Journal of Experimental and Clinical Application of Chinese Medicine

REVIEW

Open Access

Pharmacological Effects of Polygonati Rhizoma on "Tonifying the Kidney" and Its Development Status in the Field of Health Care

Wenlong Zhang [1], Kejian Wei [1], Su Gao [1], Zimo Dong [1], Jie Su [1,*]

[1.] College of Pharmaceutical Sciences, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China

DOI: https://doi.org/10.62767/jecacm502.9533

Keywords

Polygonati Rhizoma

Kidney-tonifying

Prescription

Pharmacological actions

Health-care product

* **Correspondence**

Jie Su

An associate researcher, the supervisor of postgraduates,

College of Pharmaceutical Sciences, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China.

E-mail: sujie198169@126.com

Received: 11 April 2024

Revised: 26 April 2024

Accepted: 10 May 2024

Published: 4 June 2024

***Journal of Experimental and Clinical Application of Chinese Medicine* 2024; 5(2): 49-67.**

Abstract

Polygonati Rhizoma has traditional effects of tonifying the kidney, with a wide clinical application. The record of Polygonati Rhizoma can be traced back to Miscellaneous Records of Famous Physicians, where Polygonati Rhizoma was catalogued "to mainly tonify and replenish qi, and long-time administration can make the body agile, prolong life and relieve hunger". In modern times, Pharmacopoeia of the People's Republic of China 2020 also records its effect of tonifying the kidney. In this study, the records of the related functions of Polygonati Rhizoma mainly in three aspects, "prolonging life", "tonifying essence and marrow", and "strengthening muscles and bones", were first sorted out in ancient and modern classics. This study also collected relevant prescriptions, such as Polygonati Rhizoma pill, and Polygonati Rhizoma and Radix Rehmanniae pill, with kidney-tonifying effects from 8 medical books including Arcane Essentials from the Imperial Library, Formulas from Benevolent Sages Compiled during the Taiping Era, Comprehensive Recording of Divine Assistance, etc. Through further retrieval of literature and analyses, it was confirmed that the pharmacological effects of Polygonati Rhizoma on "tonifying the kidney" contain improvement of arthritis and osteoporosis, anti-aging, immunoregulation, anti-fatigue, improvement of renal injury, improvement of reproductive function and anti-hypertension. The search and statistical analyses of special food information in State Administration for Market Regulation revealed that there are 409 kinds of health-care foods, with Polygonati Rhizoma as the main raw material, which have 15 kinds of health-care functions. Among them, "kidney-tonifying" health-care products that can enhance immunity, resist fatigue, elevate bone density or delay aging accounts over 80%. The last part of this study discussed and analyzed the pharmacological research progression of Polygonati Rhizoma on "tonifying the kidney" and its development status in the field of health care, so as to provide reference for in-depth development and application of Polygonati Rhizoma.

1 Introduction

Polygonati Rhizoma is the dry root of *Polygonatum kingianum* Coll. et Hemsl., *Polygonati rhizoma* Red. or *Polygonatum cyrtonema* Hua, which has sweet flavor and mild nature, and functions in kidney, spleen and lung [1]. With defined "kidney-tonifying" effects, many traditional Chinese medicine (TCM) classics records the clinical application and health-care function of Polygonati Rhizoma. Based on the TCM theories that "the kidney stores essence and governs the bones", TCM efficacy discussions related to "kidney tonification" can be searched, such as "prolonging life", "tonifying essence and marrow", and "strengthening muscles and bones", and relevant prescriptions with kidney-tonifying Polygonati Rhizoma were collected from medical books including Arcane Essentials from the Imperial Library, Formulas from Benevolent Sages Compiled during the Taiping Era, Comprehensive Recording of Divine Assistance, etc. As the research on the pharmacological effects of Polygonati Rhizoma has been deepening domestically and internationally [2,3], Polygonati Rhizoma has been confirmed to protect cardiomyocytes, regulate blood glucose, and mediate blood lipids, but the scientific connotation of its kidney-tonifying effects has not been expounded systematically through the results of pharmacological studies. Hence, after systematically sorting out ancient books and literature related to Polygonati Rhizoma and its "kidney-tonifying" effects, this study reviewed its pharmacological effects associated with "kidney tonification", such as improvement of arthritis and osteoporosis, anti-aging, immunoregulation, anti-fatigue, amelioration of renal injury, promotion of sexual function, and anti-hypertension. This study discussed the application prospect of Polygonati Rhizoma, and analyzed the pharmacological research, health-care function, and product research and development status of Polygonati Rhizoma from the perspective of health-care food development, with the aim of providing reference for in-depth development and application of Polygonati Rhizoma.

2 Relevant records and prescription statistics in TCM classics

2.1 Relevant records in TCM classics

The "kidney-tonifying" effects of Polygonati Rhizoma were first described in Miscellaneous Records of Famous Physicians in the Liang Dynasty under the Southern and Northern Dynasties, where "Polygonati Rhizoma is sweet in taste, mild in nature and non-toxic, and has main functions of tonifying and replenishing qi, removing wind and dampness, and calming the five organs. Long-term administration can make the body agile, prolong life and relieve hunger". Materia Medica for Dietary therapy in the Tang Dynasty stated that "Administration of Polygonati Rhizoma can resist aging and relieve hunger". In the Ming Dynasty, Materia Medica in Southern Yunnan supplemented "its effects to mitigate infirmities and diseases, strengthen physique, relieve hunger, treat deficiency with reinforcement, and tonify essence". The Grand Compendium of Materia Medica summarized expositions of the past dynasties, which described that "long-term administration of Polygonati Rhizoma can make the body agile, prolong life and relieve hunger. It also can treat any deficiencies, relieve cold and heat, tonify essence and marrow, and clear Toxoplasma gondii (existing in brain, chest and abdomen)". Thoroughly Revised Materia Medica written by Wu Yiluo, Compilation of Materia Medica written by Tu Daohe, Materia Medica Collection written by Lin Yuyou, etc. in the Qing Dynasty all recorded the "kidney-tonifying" effects of Polygonati Rhizoma, but the contents are nothing more than the effect discussion of "calming five zang organs", "tonifying essence and marrow" and "strengthening muscles and bones".

In Encountering the Sources of the Classic of Materia Medica, Polygonati Rhizoma is superior in benefiting the spleen and stomach, and can regulate qi in the

spleen and stomach, harmonize the five zang organs, strengthen muscle, and improve bone and marrow, all of which belong to yin-nourishing effects. Collection of the Medical Community described that "raw Polygonati Rhizoma can nourish the kidneys". There are no new descriptions of "kidney-tonifying" effects of Polygonati Rhizoma in other classics. Seeking Accuracy in the Materia Medica (Huang Gongxiu), Seeking Origin in the Materia Medica (Zhao Qiguang), Essentials of Materia Medica (Wang Ang), Ben Cao Dong Quan (Shen Mu) and Summarized Dissemination of the Classic of Materia Medica (Wu Shikai) in the Qing Dynasty all concentrates on the efficacy of Polygonati Rhizoma in the aspects of "calming the five zang organs", "tonifying essence and marrow" and "prolonging life by long-term administration". In recent times, Pharmacopoeia of the People's Republic of China 2020 has recorded its functions and treatments as "tonifying qi and nourishing yin, strengthening the spleen, moistening the lungs and tonifying the kidneys, as well as treating essence and blood deficiency pattern, soreness and weakness of waist and knees, premature graying of hair, and internal heat and wasting thirst disorders".

From the earliest record of "calming the five zang organs" and "prolonging life by long-term administration" in the Northern and Southern Dynasties, to "tonifying essence and marrow" and "strengthening muscles and bones" in Ming and Qing Dynasties, and to the modern concept that Polygonati Rhizoma has traditional "kidney-tonifying" effects, it can be concluded that its "kidney-tonifying" effects are mainly reflected in "prolonging life", "tonifying essence and marrow", and "strengthening muscles and bones".

2.2 Prescription statistics

Multiple TCM books in Chinese past dynasties have recorded the prescription containing Polygonati Rhizoma, and most of the efficacy is related to "kidney tonification". This study summarized the contents of Polygonati Rhizoma prescription in medical books such as Arcane Essentials from the Imperial Library, Formulas from Benevolent Sages Compiled during the Taiping Era, Comprehensive Recording of Divine Assistance, Formulas for Universal Relief, Numerous Miraculous Prescriptions for Health Cultivation, The Complete Compendium of Ancient and Modern Medical Works, Introduction to Medicine, and Orthodox Lineage of External Medicine. With "prolonging life", "tonifying essence and marrow" and "strengthening muscles and bones" as the specific "kidney-tonifying" effects, in addition to the Polygonati Rhizoma decoction and Radix Rehmanniae decoction recorded in the Comprehensive Recording of Divine Assistance and the Jinsuo Buzhen pill recorded in Formulas for Universal Relief, which have no corresponding effects, the other 16 prescriptions are all related to "kidney tonification" as shown in Table 1.

