperature at the base of the mountain averaging −3°C and peaking at −9°C in January and averaging 26°C and peaking at 18°C in July[19]. Annual precipitation increases with altitude, amounting to 1,132 mm at the mountain peak but only 22.6 mm at the bottom of the mountain[9] (Fig. 1) compared to that in other areas.

3 The natural products in Mount Tai-Rhizome *polygonati*, and nutritional values for potentially fighting chronic and hidden hunger

3.1 Trace elements

Trace elements are closely related to the following four properties of Chinese medicine: cold, cool, warm, and hot. Studies have discovered that Mount Tai-Rhizome *polygonati* is extremely rich in magnesium, iron, zinc, and calcium; however, the toxic presence of heavy metals such as Pb is significantly lower than that in fruits and satisfactorily safe[20-21]. Other elements of relatively high content include strontium, manganese, barium, boron, copper, titanium, cadmium, etc[20-21]. One study demonstrated that in an extract of Mount Tai-Rhizome *polygonate*, the first bench dissolution was approximately 30%, and the total dissolution of trace elements after leaching thrice was approximately 40%, suggesting the difficulty of dissolving all the trace elements[22-23]. The dissolution rate of Mg, Mn, Cr, Zn, Pb, and Fe is high, but rates of Cu and Ca are low[22-23]. Studies have shown that the actual potassium and sodium content in traditional Chinese medicine is similar to that in clinical drugs. However, that of other elements is quite different[22-23].

![Figure 1](image_url). The average temperature, humidity, and precipitation of five different regions: Jinhua Zhejiang, Jiuhua Mountain Anhui, Kunming Yunnan, Mountain Tai, and Tai’an.
3.2 Natural products

Studies have demonstrated that the chemical constituents of Mount Tai-Rhizome Polygonati mainly include polygonum polysaccharides, steroidal saponins, anthaquinone compounds, alkaloids, lignin, vitamins, and a variety of useful amino acids and other compounds. Polygonum polysaccharides are plant polysaccharides extracted from rhizomes, and they comprise the following three carbohydrates: glucose, mannose, and galacturonic acid in a ratio of 6:26:1, without obvious toxic side effects. The component is affected by extraction time, times, and material-to-liquid ratio. Studies have shown that it can inhibit the formation of hydroxyl radicals and liver homogenate lipid peroxidation with antioxidant effect. The extraction methods included the use of a diethylaminoethyl cellulose-52 and Sepharose CL-6B column and hydrochloric acid deproteinization.

However, the large molecular weight of Polygonum polysaccharides leads to poor water solubility, which is not conducive for absorption by organisms. Regarding function, it has been reported to reduce blood glucose levels and fasting insulin levels in mice or improving the symptoms, reducing hepatic cell steatosis, and improve myocardial fibrosis in diabetic rats. Moreover, antiviral, antiaging, and anti-inflammatory effects as well as protection against chemical liver injury and improved immune response have been reported.

The aglycons of steroidal saponins, which are precursors of other saponins isolated from Polygonatum and Dian rhizome polygonati, vary considerably, especially diosgenin. Li et al. isolated six steroidal saponin compounds from Dian rhizome polygonati, which have anti-human immunodeficiency virus activity. Jin isolated 10 steroidal saponins from Hubei Rhizome polygonati and discovered that these compounds inhibit the proliferation of cervical cancer cells. The volatile components of Rhizome polygonati mainly include furans, ketones, organic acids, olefins, alkanes, aldehydes, alcohols, and esters of which furans constitute the highest content. Rhizome polygonati also contains 11 amino acids, including lysine. In addition, a partial compound list is shown in Table 1.

