

Review Article

Pharmacological Activities of Sijunzi Decoction Which Are Related to Its Antioxidant Properties

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This paper introduces the antioxidant constituents and pharmacological effects of Sijunzi decoction by looking up literatures in recent years. Sijunzi decoction is composed of Ginseng, Atractylodes, Tuckahoe, and Glycyrrhiza. The antioxidant ingredients of Sijunzi decoction include paeonol, dauricine, naringin, and isoliquiritigenin. The study has proved that it possesses wide pharmacological effects of antiscavenger diseases, antinervous system disease, antidiabetes, antimetabolic syndrome, and antitumor. Research on the antioxidant components of Sijunzi decoction and their targets is a promising study area in the future.

1. Introduction

Phagocytic cells release a significant amount of reactive oxygen species (ROS) through respiratory burst under the stimulus of pathogenic microorganisms when “spleen qi deficiency” occurs, which is often associated with gastrointestinal inflammation. Through NADPH oxidation, ROS can cause oxidative damage and further aggravate the inflammation. Studies have shown that Sijunzi decoction has evident antioxidant effects [1] and can eliminate or reduce biological membrane lipid peroxidation caused by free radicals [2]. Moreover, Sijunzi decoction can increase superoxide dismutase (SOD) activity and reduce MDA generation to speed up the elimination of free radicals and other harmful substances to protect biological macromolecules from damage and improve the DNA repair. Sijunzi decoction has an antioxidant effect because it contains a wide variety of free radical scavenging molecules. These antioxidant compounds possess anti-inflammatory, antiatherosclerotic, antitumor, antimutagenic, anticarcinogenic, or antibacterial properties. The antioxidants derived from Sijunzi decoction are summarized in this study. The source of antioxidants discussed in this study is shown in Table 1.

2. The Role of Antioxidants from Sijunzi Decoction

2.1. Antioxidants of Anticardiovascular Disease. Several components of Sijunzi soup have antioxidant activity and decrease the occurrence of cardiovascular diseases. Studies have shown that isoliquiritigenin, which is a natural antioxidant derived from liquorice, has a significant role in anticardiovascular disease through activation of the AMP-activated protein kinase (AMPK) and ERK signaling pathways and balance of cellular redox status [3]. Naringin derived from liquorice, which is the second most important antioxidant component, inhibits reactive oxygen species- (ROS-) activated MAPK pathway involved in high glucose-induced injuries of H9c2 cardiac cells [4]. Naringin mitigates hypertension and thrombosis by increasing the bioavailability of nitrogen oxide (NO) and protecting the endothelial function from ROS [5]. Moreover, naringin can improve redox-sensitive myocardial ischemia reperfusion injury [6]. Glabridin, which is derived from liquorice and is responsible for its antioxidative characteristics in low-density lipoprotein (LDL) oxidation, is also important [7]. Isorhamnetin, which is also derived from liquorice, can inhibit the H₂O₂-induced activation of the

TABLE 1

Source of ingredient	Antioxidant ingredient
Ginseng	Paeonol, dauricine, pancratistatin
Licorice	Isoliquiritigenin, naringin, glabridin, isorhamnetin, calycosin, pinocembrin, nicotiflorin, liquiritigenin, kaempferol, licoflavone, isobavachalcone, morusin, licochalcone A, licochalcone B, rutin, quercetin

intrinsic apoptotic pathway through ROS scavenging and ERK inactivation. Therefore, isorhamnetin is a promising reagent for the treatment of ROS-induced cardiomyopathy [8].

Paeonol, which is mainly collected from ginseng, affects the development of cardiovascular tissues. Paeonol has antioxidant and anti-inflammatory properties, which can be developed for use in anti-inflammatory and vascular disorders [9]. The therapeutic mechanism of paeonol prevents monocyte adhesion onto vascular endothelial cells (VECs) induced by ox-LDL [10]. Paeonol has a protective effect on the hypoxia/reoxygenation damage of myocardial cells; therefore, it can prevent myocardial infarction induced by isoproterenol in rats [11]. Paeonol can also decrease oxidative injury and repair blood vessel endothelium, as well as prevent the development of coronary diseases [12].