Table 1 The prescription containing Polygonati Rhizoma in medical books and its function of tonifying the kidney.

Medical books	Name of prescription "kidney-tonifying" effects	Ingredients
Arcane Essentials from the Imperial Library	Wujing alcohol (prolong life)	Fructus Lycii, Pine Leaf, **Polygonati Rhizoma**, Rhizoma Atractylodis Macrocephalae, Radix Asparagi, Polished Glutinous Rice, Medicated Leaven
Formulas from Benevolent Sages Compiled during the Taiping Era	Polygonati Rhizoma pill (prolong life)	**Polygonati Rhizoma**, Whitish Honey, Radix Asparagi
	Polygonati Rhizoma alcohol (prolong life)	**Polygonati Rhizoma**, Rhizoma Atractylodis Macrocephalae, Pine Leaf, Radix Asparagi, Root of Fructus

		Lycii
	Erjing pill (tonify essence and marrow)	**Polygonati Rhizoma**, Fructus Lycii
	Polygonati Rhizoma pill (prolong life)	**Polygonati Rhizoma**, Whitish Honey, Radix Asparagi
	Polygonati Rhizoma alcohol (prolong life)	**Polygonati Rhizoma**, Radix Asparagi, Pine Leaf, Root of Fructus Lycii
	Wujing decocted pill (prolong life)	White Poria, Matricaria Recutita, Calamus, *Cinnamomum cassia Blume*, Radix Asparagi, Rhizoma Atractylodis Macrocephalae, Radix Ginseng, Radix Achyranthis Bidentatae, Raw **Polygonati Rhizoma**, Raw Radix Rehmanniae
Comprehensive Recording of Divine Assistance	Baishu pill (prolong life)	Rhizoma Atractylodis Macrocephalae, Raw **Polygonati Rhizoma**, Mel
	Polygonati Rhizoma and Radix Rehmanniae pill (prolong life)	Raw **Polygonati Rhizoma**, Raw Radix Rehmanniae
	Polygonati Rhizoma decoction (/)	Raw **Polygonati Rhizoma**, Whitish Honey, Raw Radix Rehmanniae
	Radix Rehmanniae decoction (/)	Ripe Dry Radix Rehmanniae, Radix Astragali, *Cinnamomum cassia Blume*, Liquorice, Angelica Sinensis Radix, *Paeonia lactiflora*, **Polygonati Rhizoma**, *Scutellaria baicalensis*, Radix Ophiopogonis
	Ling Xian San (tonify essence and marrow)	White Poria, *Sesamum indicum*, Radix Asparagi, Rhizoma Atractylodis Macrocephalae, Semen Persicae, Dry **Polygonati Rhizoma**
Formulas for Universal Relief	Da Chen Xiang pill (tonify essence and marrow)	Lignum Aquilariae Resinatum, Radix Aucklandiae, *Syzygium aromaticum*, White Lignum Santali Albi, English Walnut Seed, Fructus Lycii, Fructus Anisi Stellati, Fructus Foeniculi, Trigonellae Semen, Scorpion, Squama Manitis, Fructus Toosendan, Caulis Akebiae, *Cistanche deserticola*, Radix Polygalae, Chinese Leek Seed, Sarmentose Pepper, Dry Dioscoreae Rhizoma, Fructus Corni, Rhizoma Anemarrhenae, White Poria, **Polygonati Rhizoma**, Radix Asparagi, Radix Ophiopogonis, Radix Ginseng, Ripe Radix Rehmanniae, Olibanum, Pine-Soot Ink, Raw Radix Rehmanniae, *Sesamum indicum*, Semen Cuscutae, Northern Fructus Schisandrae, Lotus Stamen, Pericarpium Citri Reticulatae, Herba Epimedii, Pericarpium Citri Reticulatae Viride, Radix Achyranthis Bidentatae

	Jin Suo Bu Zhen pill (/)	Radix Dipsaci, Radix Angelicae Pubescentis, Flos Eriocauli, **Polygonati Rhizoma** grass, Lotus Stamen, Semen Euryales, Cornu Cervi Degelatinatum, Fructus Rosae Laevigatae
Numerous Miraculous Prescriptions for Health Cultivation	Wu Xu Gu Ben pill (prolong life)	Polygoni Multiflori Radix, **Polygonati Rhizoma**, Raw Radix Rehmanniae, Ripe Radix Rehmanniae, Radix Asparagi, Radix Ophiopogonis, Light Red Poria, Rhizoma Atractylodis Macrocephalae, Radix Ginseng, Cortex Acanthopanacis, *Sesamum indicum*, Pine Nut, Semen Platycladi, Walnut Kernel, *Lycium dasystemum Pojark.*
	Huan Shan Ru Wu pill (prolong life, and tonify essence and marrow)	Polygoni Multiflori Radix, Fructus Lycii, Radix Achyranthis Bidentatae, Poria, **Polygonati Rhizoma**, Dry Mulberry, Radix Asparagi, Radix Ophiopogonis, Ripe Radix Rehmanniae, Raw Radix Rehmanniae
The Complete Compendium of Ancient and Modern Medical Works	Huan Zhen Er Qi pill (tonify essence and marrow, and strengthen muscles and bones)	Polygoni Multiflori Radix, Black Mulberry, Raw Radix Rehmanniae, Herba Ecliptae, Deerhorn Glue, Ginger Juice, Whitish Honey, **Polygonati Rhizoma**, Radix Ginseng, White Poria, Fructus Foeniculi, Fructus Lycii, Cornu Cervi Degelatinatum, *Xanthoxylum piperitum*
Introduction to Medicine	Yu Xian Bu Shou pill (prolong life, and tonify essence and marrow)	Bat, Purple-Black Mulberry, Cortex Eucommiae, Crinis Carbonisatus, Radix Asparagi, **Polygonati Rhizoma**, Polygoni Multiflori Radix, Radix Rehmanniae Preparata, Pericarpium Zanthoxyli, Herba Ecliptae, Prepared Salt, Rhizoma Corydalis, *Lycium chinensis*, Angelica Sinensis Radix
Orthodox Lineage of External Medicine	Xian Tian Da Zao pill (strengthen muscles and bones)	Placenta Hominis, Radix Rehmanniae Preparata, Dry Root of *Angelica sinensis* (Oliv.) Diels, Poria, Radix Ginseng, *Lycium chinensis*, Semen Cuscutae, *Cistanche deserticola*, **Polygonati Rhizoma**, Rhizoma Atractylodis Macrocephalae, Polygoni Multiflori Radix, Radix Achyranthis Bidentatae, Curculiginis Rhizoma, Drynariae Rhizoma, Sarmentose Pepper, Fructus Psoraleae, Radix Polygalae, Radix Aucklandiae, Halitum, *Syzygium aromaticum*, Black Date

3 Study on modern pharmacological effects

3.1 Improvement of arthritis and osteoporosis

TCM believes that bone marrow is transformed from kidney essence, and the rise and fall of kidney essence directly affect the growth, nutrition, and function of bones, which constitutes the concept that "The kidney governs the bones". Polygonati Rhizoma, as a "kidney-tonifying" medicine, has a traditional effect of strengthening muscles and bones, which therefore

can play a role in treating common orthopedic diseases such as arthritis and osteoporosis.

For treating arthritis, Polygonati Rhizoma single-medicine preparations with the main ingredient of Polygonati Rhizoma polysaccharides can effectively relieve the symptoms of knee osteoarthritis such as joint pain, flexion contracture, and the absence of knee extension and alignment in clinical application. After drug therapy for 3 times/day, 2 bags/time, and a total of 3 courses (discontinue the medication for 1 week after 3 weeks, with 4 weeks as a course of treatment), the levels of interleukin-1 (IL-1) and matrix metalloproteinase-13 (MMP-13) in patients with knee osteoarthritis are apparently decreased. Polygonati Rhizoma polysaccharides may repress the apoptosis of chondrocytes by inhibiting IL-1/mitogen-activated protein kinase (MAPK) signaling pathway and preventing MMP-13 from degrading type II collagen; while promoting chondrocyte proliferation and inhibiting apoptosis through activation of phosphatidylinoinosiol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, thereby alleviating synovial inflammation in osteoarthritis [4]. When studying rheumatoid arthritis, Tibetan Hospital of Qinghai Province found that Tibetan medicine Siwei Huangjing alcohol can effectively improve headache, tinnitus, and joint swelling and pain in patients [5]. Moreover, Zhang L et al. [6] unveiled that Polygonati Rhizoma polysaccharides can markedly alleviate IL-1β-induced rat inflammatory chondrocytes in vitro. The drug at dosages of 30, 120, and 480 mg/L can elevate the survival rate of inflammatory chondrocytes, while reducing apoptosis rate and the secretion of tumor necrosis factor (TNF)-α and IL-6, with Polygonati Rhizoma polysaccharides at 120 mg/L having the strongest effect.