Table 1. Partial and main chemical compounds in Rhizoma polygonati (https://www.symmap.org/detail/SMHB00185).

| Compound name         | Molecular formula | Molecular weight |
|-----------------------|-------------------|------------------|
| Apigenin              | C_{15}H_{20}O_{5} | 270.25           |
| Citral                | C_{15}H_{16}O_{5} | 252.26           |
| Succinic acid         | C_{4}H_{6}O_{4}   | 118.10           |
| Beta-sitosterol       | C_{30}H_{50}O_{1} | 414.69           |
| Diosgenin             | C_{15}H_{22}O_{3} | 216.31           |
| Prunasin              | C_{15}H_{24}N_{6}O_{5} | 295.32       |
| Isoliquiritigenin      | C_{15}H_{20}O_{4} | 256.27           |
| Salicylic acid        | C_{7}H_{6}O_{3}   | 138.13           |
| Baccatin               | C_{9}H_{4}O_{3} | 270.25           |
| Glucuronic acid       | C_{7}H_{20}O_{7} | 194.16           |
| Liriodendrin          | C_{16}H_{20}O_{8} | 742.80           |
| Neoliquiritin         | C_{20}H_{32}O_{8} | 418.43           |
| Methylprotopodioscin   | C_{13}H_{20}O_{12} | 1,063.38        |
| Amygdalin             | C_{8}H_{20}N_{1}O_{11} | 457.429     |
| Linsinine             | C_{20}H_{28}N_{1}O_{8} | 610.749       |
| Neferine              | C_{14}H_{26}N_{2}O_{7} | 624.775       |
| Higenamine             | C_{12}H_{18}N_{2}O_{3} | 271.32        |

3.3 Changes in chemical composition before and after processing: potential remediation of food shortages

Rhizome polygonati raw products reportedly can irritate the throat; thus, the plant needs to be processed to reduce potential discomfort. The pharmacological effects and effective ingredient content have been reported to change after processing. With prolonged processing, the content of Polygonum polysaccharides can be decreased. Yang et al. found that by simulating the nine-times steamed and nine-times sun-dried method during processing, the polysaccharide content in dried samples was reduced to approximately 12%. During the third steaming, the polysaccharide content of xanthine decreased to approximately 1%. Studies have shown that the polysaccharide content in raw Rhizome polygonati significantly decreased after processing, possibly owing to the conversion of monosaccharides. However, the saponin content in xanthine was increased during the process. Yang et al. discovered that the total-saponin content in Rhizome polygonati increased from 2% with “non-steaming” to approximately 14% after steaming for the fourth time, an increase of nearly seven times. Moreover, steroidal saponins produced secondary glycosides and aglycones after processing. Additionally, 5-hydroxymethylglycolaldehyde levels increased, which relates to an immune system enhancement, whereas some essential-oil components, such as n-hexaldehyde, 1,7,7-trimethyltricycloheptane, camphene, 2-n-pentyl furan, and 4-diene, decreased.

The following oligosaccharides including D-sucrose, and raffinose, produced qualitative changes during processing and were hydrolyzed to their constituent monosaccharide or disaccharide. Figure 2 summarizes the changes in chemical compounds during processing.

4 The pharmacological effects of Mount Tai-Rhizome polygonati

Several studies have reported the pharmacological effects of other types of Rhizome polygonati, such as anti-diabetic, antiaging, blood-fat lowering, immune regulation, and infertility treatment functions, among others, though less prevalent in Mount Tai-Rhizome polygonati. Reference can be made to previously published reviews regarding other types of Rhizome polygonati. The current study focused exclusively on Mount Tai-Rhizome polygonati.

4.1 Antiaging effect

A previous study demonstrated the function of Mount Tai-Rhizome Polygonati against lung cancer. In a study on urethane-induced lung cancer in mice, in which the mice were fed with Mount Tai-Rhizome polygonati by intragastric administration on eight occasions, lung adenocarcinoma was inhibited, thus enhancing the immunity of mice with lung cancer and improving their survival status.

4.2 Potential anti-inflammatory and antioxidant effects

Zhang et al. discovered that in a mouse model of ear swelling/inflammation induced by xylene, Mount Tai-Rhizome polygonati could disrupt swelling, suggesting
Dried, rich in various trace elements. According to previous reports [71-72], the content of iron, zinc, and magnesium that of 2,432.75 μg/g [71-72]. These elements play an important role in human metabolism.