For treating osteoporosis, gavage administration of Polygonati Rhizoma polysaccharides (400 mg/kg) mitigates osteoporosis in ovariectomized rats via clearing arrangements of bone trabeculae, up-regulating the expression of bone morphogenetic proteins (BMP) and basic fibroblast growth factor (bFGF), reducing the levels of bone Gla protein (BGP), bone alkaline phosphatase (BALP), tartrate-resistant acid phosphatase (TRAP) and TNF-α expression [7]. Yan FN et al. [8] unveiled that Polygonati Rhizoma polysaccharides (800 mg/kg) can treat model rats with osteoporotic fracture caused by complete ovariectomy via improving the microstructure of trabecular bone, reducing bone turnover, increasing osteoprotegerin (OPG) and reducing receptor activator of nuclear factor-κB ligand (RANKL) expression. With the same molding method and dosage, Zhang L et al. [9] confirmed that Polygonati Rhizoma can also promote the expression levels of osteoblast-related genes (alkaline phosphatase, Runx family transcription factor 2 (Runx2), collagen type I alpha 1 chain Gene (Col1a1) and osteocalcin), and inhibit the expression levels of osteoblast-related genes (ACP5 and CTSK).Ye S et al. [10] found that Polygonati Rhizoma polysaccharides effectively treat model rats with osteoporotic fracture caused by complete ovariectomy and the broken middle segment of the right femoral shaft. Gavage administration of 500 and 1000 mg/kg Polygonati Rhizoma polysaccharides can significantly elevate bone mineral density, reduce levels of TRAP and procollagen type I N-terminal propeptide (PINP) in serum, and increase levels of alkaline phosphatase (ALP), OPG, and BGP in serum. These reflected that Polygonati Rhizoma polysaccharides may up-regulate G protein-coupled receptor 48 (GPR48), BMP-2 and bone metabolic factors in bone tissues to improve the biomechanical properties and bone density of rats. Cheng Y et al. [11] confirmed that gavage administration of Polygonati Rhizoma polysaccharides (700 mg/kg) mitigates osteoporosis in diabetic rats via activating the OPG/RANKL signaling pathway to regulate bone

metabolism balance and increase femur bone mineral density. In addition, for zebrafish with osteoporosis caused by microinjection of streptozotocin, exposure to polysaccharide from Polygonatum cyrtonema (60, 120, and 240 μg/mL) aqueous solution can increase the mineralization area and bone mineral density of zebrafish skulls [12]. Apart from the above experiments with osteoporosis animal model, the pharmacological effect of Polygonati Rhizoma ameliorating osteoporosis has also been demonstrated through different in vitro assays. Polygonati Rhizoma polysaccharides can notably enhance the osteogenic differentiation ability of adipose stem cells and augment the expression levels of Core-binding factor α1 (Cbfα1)/osteogenic specific transcription factor/Cbf α1 antibody (Runx2), osteopontin (OPN), β-catenin and p-Glycogen Synthase Kinase 3 (GSK-3β) proteins in complete ovariectomy-induced osteoporosis model mice [13]. Du L et al. [14] confirmed that Polygonati Rhizoma polysaccharides at 10, 25 and 50 mg/L can mitigate osteoporosis in a dose-dependent manner via Wnt/ β -catenin signaling pathway to promote the osteogenic differentiation of mouse bone marrow stromal cells (BMSCs) and suppress osteoclastogenesis. On this basis, Peng X et al. [15] unveiled that Polygonatum cyrtonema polysaccharides promotes differentiation and mineralization of osteoblasts in vitro through extracellular signal-regulated kinase (ERK)/GSK-3 β / β -catenin signaling pathway, up-regulates the nucleus β-catenin level via effectively activating Wnt signaling independent of low-density lipoprotein receptor associated protein (LRP5), inhibits GSK-3β activity, and ultimately phosphorylates and destroys β-catenin stability by regulating ERK signaling pathway. Li B et al. [16] proved that Polygonati Rhizoma polysaccharides can inhibit miR-1224 expression in osteoclasts through the Hippo signaling pathway, thereby improving osteoporosis. In network pharmacology, Zhang J et al. [17] affirmed that Polygonati Rhizoma also regulate osteoporosis through the HIF-1 signaling pathway, PI3K-AKT signaling pathway and estrogen signaling pathway.

3.2 Anti-aging

In TCM, “Kidney deficiency” is the root cause of human aging. The kidney is the congenital foundation, and kidney qi can impact qi-blood circulation to maintain vital movement. Therefore, people with the abundance of kidney qi that unblocks qi and collaterals will definitely live longer [18]. There are numerous experiments on aging animal models in modern pharmacology that have demonstrated the anti-aging effect of Polygonati Rhizoma. Also, Polygonati Rhizoma has been proven to exert its “kidney-tonifying” effect, replenish yang qi and essence qi of kidneys, and unblock qi and blood in five zang organs, so as to delay aging.

In D-Galactose-triggered aging model mice, Polygonati Rhizoma polysaccharides administered at doses of 0.3 and 0.6 g/kg by gavage can obviously increase the level of superoxide dismutase (SOD) and activity of glutathione peroxidase (GSH-Px), and decrease the content of malondialdehyde (MAD) in serum, while augmenting the content of glutamate (GLU) and acetylcholine (Ach), and diminishing γ -aminobutyric acid (GABA) content in brain tissues, hence improving learning ability and memory of mice [19]. Zheng S [20] found that intraperitoneal injection of Polygonati Rhizoma polysaccharide (120 mg/kg) can up-regulate the mRNA and protein expressions of Klotho in the renal cortex, down-regulate the expressions of forkhead box O3 (FOXO3a) mRNA and p-FOXO3a protein in renal tissues, dampen the expression of fibroblast growth factor 23 (FGF-23) protein in the femur, reduce oxidative stress through modulation of the Klotho/FGF23 endocrine axis, and regulate calcium and phosphorus metabolism balance to exert anti-aging effects. In addition, oral administration of 0.5, 1, and 2 g/kg alcohol extracts of

Polygonati Rhizoma can improve aging and damage in important organs such as the liver, kidney, and heart possibly via inhibition of the p53/p21 and p16-RB pathways, as well as the Keap1/NF-E2-related factor 2 (Nrf2)/heme oxygenase (HO)-1 pathway [21].

For naturally aging model rats, gavage administration of 400 mg/kg Polygonati Rhizoma aqueous extract can delay vascular aging, reduce the relative contents of aortic smooth muscle cells (SMC) and collagen fibers (CF), and increase the total antioxidant capacity (T-AOC) and GSH-Px activity of the aorta through blocking the ATR/Chk1 pathway [22]. Besides, oral administration of Polygonati Rhizoma (125 and 500 mg/kg)-mixed feed can postpone the decline of testicular spermatogenic function, increase the levels of SOD, catalase (CAT) and GSH-Px in testicular tissues, reduce the apoptosis of testicular spermatogenic cells, boost Nrf2 nuclear translocation, promote Nrf2, HO-1 and NAD(P)H quinone dehydrogenase 1 (NQO1) protein expressions, and suppress Bax and cleared cysteinyl aspartate specific proteinase (Caspase)-3 protein expressions via the activation of Nrf2 signaling pathway [23]. Gavage treatment of 0.2, 0.4, and 0.8 g/kg aqueous extract of Polygonati Rhizoma and Pheretima in combination (1:1 ratio of Polygonati Rhizoma alcohol and roasted Pheretima) is able to extend the central activity time and total activity distance of naturally aging mice, increase neurons in the CA1 and CA3 regions of the hippocampus and Bcl-2-like immunoreactive neurons, and reduce Caspase-3-like immunoreactive neurons [24].

In other aging model animals, Qin Z et al. [25] revealed that Polygonati Rhizoma aqueous extract can dampen the activation of the ataxia telangiectasia-mutated (ATM)/ATM and Rad3-related (ATR) protein kinase pathway at the DNA damage detection point in vitro, thereby reducing the cell cycle of aging rat endothelial progenitor cells (EPCs) in G1 phase and increasing in S phase during passage culture. Also, it significantly down-regulates the mRNA and protein expressions of ATM, ATR, checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2) in cells, delaying aging of EPCs during passage culture in vitro. Luan Y et al. [26] affirmed that Polygonati Rhizoma polysaccharides can prolong the lifespan of caenorhabditis elegans, the action of which may be realized through mediating 4,5-Diaminofluorescein (DAF)-2, DAF16, and SOD-3 in the insulin signaling pathway.

3.3 Immunoregulation

In TCM theory, the kidney stores natural essence, and Wei-defensive qi is innate, which therefore is also termed “Wei-defensive yang”. Remnants of Medical Decree-Zong-pectoral qi, Ying-nutrient qi and Wei-defensive qi recorded that “Wei-defensive qi protects the whole body to defend external pathogenic factor invasion”, based on which it can be concluded that the abundance and weakness of kidney yang make impacts upon the immunoregulation ability of human body. The modern medicine also has relevant researches. For example, when the level of kidney toxins is high, aberrant levels of blood creatinine and urea nitrogen can affect bone marrow hematopoiesis, white blood cell production, and lymphocyte production. Under this circumstance, the survival ability of immune cells is decreased, affecting immune function. Fortunately, Polygonati Rhizoma can exert its “kidney-tonifying” effect to improve kidney deficiency, and thereby regulate the body’s immune function.

In clinical application, Xiao X et al. [27] indicated that Polygonati Rhizoma polysaccharides (37.5-300 μg/mL) can dose-dependently increase the red blood cell C3b receptor (RBC-C3b) rosette rate, by which the immune function of red blood cells is enhanced in children with nephrotic syndrome. In addition to clinical applications, there are also many studies on the immunomodulatory effects of Polygonati Rhizoma

polysaccharides and Polygonati Rhizoma compound in animal experiments.

Deng X et al. [28] verified that Polygonati Rhizoma polysaccharides have an antagonistic effect on cyclophosphamide-induced immunosuppression in mice. After a week of gastric administration at a dose of 150 mg/kg, Polygonati Rhizoma polysaccharides evidently rises the indexes of the spleen and thymus, and strengthens the phagocytic function of macrophages and the secretion of IL-6 and TNF-α. Subsequent treatment of drugs at 200 and 400 μg/mL can promote the proliferation of spleen and thymus cells stimulated by concanavalin (ConA) in vitro. Furthermore, the immune stimulation mechanism of Polygonati Rhizoma polysaccharides is similar to that of lipopolysaccharides involving nuclear factors κB (NF-κB) and p38 mitogen-activated protein kinase (MAPK) pathway, which can promote TNF-α and IL-6 mRNA accumulation, cause IκB-α degradation and NF-κB p65 translocation to the nucleus transcriptionally and translationally, and elevates levels of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), NF-κB and phosphorylated p38 MAPK in mouse mononuclear macrophage leukemia cells (RAW 264.7) [29].

In terms of Polygonati Rhizoma compound, the study of Shen H et al. [30] unraveled that gastric administration of Ginseng-Polygonati Rhizoma decoction (4, 8 g crude drug/kg) significantly increases the liver, spleen, and thymus coefficients of model mice with kidney yang deficiency resulting from intramuscular injection of hydrocortisone. Yang Y et al. [31] discovered that Polygonati Rhizoma tea drink is capable of enhancing immunity, which at 500 μg/mL can facilitate the proliferation of RAW 264.7 cells in vitro, stimulate the phagocytosis of neutral red by RAW 264.7 cells, and promote the recovery of spleen and thymus indexes in cyclophosphamide-induced immunosuppressive model mice. Zhang M et al. [32] found that Polygonati Rhizoma and silky chicken extract promotes immunity of cyclophosphamide-induced immunosuppressive model mice, enhance proliferation of splenic lymphocytes, viability of NK cells and phagocytic ability of macrophages.

3.4 Anti-fatigue

TCM theory believes that essence and blood share the same source, and long-time heavy work will damage kidney essence and qi and bring about kidney deficiency, accompanied by soreness and weakness of waist and knees, blurred vision, tinnitus and other symptoms. Polygonati Rhizoma can modulate kidney by means of its “kidney-tonifying” effects, replenish kidney essence and qi in human body and relieve the negative impact from overwork. In network pharmacology, Wang ZF et al. [33] discovered that the anti-fatigue effect of Polygonati Rhizoma arises from the interaction between E2F1 and PI3K-AKT signaling pathway. The modern pharmacology has confirmed the anti-fatigue effect of Polygonati Rhizoma polysaccharides, Polygonati Rhizoma aqueous extract, and Polygonati Rhizoma compound through heaps of animal experiments.

For Polygonati Rhizoma polysaccharides, Ma H et al. [34] found that gavage administration of Polygonati Rhizoma polysaccharides at 120 mg/kg has an anti-fatigue effect, prominently extending the load swimming time of mice and increasing liver glycogen content. Besides, Fu L [35] identified that *Polygonatum kingianum* Coll. et Hemsl crude polysaccharide is superior to *Polygonatum sibiricum* Red crude polysaccharide and *Polygonatum cyrtonema* Hua crude polysaccharide in prolonging the swimming time of mice.

For Polygonati Rhizoma aqueous extract, a study has shown that both Polygonati Rhizoma extract made in ancient processing method [36] and multiprocess Polygonati Rhizoma decoction [37] have good

anti-fatigue effects. Of them, oral administration of multiprocess Polygonatum sibiricum decoction at doses of 5, 10, and 15 g/kg can extend the swimming time of mice, increase liver glycogen content, promote SOD activity, and decrease malondialdehyde (MDA) content.

For Polygonati Rhizoma compound, Renshen Huangjing (Gingsen-Polygonati Rhizoma) decoction [30], Polygonatum Cistanche capsule [38], and Polygonati Rhizoma and Notoginseng Radix et Rhizoma compound [39] all generate anti-fatigue effects and prolongs the load swimming time of mice. Among them, Gingsen-Polygonati Rhizoma decoction can augment the content of liver glycogen, and decline serum urea nitrogen level and blood lactate level to improve endurance of mice. Polygonati Rhizoma and Notoginseng Radix et Rhizoma compound can alleviate muscle fatigue in mice by promoting energy metabolism and antioxidant capacity.

3.5 Improvement of renal injury

The Yellow Emperor's Inner Classic: Basic Questions-Imbalance proposed that "kidney is a water-related organ that modulates body fluids", hinting the pivotal role of kidney in regulating body fluid balance. Renal injury is one of the common diseases occurring in kidney, together with primary clinical symptoms of foamy urine, urine color change, edema and renal dysfunction, so the modern disease "renal injury" is classified as "the dysfunction of kidney in governing water". Polygonati Rhizoma can enhance "the function of kidney in governing water", thereby improving renal injury. Studies have shown that Polygonati Rhizoma polysaccharides and saponins, the main chemical components of Polygonati Rhizoma, can mitigate renal injury.

Polygonati Rhizoma polysaccharides inhibit p38MAPK/activating transcription factor 2 (ATF2) signaling pathway and the production of inflammatory cytokines TNF-α, IL-1β, and IL-6 via diminishing expressions of neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) in renal tissues, through which intramuscular gentamicin injection-triggered renal injury can be ameliorated [40]. Gavage administration of 150 mg/kg Polygonati Rhizoma polysaccharides can enhance the glomerular filtration function, elevate the activity of antioxidant enzymes in kidney tissues, and dampen the generation of free radicals in rats with renal injury resulting from high-intensity exercise; and the Polygonati Rhizoma polysaccharides reduce the toxic side effects of nitric oxide (NO) metabolites on kidney tissues and increase the activity of adenosine triphosphatase (ATPase) through regulating the activities of iNOS and endothelial nitric oxide synthase (eNOS) [41].

Polygonati Rhizoma saponins can block the activation of Wnt/ β -catenin signaling pathway and inhibit tubulointerstitial fibrosis to exert a renal protective effect. Polygonati Rhizoma saponins have a good ameliorating effect on streptozotocin-induced diabetic nephropathy in rats, intragastric administration of which at 35 and 70 mg/kg can improve the general state and renal pathological morphology to a certain extent, signally reduce the renal weight index, urea nitrogen, serum creatinine and total urine protein, and suppress the expression of type IV collagen [42].

3.6 Improvement of reproductive function

The relation between kidney and reproduction has been widely discussed in TCM classics. For instance, in The Classic of Difficult Issues, "the kidney is a place to store sperms or maintain and nourish the uterus". It is believed that the "kidney" is connected to the brain above and to the Chong and Ren meridians below to main the uterus. This mirrored that the "kidney" regulates the reproductive system through the "brain-Chong and Ren-uterus" axis, which is consistent with the concept of the hypothalamic-pituitary-gonadal (HPG) axis in modern

medicine [43]. Therefore, when tracing the root cause of male and female reproductive function-related diseases, the crux can be confirmed based on the kidney deficiency. The therapeutic drugs can be found from the perspective of the role of Polygonati Rhizoma in "tonifying the kidney", combined with the above-mentioned TCM concept of "kidney governing reproduction", and according to its pharmacological effect on improving reproductive function.

In clinical application, Deng G [44] found that Huangjing Zanyu Capsule can improve soreness and weakness of waist and knees and dampness of the scrotum, and increase the survival rate of the sperm, to effectively treat oligospermia in male patients. In addition, there are also many pharmacological studies regarding the impact of Polygonati Rhizoma on animal models such as natural perimenopausal syndrome, testicular injury, and oligozoospermia.

For natural perimenopausal syndrome model rats, Chen S et al. [45] identified that gavage administration of the superfine powder and aqueous extract of Polygonati Rhizoma at doses of 0.25 and 0.5 g/kg can strengthen ovarian function and immune function, markedly reduce the rate of estrous cycle disorder, serum follicle stimulating hormone (FSH) level and luteinizing hormone (LH) content, improve ovarian tissue morphology and cell apoptosis, increase uterine wet weight and coefficient, ovarian wet weight, the levels of serum inhibin B (INHB), estradiol (E2) and anti-Mullerian hormone (AMH), and the protein expressions of ovarian cytochrome P450-11A1 (CYP11A1) and aromatase (CYP19A1) possibly through promoting estrogen synthesis and regulating the function of hypothalamic-pituitary-ovarian axis.