5.2 Potent quality markers of Mount Tai-Rhizome Polygonati for medicinal values

Morphological and molecular markers are potentially useful in distinguishing the varieties. Therefore, these markers are widely used in Rhizome polygonati phylogenetic analysis and identification. Molecular markers, including restriction fragment length polymorphism, random amplified polymorphic DNA technology, simple-sequence repeat (SSR) markers, and other markers, are used in the morphological classification and traditional breeding of Polygonatum. Furthermore, DNA barcodes are mainly applied in classifying and identifying the systematic evolution of Polygonatum, genetic relationship, diversity analysis, etc [73-75]. Two molecular methods are commonly used, namely, DNA barcoding and molecular labeling, which are both applied to Polygonatum with universal Internal Transcribed Space 2 (ITS2) primers and DNA chips for a polymerase chain reaction, sequencing, and phylogenetic analysis [73-75]. Inter-SSR markers can effectively reveal the genetic diversity and accuracy of the genetic relationships among Rhizome polygonati species and can effectively distinguish the Rhizome polygonati species [76-79].

Rhizome polygonati is characterized by cold resistance and the affinity for a cool, wet environment. The Mount Tai area exhibits lower levels of humidity, average temperature, and average annual precipitation than other areas in which natural growth occurs [Fig. 1] [80-86]. In addition, the dense mountain forests in Mount Tai have natural geographical advantages for Rhizome polygonati plantations. The large-scale cultivation of Mount Tai-Rhizome polygonati may initially promote the development of the planting industry and increase farmers' income. Because Rhizome polygonati has important medicinal value, it can be directly processed into a Chinese medicinal decoction or an important ingredient of health products. Due to its sweet taste, it can be mixed with other nutrients to produce various nutritious food products.

5.3 Potential anti-COVID-19-drug development using Mount Tai-Rhizome polygonati

The recent COVID-19 pandemic has caused the large-scale infection, and traditional Chinese medicine has played essential roles in prevention, treatment, and recovery. Rhizome polygonati has been used as a component in the complex receipt of more than 60% of anti-COVID-19 Chinese medicines, based on doctors’ or official recommendations [87]. One example is that of the First Affiliated Hospital of Zhejiang University, as evidenced in a handbook of clinical treatment [88]. After rehabilitation and discharge during the recovery period, new coronary, lung, and spleen qi deficiency in patients are the main manifestations. Among many official recommendations for COVID-19 patients, Rhizoma polygonati use is included [89-91]. For example, for the recovery of lung fibrosis using traditional Chinese medicine to qi and phlegm, qi filling, and essence, the herbs of Rhizoma polygonati, Peach Kernel, Red Peony, Tangerine, and others are used to reduce fibrosis lesions and prevent further damage of lung function [90-91].

Figure 2. Differences in the chemical composition of Rhizome polygonati before and after processing (△—“nine-times steamed, nine-times sun-dried,” ○—steamed, and □—stewed).
Recently, we reported the computer-based analysis of the molecular docking of potential *Rhizoma polygonati* chemical compounds in combating COVID-19 and identified certain high-ranked compounds which may bind to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) target proteins\(^{[92-93]}\). For example, (+)-syringaresinol-O-beta-D-glucoside potentially binds to the angiotensin-converting enzyme 2 (ACE2) of SARS-CoV-2, whereas diosgenin may bind to both ACE2 and RNA-dependent RNA polymerase based on calculation and computer modeling. All target genes of host cells are identified using computer modeling from the database\(^{[93]}\). Finally, in the future, relevant chemical compounds need to be identified to extract necessary drug-development chemicals.

### 5.4 Network pharmacology analysis of whole compounds in *Rhizome polygonati* suggesting the drug mechanisms

Network pharmacology has allowed us to identify all potential gene-protein-drug target networks and establish signaling pathways to explore specific disease targets. Using a traditional Chinese medicine database, we established a pharmacology network of *Rhizome polygonati* based on all current published and potential databases on compound analysis. The results demonstrated that *Rhizome polygonati* potentially target many kinases, including c-Jun, sarcoma, and mitogen-activated protein kinase, as well as the cell cycle and cell death (Fig. 3)\(^{[94-97]}\). Thus, to enhance the availability of the corresponding chemical compound for specific drug targets in precision medicine, environmental control of Mount Tai-Rhizome polygonati may be helpful.