In cadmium-induced testicular injury model mice, Yang Z [46] discovered that gavage administration of Polygonati Rhizoma aqueous extract at 10 g/kg notably ameliorates the structure and physiological function of testicular tissues by modulating the thioredoxin-interactingprotein (TXNIP)-NOD-like receptor thermal protein domain associated protein 3 (NLRP3)-Caspase-1 and Cytochrome C (CytC)-Caspase-9-Caspase-3 signaling pathways. Han C et al. [47] further confirmed that intragastric administration of 10 g/kg aqueous extract of Polygonati Rhizoma can enhance sperm viability, reduce sperm abnormality rate, increase testosterone level, down-regulate reactive oxygen species (ROS) level, inhibit testicular cell apoptosis, and restore damaged testicular tissue to near-normal levels, which also modulates oxidative stress through the TXNIP-NLRP3-Casepase-1 signaling pathway, and dampens mitochondrial apoptosis via the CytC-Caspase-9-Caspase-3 pathway.

After asthenozoospermia mouse modeling through microwave radiation, Chen T et al. [48] found that administration of Hailong Huangjing (Polygonati Rhizoma) powder (1.2 g/kg) is capable of improving the symptoms, including thinning of seminiferous tubules, loose arrangement of cells, enlargement of the lumen of the tube, decreases in spermatogenic cells and sperms, and loss of Sertoli cells.

3.7 Anti-hypertension

In TCM, kidney yang deficiency and lucid yang failing to rise will bring about the absence of nutrition for brain, and later trigger main symptoms of hypertension, such as dizziness and headache [49]. The kidney has the function of regulating water-electrolyte balance, as well as various endocrine functions, which is a critical organ for blood pressure regulation, and one of the main target organs of hypertension [50]. On the basis of the above discussion, the pharmacological effects of Polygonati Rhizoma on hypertension can be linked to its "kidney-tonifying" effect.

In clinical application, Ning W [51] verified that compared with amlodipine tablets alone in the treatment of patients with yin deficiency and yang

hyperactivity hypertension, Huangjing Sicao (the combination of Polygonati Rhizoma and four kinds of herbs) decoction combined with amlodipine has a better therapeutic effect through reducing systolic and diastolic blood pressure to the normal range. Clinically, Huangjing Yiyin (Yin-tonifying Polygonati Rhizoma) decoction can also achieve this effect in elderly patients with hypertension, and improve kidney function [52]. Another study has shown that for hypertensive patients with kidney disease, oral administration of irbesartan tablets combined with modified Huangjing Sicao decoction for 2 months can lower blood pressure and has better effects than irbesartan treatment alone. The combination therapy can effectively relieve the symptoms, including soreness and weakness of waist and knees, feverish sensation over the five centers, dry eyes, etc., delay the damage of hypertension to the kidneys, and protect renal function [53].

In experimental pharmacology, Su J et al. [54] found that gavage administration of Polygonati Rhizoma superfine powder (0.5 and 1.0 g/kg) can improve blood pressure and dyslipidemia in rats with metabolic hypertension induced by high sugar high fat and alcohol consumption. The mechanism refers to the inhibition of enterogenous lipopolysaccharide (LPS)/Toll-like receptor 4 (TLR4) pathway that can mediate the structure of intestinal microbiota, reduce the production of LPS, increase the content of short-chain fatty acids (SCFAs) in feces, up-regulate the expressions of intestinal SCFAs transportprotein G protein coupled receptor (GPCR)41/43 and tight junction proteins Claudin-1 and Occludin, enhance intestinal barrier function and decline LPS translocation into the blood. Also, the suppression of LPS-mediated vascular TLR4/myeloid differentiation primary response protein 88 (MyD88) pathway participates in alleviating vascular endothelial cell shedding and regulating NO/endothelin (ET-1) balance, so as to improve vascular endothelial function.

4 Application progress

4.1 Information sources and screening

This study provides the application progress of Polygonati Rhizoma based on healthcare food declaration with Polygonati Rhizoma as a raw material in China. The keyword “Polygonati Rhizoma” under “Main Ingredients” was searched on the Special Food Information Query Platform of the State Administration for Market Regulation. The registered national healthcare food information was retrieved from April, 1997 to October, 2023, and 409 pieces of domestic healthcare food information were obtained. The terms “anti-fatigue” and “relief of physical fatigue” were unified as “anti-fatigue”; “immunoregulation” and “enhancing immunity” as “enhancing immunity”; “regulation of blood sugar” and “assistance in lowering blood sugar” as “assistance in lowering blood sugar”; “delaying aging” and “improving memory” as “anti-aging”; “modulating blood lipids” and “assisting in decreasing blood lipids” as “assisting in decreasing blood lipids”; and “hypoxia tolerance” and “improving hypoxia tolerance” as “hypoxia tolerance”.

4.2 Healthcare function

The 409 kinds of Polygonati Rhizoma healthcare food have 15 kinds of healthcare functions, and the statistical analysis suggested that “anti-fatigue” appears 202 times (37.00%), which is the key healthcare function of Polygonati Rhizoma. The next is “enhancing immunity”, which occurs 196 times (35.90%). There are 39 times (7.14%) of “assistance in lowering blood sugar”, 36 times (6.59%) of “anti-aging”, 15 times (2.75%) of “assisting in decreasing blood lipids”, 14 times (2.56%) of “sleep improvement”, 12 times (2.20%) of “assisting in protecting against chemical liver injury”, 8 times (1.47%) of “increase of bone mineral density”, 5 times (0.92%) each of “antioxidant” and “improvement of

nutritional anemia", 4 times (0.73%) each of "melasma removal" and "hypoxia tolerance", 3 times (0.55%) of "maintaining the bowel movement", 2 times (0.37%) of "weight loss", and 1 time (0.18%) of throat clearing and moistening (Figure 1).

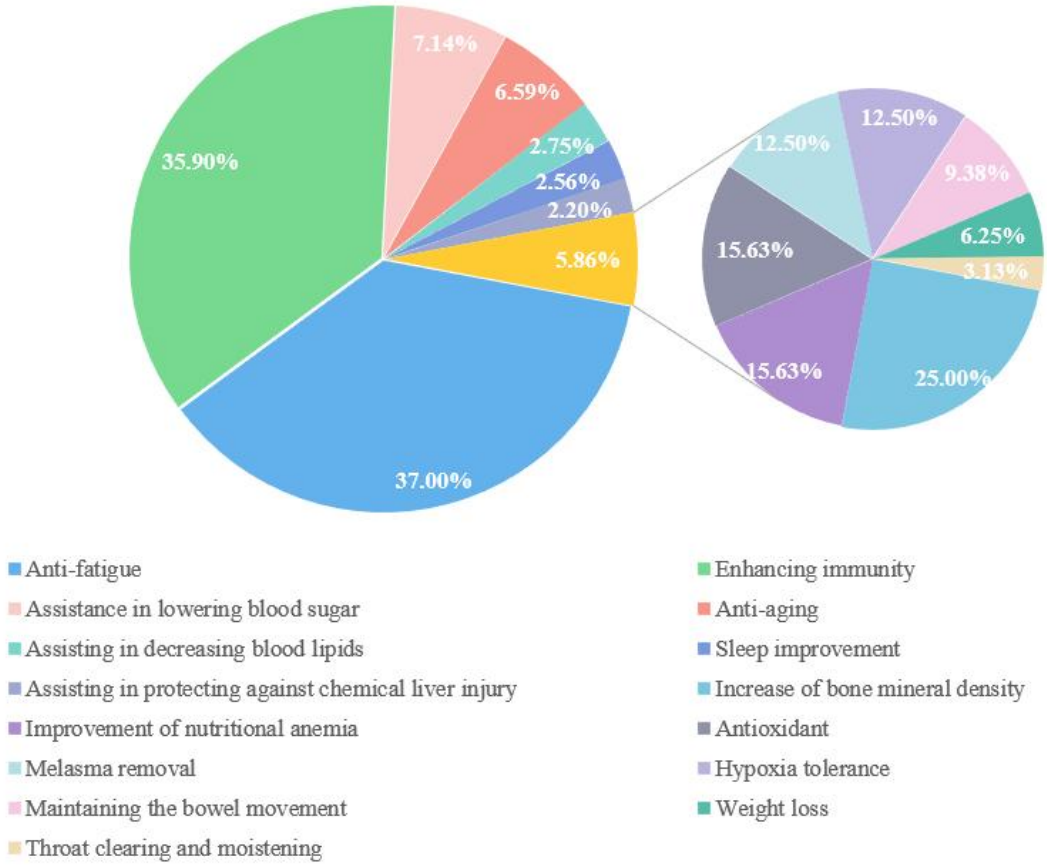

Figure 1 Proportion of products with different health function of Polygonati Rhizoma.

5 Conclusion and prospect

5.1 Polygonati Rhizoma has a defined "kidney-tonifying" effect and wide pharmacological actions, with great broad development prospects

Since ancient times, there are elucidations and application of Polygonati Rhizoma for its "kidney-tonifying" effect. The clinical symptoms of kidney deficiency comprise decline in reproductive function, poor growth and development, senilism in adults, disorders of excretion and urination function, weak respiratory function, waist and knee pain, fear of cold and heat, and weak pulse [55], which can be treated based on 4 pharmacological effects of Polygonati Rhizoma, including improvement of sexual function, relief of osteoporosis, anti-aging and anti-fatigue. This suggested that Polygonati Rhizoma has potential in preventing and treating decline in reproductive function, poor growth and development, senilism in adults, and waist and knee pain. The survey revealed that the proportion of middle-aged and elderly people suffering from osteoporosis is relatively high [56], "delaying aging" is a means to achieve healthy aging [57], and most urban youth develops kidney deficiency syndrome [58,59]. Therefore, the development of corresponding products based on the "kidney-tonifying" effect of Polygonati Rhizoma has broad development prospects in the massive health industry.

Among the 15 healthcare functions above, 4 functions, including "increase of bone mineral density", "anti-fatigue", "enhancing immunity" and "relieving physical fatigue" are related to the "kidney-tonifying"

pharmacological effect of Polygonati Rhizoma (Figure 2). The results of product declaration for these 4 healthcare functions showed that the declaration time interval of healthcare food related to "increase of bone mineral density" is long and the number of declarations is small. The declaration time of healthcare food related to "anti-aging" is concentrated from 1997 to 2004, but the overall number of declarations is still small. The declaration of healthcare food related to "enhancing immunity" and "relieving physical fatigue" is made annually, and the number of declarations has been increased sharply in the past two years. According to the overall declaration results, from 1997 to 2009, the number of declarations for Polygonati Rhizoma healthcare food is first increased and then decreased, with 2004 being the highest and 2005 the second highest. The reason mainly lies in that healthcare food was in the transition period of approval function transfer in 2003, and some leftover products were only approved in 2004, resulting in a sharp increase of product declarations in 2004. In 2005, the country introduced new "Measures for the administration of registration of healthcare food (Trial)", which made some applicants fail to declare products with a wait-and-see attitude towards this policy, leading to a decrease in the total number of product declarations in 2005 compared to 2004 [60]. In 2011, the "Twelfth Five-Year Plan" for the food industry development included the healthcare food manufacturing industry in the national development plan, making an overall upward trend in the number of product declarations from 2011 to 2021. As the report of the 19th National Congress of the Communist Party of China pointed out that healthy China strategy should be implemented, and the research and development of TCM health products has been paid attention to, so that the number of healthcare food declarations peaked in 2020 and 2021.

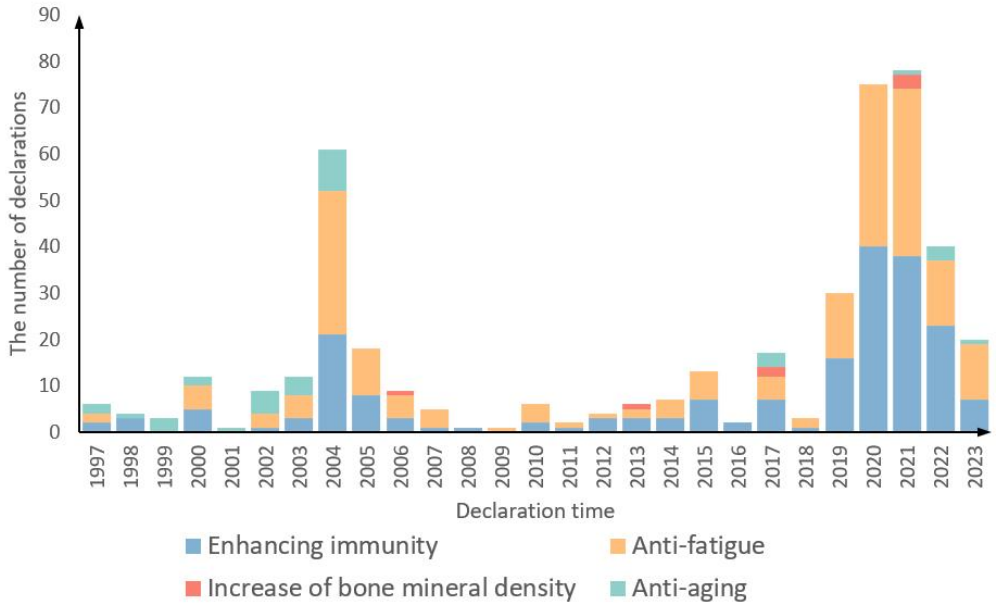

Figure 2 The relationship between the year of filing and the quantity declared.

5.2 Polygonati Rhizoma can be used both as medicine and food with high safety and has great potential in life cultivation and health preservation

Polygonati Rhizoma not only has significant "kidney-tonifying" effects, but also is a TCM as a source of drug and food. There are various administration forms of Polygonati Rhizoma, which can be combined with other TCM to make Polygonati Rhizoma compound, or be made into superfine powder using an ultra-fine grinder, or be made into dry powder from water decoction. There are also assorted

types of Polygonati Rhizoma food. People in daily life may process Polygonati Rhizoma into tonic diet, such as Polygonati Rhizoma beef soup, Polygonati Rhizoma rice porridge, Polygonati Rhizoma-tuber fleeceflower wine, etc. In the food industry, Polygonati Rhizoma functional drinks, Polygonati Rhizoma yogurt, Polygonati Rhizoma wine and other healthcare food are mainly developed [61].

In 2016, an outline for the "Healthy China 2030" initiative issued by the Central Committee of the Communist Party of China and the State Council for the first time proposed the development strategy of a healthy China, providing maximum policy support for the massive health industry. The Outline of the Strategic Plan for the Development of Traditional Chinese Medicine (2016-2030) put forward that the leading role of TCM in preventing a disease before it arises, the synergistic role in the treating major diseases, and the core role in disease rehabilitation will be given into full play by 2030. The country puts a premium on the role of TCM in the massive health industry. TCM healthcare food constitutes a great part of the massive health industry in China, which is produced under the guidance of TCM theory, with the raw materials mostly TCM as sources of drug and food. The healthcare food with primary component of Polygonati Rhizoma, a TCM as sources of drug and food, has high safety, precise healthcare function, and many healthcare products. Based on the "kidney-tonifying" effects, Polygonati Rhizoma has great potential in life cultivation and health preservation by virtue of its functions such as delaying aging, enhancing immunity, increasing bone mineral density, and alleviating physical fatigue.

5.3 The products of Polygonati Rhizoma in market has limitations and the pharmacological effects await in-depth investigation

The development of products associated with the "kidney-tonifying" effect of Polygonati Rhizoma still has some limitations. This study summarizes the 7 pharmacological effects of the "kidney-tonifying" effect of Polygonati Rhizoma. However, the functions of relevant healthcare food only concentrate on increasing bone mineral density, delaying aging, enhancing immunity, and alleviating physical fatigue. Further, the declaration number of healthcare foods related to "increase of bone density" and "anti-aging" effects of Polygonati Rhizoma is small, and the development is far from sufficient. Despite the strong kidney-tonifying effects of Polygonati Rhizoma, the products still have limited functions and the target group is small, which are caused by insufficient pharmacological research, so that the processing characteristics, material basis, and the mechanism of action all need to be further studied.

For the processing of Polygonati Rhizoma, the process refers to "raw use, single steaming, re-steaming, nine times of both steaming and drying" [62]. Nonetheless, due to the influence of factors such as the time and temperature of processing, the origin and variety of Polygonati Rhizoma and the different processing methods in various regions, there is no specific quality evaluation standard for the processing method of Polygonati Rhizoma with several steaming and drying. At present, many reports have been published pertaining to the effect of different times of steaming on active ingredients of Polygonati Rhizoma [63-65]. For example, Polygonati Rhizoma polysaccharides are generally decreased with the extension of steaming time, and the content of diosgenin in Polygonati Rhizoma is increased after processing. However, nine times of steaming and drying has not been confirmed as the best processing method for Polygonati Rhizoma yet, so the effect of different times of steaming on its efficacy can be explored deeply. For the research on the material basis and mechanism of action of Polygonati Rhizoma, among the 7 pharmacological effects related to the "kidney-tonifying" Polygonati Rhizoma summarized earlier, the active chemical

components associated with these pharmacological effects lack in-depth research or there is a dearth of corresponding experimental studies on biological mechanisms. For example, there is no available report on the specific chemical components of Polygonati Rhizoma that can improve reproductive function and hypertension, and on the specific mechanism of the anti-fatigue effect of Polygonati Rhizoma. Therefore, future attention can be paid to deeply study the material basis of Polygonati Rhizoma in improving reproductive system and hypertension, as well as the biological mechanism of the anti-fatigue and other "kidney-tonifying" effects of Polygonati Rhizoma.