### 5.5 Use of Mount Tai-Rhizome polygonati in nanomedicine: nanozymes and herbzyme

Nanotechnology has been applied in herbal medicine for efficient drug delivery, controlled release, and antibacterial infection\(^{[98]}\). Self-assembly can be achieved using natural products from herbs, and different chemical compounds have exhibited distinct assembly patterns\(^{[99]}\). We recently found that nanoscale Mount Tai-Rhizome polygonati extract can be self-assembled to form nanoflower after sun-dried and steam processing. The assembly is related to chemical compounds such as Polygonatum polysaccharides, based on computational modeling and calculation\(^{[100]}\).

Moreover, nanoscale Mount Tai-Rhizome polygonati extract has nanozyme activity, including peptide digestion, related protease activity, and pH-dependent phosphatase activity. Although nanozymes have initially been considered to be metal nanoparticles, few studies have associated them with natural products, especially herbal particles\(^{[100]}\). The nanoparticles from Mount Tai-Rhizome polygonati extract are related to nanozyme activity under extreme pH conditions, suggesting the artificial enzymatic power that protein-based enzymes cannot exude\(^{[101]}\) (Fig. 4). We proposed the term “herbzyme,” which refers to a herb-derived natural nanozyme that has not undergone artificial synthesis or addition of metals. This would be a natural, green nanozyme.

In addition, at mild pH, nanoscale Mount Tai-Rhizome polygonati extract has exhibited biofuel- and phosphatase-enhancing functions by catalyzing the breakdown of p-nitrophenyl glucopyranoside to p-nitrophenol\(^{[102]}\), which is consistent with our finding in which enzyme...
activity with cofactor or coenzyme potential was observed. This might have been due to the nanoparticle surface effect or other unknown effects.

6 Conclusions and future perspective

In summary, Mount Tai-Rhizome polygonati is uniquely characterized by its prolific growth in the Mount Tai environment; richness in trace elements; and pharmacological functions, namely, its antiaging, anti-inflammatory, and potent antibacterial effects. In addition, its processed water extract’s potential surface effect, nanzyme characteristics, and other novel functions may allow us to critically consider the multiple facets of traditional Chinese medicine from its energy storage during processing, based on the energy theory of matters, and potentially through mechanisms of quantum theory at an atomic scale. Thus, further nanoscale, or even smaller, materials should be investigated in herbs. Finally, our finding regarding herbzyme is a breakthrough for the application of the processing of Mount-Tai Rhizome polygonati as a carrier of natural compounds through the combination of Western and Eastern medicine in clinical application. Mount Tai-Rhizome polygonati may be potentially useful both as a therapy drug, in drug delivery, in clinical application, and as an edible plant food in emergencies due to its high content of polysaccharides and other nutrients. Importantly, classification using genome studies should be carried out in the future to completely understand the metabolism and phylogenetic evolution of different types. Recently, research has made progress in sequencing the completed chloroplast genome of Polygonatum sibiricum, which is 152,960bp long, is AT-rich, and comprises 16 genes, 90 of which are protein-coding. A close relationship between P. sibiricum and Polygonatum cyrtonema has been shown in phylegenetic trees. Thus, in future, whole-genome sequencing may reveal further knowledge to enhance the application in medicine and food. In addition, the metabolism pathways are being revealed to show more evidence that modifications or gene editing of the genome which is ongoing being studied may potentially uncover the secrets and applications in fighting hunger and can provide the new clues to be used for new generations of nutritional food.

Conflicts of interest statement

Yingqiu Xie is the editorial board member of this journal. Yingqiu Xie received financial support for research and consulting and Qian Wang received wages from Shandong Taishanghuangjing Biotechnology Co. Ltd.

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Author contributions

Yingqiu Xie supervised, designed the project, wrote the paper and drew the summary figure; Lazzat Nurtay wrote the draft, drew the figures; Qinglei Sun provided consulting, revision and comments; Zhongshan Cao and Cuiping Ma provided consulting, supervising, and comments; Amr Amin provided consulting, supervising and comments; Xugang Li provided revising, supervising and comments.

Ethical approval of studies and informed consent

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