Polygonati Rhizoma has many pharmacological effects correlated to its "kidney-tonifying" roles and has high medicinal value that can be applied to develop healthcare food with high safety. Its "kidney-tonifying" products are suitable for urban youth and middle-aged and elderly people, with a broad market. A survey [66] revealed that the purchase rate of healthcare products for the elderly is relatively high, accounting for 48.2%. In line with the purchase situation in this survey, the price for elderly people to purchase a single healthcare food at once is approximately 150 yuan. The healthcare food related to Polygonati Rhizoma includes Polygonati Rhizoma steamed chicken, Polygonati Rhizoma pig tripe, Polygonati Rhizoma rice porridge and other foods to enhance human immunity [67], and the market price of Polygonati Rhizoma is about 70-85 yuan/kg. It can be concluded that from the aspects of medicinal value, safety, suitable population, market price, etc., Polygonati Rhizoma is a kind of medicinal and edible TCM with high performance cost ratio, huge consumption potential and good development environment. Unfortunately, the current transformation and upgrading of the Polygonati Rhizoma development industry are restricted by weak product development ability, single product sales, lagging deep processing, lagging quality standards and brand building, etc. Hence, it is imperative to achieve breakthroughs in the product development based on the "kidney-tonifying" effects of Polygonati Rhizoma, and supplement the contents in processing, quality evaluation standards and pharmacological research according to the needs of clinical application, so as to provide theoretical basis and technical support for the application of Polygonati Rhizoma and its product development.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare that they have no competing financial interests or personal relationships that could appear to influence the work reported in this paper.

Author Contributions

Conceptualization, W.Z.; Data curation, K.W.; Formal analysis, S.G.; Methodology, Z.D.; Writing - original draft, J.S.; Writing - review and editing, J.S. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

No ethical approval was required for this article.

Funding

National Natural Science Foundation of China (NSFC) (No. 82274139), the Huadong Medicine Joint Funds of the Zhejiang Provincial Natural Science Foundation of China (No. LHDMZ22H280002), the Key Research and Development Program of Zhejiang Province (No. 2020C04020), Zhejiang Provincial Key Laboratory Project (No. 2012E10002).

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable.

References

[1] Chinese Pharmacopoeia Commission. *Pharmacopoeia of the People's Republic of China 2020*, Volume I; China Medical Science Press: Beijing, China, 2020; p. 319.

[2] Zhao W, Zhao Y, Yiider T. Research progress on pharmacological effects of Polygonati Rhizoma. *Chinese Herbal Hedicine* 2018; 49(18): 4439.

[3] Tu M, Ye W. Research Progress of Pharmacological Effects and Clinical Application of *Polygonatum sibiricum*. *Journal of Yichun University* 2018; 40(09): 27.

[4] Zhu J, Feng X, Wang J, et al. Effect of Polygonatum Sibiricum Preparation on Serum IL-1 and MMP-13 in Patients with Knee Osteoarthritis. *Chinese Journal of Surgery of Integrated Traditional and Western Medicine* 2018; 24(05): 568.

[5] Gongbao CD. Treatment of Rheumatoid Arthritis Using Tibetan Medicine Polygonatum Sibiricum Wine with Four Flavors. *Journal of Medicine & Pharmacy of Chinese Minorities* 2018; 24(12): 37.

[6] Zhang L, Chen J, Luo L, et al. Study on the Regulation of Chondrocyte Proliferation and Apoptosis in Osteoarthritis by Combination of Polygona-polysaccharose and MiR-204. *China Pharmacist* 2021; 24(04): 641.

[7] Zeng GF, Zhang ZY, Lu L, et al. Protective effects of Polygonatum sibiricum polysaccharide on ovariectomy-induced bone loss in rats. *Journal of Ethnopharmacology* 2011; 136(1): 224-229.

[8] Yan F, Zeng G, Zong S, et al. The Effect of Polygonatum Sibiricum Polysaccharide on the Expression of OPG and RANKL in the Rat Model of Ovariectomy-Induced Osteoporosis. *The Journal of Practical Medicine* 2017; 33(08): 1243-1246.

[9] Zhang L, Zeng G, Zong S, et al. Molecular Mechanism of Polygonatum Sibiricum Polysaccharide in the Prevention and Treatment of Postmenopausal Osteoporosis. *Chinese Journal of Tissue Engineering Research* 2018; 22(04): 493-498.

[10] Ye S, Li Y. Effect of polysaccharide on bone repair and bone metabolic factor in rats with osteoporotic fracture. *The Chinese Journal of Clinical Pharmacology* 2019; 35(18): 2128.

[11] Cheng Y, Zhang S, Li Y. Polygonatum Sibiricum Polysaccharides Affects Bone Metabolism of Diabetic Osteoporosis Rats via OPG/RANKL Signaling Pathway. *Chinese Journal of Gerontology* 2023; 43(16): 4029-4033.

[12] Cao Y, Wang K, Wang Z, et al. Pharmacodynamics study of polysaccharide from Polygonatum cyrtonema on zebrafish model with type 2 diabetic and osteoporosis. *Chinese Herbal Medicine* 2021; 52(21): 6545.

[13] Lu S, He Q, Lou F, et al. Effect of Polygonatum Sibiricum Polysaccharides on Osteogenic Differentiation of Adipose Derived Stem Cells in Osteoporosis Mice. *Journal of Oral Science Research* 2022; 38(02): 157.

[14] Du L, Nong MN, Zhao JM, et al. Polygonatum sibiricum polysaccharide inhibits osteoporosis by promoting osteoblast formation and blocking osteoclastogenesis through Wnt/β-catenin signalling pathway. *Scientific Reports* 2016; 6: 32261.

[15] Peng X, He J, Zhao J, et al. Polygonatum Sibiricum Polysaccharide Promotes Osteoblastic Differentiation Through the ERK/GSK-3β/β-Catenin Signaling Pathway In Vitro. *Rejuvenation Research* 2018; 21(1): 44.

[16] Li B, Wu P, Fu W, et al. The Role and Mechanism of miRNA-1224 in the Polygonatum sibiricum Polysaccharide Regulation of Bone Marrow-Derived Macrophages to Osteoclast Differentiation. *Rejuvenation Research* 2019; 22(5): 420.

[17] Zhao J, Lin F, Liang G, et al. Exploration of the Molecular Mechanism of Polygonati Rhizoma in the Treatment of Osteoporosis Based on Network Pharmacology and Molecular Docking. *Frontiers in Endocrinology* 2022; 12: 815891.

[18] Feng F, Yang D. The Research Progress of TCM Anti-Aging. *Chinese Journal of Aesthetic Medicine* 2017; 26(1): 36.

[19] Liu L, Li H, Yuan G. Effect of Polygonatum Sibiricum Polysaccharides on Learning and Memory in D-galactose-induced Aging Mice. *Journal of Beihua University (Natural Science Edition)* 2021; 22(02): 192.

[20] Zheng S. Protective effect of Polygonatum sibiricum Polysaccharide on D-galactose-induced aging rats model. *Scientific Reports* 2020; 10(1): 2246.

[21] Xie X, Hu G, Pan L, et al. Effect of Polygonatum sibiricum Extract in Improving the Organ Function of D-Galactose-induced Aging Mice and Its Mechanism. *Science and Technology of Food Industry* 2023; 44(18): 449-457.

[22] Shi Y, Feng J, Liang M, et al. Effect of Polygonati Rhizoma Regulating ATR/Chk1 Pathway on Vascular Aging in Naturally Aged Rats. *Traditional Chinese Drug Research and*

Clinical Pharmacology 2023; 34(06): 747-753.

[23] Zhao H, Ye Y, Zhang C, et al. Protective effects of Polygonatum sibiricum on testicular spermatogenic dysfunction in natural aging rats based on Nrf2 signaling pathway. *Chinese Medicinal Materials* 2023; 46(02): 454-461.

[24] Qian H, Xiao Y, Hou J, et al. Effect of Compatibility of Huangjing and Dilong on Learning and Memory and Hippocampal Nerve Apoptosis in Natural Aging Mice. *Asia-Pacific Traditional Medicine* 2021; 17(01): 25.

[25] Qin Z, Wei Z, Xu J. The Effect of Polygonati Rhizoma on DNA Damage Checkpoint ATM/ATR of Endothelail Progenitor Cells in Aged Rats. *Traditional Chinese Drug Research and Clinical Pharmacology* 2019; 30(05): 529.

[26] Luan Y, Jiang Y, Huang R, et al. Polygonati Rhizoma Polysaccharide Prolongs Lifespan and Healthspan in Caenorhabditis elegans. *Molecules* 2023; 28(5): 2235.

[27] Xiao X, Shen X, Zhang G, et al. Effect of Polygonatum Sibiricum Polysaccharides on Erythrocyte Immune in Children with Idiopathic Nephrotic Syndrome. *Journal of Gannan Medical University* 2018; 38(02): 134.

[28] Deng X, Duan H, Liu Z et al. Effects of Polygonatum Sibiricum Polysaccharide on Immunosuppressive Action Induced by Cyclophosphamide in Mice. *Journal of South-Central University for Nationalities* 2018; 37(02): 49.

[29] Zhang J, Liu N, Sun C, et al. Polysaccharides from Polygonatum sibiricum Delar. ex Redoute induce an immune response in the RAW264.7 cell line via an NF-κB/MAPK pathway. *RSC Advances* 2019; 9(31): 17988.

[30] Shen H, Wang F, Sun J, et al. Kidney-tonifying and Yang-strengthening effects and Immune Regulation Effects of Renshen Huangjing Decoction and Xiyangshen Dihuang Decoction. *World Chinese Medicine* 2021; 16(15): 2306.

[31] Yang Y, Hou T, Wang C, et al. Research on Preparation Technology of Polygonatum Sibiricum Tea and Its Immunoregulatory Effects. *Journal of Food Safety and Quality* 2022; 13(21): 7083.

[32] Zhang M, Feng J, Liu Z, et al. Nutritional components of Polygonatum sibiricum and Silky Chicken Extract and their effects on the morphology and immune performance of intestinal mucosa in mice with different immune status. *Food and Fermentation Industries* 2024; 1-12.

[33] Wang ZF, Hu YQ, Wu QG, et al. Virtual Screening of Potential Anti-fatigue Mechanism of Polygonati Rhizoma Based on Network Pharmacology. *Combinatorial Chemistry & High Throughput Screening* 2019; 22(9): 612-624.

[34] Ma H, Fang H, Liu Z. Study on the anti-fatigue effect of Polygonatum sibiricum polysaccharide. *Modern Communication* 2017; 2017(09): 190.

[35] Fu L. A Preliminary Study on Preparation Technology of Polygonatum kingianum Coll.et Hemsl polysaccharide buccal tablet and its anti-fatigue effect. *Journal of Yunnan University of Chinese Medicine* 2019.

[36] Chen L, Ke X. Study on the anti-fatigue effect of extract from Polygonatum multiflorum processed by ancient methods and its mechanism. *Scientific and Technological Innovation* 2019; 2019(04): 3.

[37] Chen Y, Hu H, Feng G, et al. Anti-Fatigue and Anti-Oxidant Effects of Crude and Processed Polygonatum Cyrtonema on Exhaustive Swimming Mice. *Pharmacology and Clinics of Chinese Materia Medica* 2021; 37(02): 92.

[38] Li W, Zhang X, Yang B, et al. Preparation of Polygonatum Cistanche Capsule and Evaluation of Its Anti-fatigue Effect. *Food and Fermentation Sciences & Technology* 2022; 58(5): 72.

[39] Yang Y, Li Y, Yu L, et al. Muscle Fatigue-Alleviating Effects of a Prescription Composed of Polygonati Rhizoma and Notoginseng Radix et Rhizoma. *BioMed Research International* 2020; 2020: 3963045.

[40] Sun T. Protective effect of Polygonatum sibiricum polysaccharide on gentamicin-induced renal injury in rats. *Journal of Anhui Agricultural University* 2019.

[41] Hua Y. Regulatory effect of polysaccharides on kidney injury induced by high-intensity exercise rats. J*ournal of Yangzhou University* 2020; 41(01): 50.

[42] Peng J. The Protective Effect of Polygonatum Sibiricum Saponins on Renal Injury in diabetes Nephropathy Rats and its Effect on Wnt/β-catenin Signal Transduction Pathway. *Chinese Traditional Patent Medicine* 2019; 41(10): 2518.

[43] Yang M, Wang J, Zhang S, et al. Analysis of the mechanism of the effect of Chinese medicine actinolite on warming the kidney and strengthening yang. *China Pharmaceuticals* 2010; 19(10): 84.

[44] Deng G. Clinical Observation on the Treatment of Asthenospermia and Hypospermia with Huangjing Zanyu Capsules. *Nei Mongol Journal of Traditional Chinese Medicine* 2017; 36(2): 14.

[45] Chen S, Su J, Jin X, et al. Effect of superfine powder and aqueous extract of Polygonati Rhizoma on rats with natural perimenopausal syndrome. *China Journal of Chinese Materia*

Medica 2023; 48(04): 1054.

[46] Yang Z. Research on the protective effect of *Polygonatum sibiricum* on testicular injury in cadmium-exposed mice. *Journal of Anhui Agricultural University* 2018.

[47] Han C, Zhu Y, Yang Z, et al. Protective effect of Polygonatum sibiricum against cadmium-induced testicular injury in mice through inhibiting oxidative stress and mitochondria-mediated apoptosis. *Journal of Ethnopharmacology* 2020; 261: 113060.

[48] Chen T, Li Z, Wang B, et al. Effects of Hailong Huangjing powder on the damaged spermatogenic cells of oligoasthenospermia mice induced by microwave radiation. *Journal of Shaanxi University of Chinese Medicine* 2022; 43(07): 823.

[49] Hu Y, Yang C. Exploring the relationship between liver, spleen, and kidney with risk factors for hypertension in the perspective of traditional Chinese medicine. *Journal of Changchun University of Chinese Medicine* 2013; 29(03): 438.

[50] Huang S, Ou S. Diagnosis and treatment of renal injury induced by hypertension. *Chinese Journal of Nephrology* 2005; 2005(10): 16.

[51] Ning W. Study on the clinical effect of Huangjing Sicao Decoction combined with amlodipine on patients with Yin deficiency and Yang hyperactivity hypertension. *Clinical Journal of Chinese Medicine* 2020; 12(06): 52.

[52] Wu Y, Yang S. The influence of the Huangjing Yiyin decoction on blood pressure, blood lipid and function of liver and kidney in elderly patients with hypertension. *Clinical Journal of Chinese Medicine* 2016; 8(29): 69.

[53] Tao C. Clinical Observation on the Treatment of Early Renal Damage in Hypertension Due to Deficiency of Liver and Kidney Yin with Modified Huangjing Sicao Decoction. *Journal of Hebei North University* 2021.

[54] Su J, Wang Y, Yan M, et al. The beneficial effects of Polygonatum sibiricum Red. superfine powder on metabolic hypertensive rats via gut-derived LPS/TLR4 pathway inhibition. *Phytomedicine* 2022; 106: 154404.

[55] Zhou F. A Brief Discussion on Clinical Manifestiatons of "Kidney Deficiency". *Nei Mongol Journal of Traditional Chinese Medicine* 2014; 33(32): 88.

[56] Yu X. Clinical Research Progress in Osteoporosis. *Chinese Medical Innovations* 2022; 19(21): 175.

[57] Peng J, Wu D. Health Aging- The Fundamental Measure to Solve Aging Problem. *Medical Journal of Chinese Civil Administration* 2001; 2001(02): 126.

[58] Chen Y, Feng X, Sun Y, et al. Understanding of kidney deficiency syndrome under the guidance of syndrome differentiation health care theory. *China Journal of Traditional Chinese Medicine and Pharmacy* 2022; 37(09): 5043.

[59] Liang Q. Urban youth health concept survey report: health consumption into universal fashion sub-health problems. *Economic Information Daily* (9 November 2022).

[60] Zhao H, Wang X, Rong W, et al. Analysis of Circumstance of Health Foods Registered from 2003 to 2005. *Chinese Journal of Food Hygiene* 2008; 2008(01): 52.

[61] Zheng L, Ma X, Sun Y. Research Progress of the Resource Distribution and Application Status of Polygonatum Sibiricum with Homology of Medicine and Food. *Journal of Zhejiang Agricultural Sciences* 2022; 63(08): 1679.

[62] Qin Y, Zhang L, Zhao Q, et al. Research progress on Polygonatum cyrtonema processed by nine times steaming and nine times shining. *Chinese Herbal Medicine* 2020; 51(21): 5631.

[63] Cai J, Zhu Y, Yi G, et al. Screening Processing Technology of Huangjing (*Polygonatum sibiricum*) by Orthogonal Test and Study on Its Validity. *Liaoning Journal of Traditional Chinese Medicine* 2020; 47(05): 153.

[64] Rong X. Changes of Polygonatum sibiricum chemical constituents and contents during the processing. *The Department of Oral Medicine Electronic Magazine* 2019; 6(02): 31.

[65] Zhang X, Tang Y, Tang L, et al. Research progress of processing and quality analysis of Polygonatum Sibiricum. *Modern Chinese Doctor* 2018; 56(22): 165.

[66] Li W, Sun Y, Yin W, et al. Study on aging health care products consumption behaviors and influence factors. *Chinese Journal of Gerontology* 2021; 41(19): 4394.

[67] He P, Zhang J, Zhao Y, et al. Advances of Medicinal Value and Health Food Application of Polygonatum. *Strait Pharmaceutical Journal* 2021; 33(12): 31.