2.2. Antioxidants against Diabetes and Metabolic Syndrome.

Metabolic syndrome is a low-grade inflammatory state, where oxidative stress is involved. Some of the antioxidants extracted from Sijunzi decoction exhibit antidiabetes activities or metabolic syndrome reversal. Isoliquiritigenin can significantly decrease the level of blood glucose [13]. Naringin exhibits significant antidiabetic effects by potentiating the antioxidant defense system and by suppressing proinflammatory cytokine production in a rat model of T2DM [14]. Naringin reverses the metabolic syndrome by decreasing inflammatory cell infiltration and plasma lipids; the process mitigates oxidative stress and improves mitochondrial function [15]. Glabridin, which is a major active flavonoid in *Glycyrrhiza glabra* (licorice), improves learning and memory in mice. Glabridin reverses learning and memory defects in diabetic rats. Glabridin treatment partially improves the reduced body weight and hyperglycemia of diabetic rats. Their mechanisms may be related to the combination of antioxidant, neuroprotective, and anticholinesterase properties of glabridin [16] or as an activator of AMP-activated protein kinase (AMPK) [17].

2.3. Antioxidants of Antineurological Diseases. Clinically, Sijunzi decoction is often used to treat several neurological diseases. Calycosin, which is derived from licorice, has a neuroprotective effect against cerebral ischemia/reperfusion injury through its antioxidant effects [55]. Isoliquiritigenin protects HT22 hippocampal neuronal cells from oxidative stress-induced glutamate. The mechanisms are related to the reversed ROS production and mitochondrial depolarization induced by glutamate, as well as the regulation expression of

the apoptotic regulators, Bcl-2 and Bax [31]. Isoliquiritigenin can protect dopaminergic cells from oxidative injury and prevent A β (25–35)-induced neuronal apoptotic death by interfering with the increase of [Ca²⁺] and ROS [32]. Liquiritigenin is derived from licorice; this compound improves behavioral performance and attenuates neuronal loss in the brain of rats [64]. Pinocembrin derived from licorice has a significant role in neurovascular protection by protecting the cerebral ischemia and increasing the viability of the mitochondrial membrane [57, 58, 80, 81]. Pinocembrin abrogates the effects of the neurotoxin 1-methyl-4-phenylpyridinium, which mimics Parkinson's disease with an elevation of intracellular ROS level and apoptotic death [82]. This phenomenon might be another mechanism for pinocembrin in mitigating nervous system diseases.

Nicotiflorin, which is derived from licorice, markedly reduces brain infarct volume and neurological deficits immediately following its administration after the onset of ischemia. Nicotiflorin also protects against memory dysfunction, energy metabolism failure, oxidative stress in multi-infarct dementia model rats, cerebral ischemic damage, aluminum chloride-induced cognitive dysfunction, and mitochondrial oxidative damage [61, 62]. Investigations about the protective mechanism of kaempferol glycosides showed the involvement of their antioxidative activity, blockage of caspase cascades, attenuation of NMDA-induced neuronal toxicity, inhibition of monoamine oxidase (MAO), excessive NO production, and others [63].

Naringin may be beneficial in mitigating 3-NP-induced neurodegeneration through its antioxidant and antiapoptotic effects [39, 40].

Glabridin has a neuroprotective effect because of the modulation of multiple pathways associated with apoptosis. Glabridin significantly attenuates the level of brain malonyldialdehyde (MDA) in MCAO rats; however, it elevates the levels of two endogenous antioxidants in the brain, namely, SOD and reduced glutathione [48].

Dauricine is derived from ginseng and has cerebral ischemia-reperfusion injury protection effect, which may be related to its inhibition of neuron apoptosis [22]. Paeonol mitigates neuronal damage not only by decreasing ROS overgeneration, but also by regulating expression of apoptosis proteins and neurotrophic factors [18, 19].

2.4. Antioxidants of Antirespiratory Diseases. Three components from Sijunzi soup have significant roles in preventing respiratory diseases.

Naringin has antitussive, anti-AHR, and anti-inflammation effects on chronic cigarette smoke exposure-induced chronic bronchitis in guinea pigs; this compound improves SOD activity in lung tissue and increases the content of lipoxin A4 in bronchoalveolar lavage fluid (BALF) in a guinea pig model for chronic bronchitis [41, 42]. Dauricine induces glutathione depletion and apoptosis in lungs of CD-1 mice and in cultured human lung cells [23]. Liquiritigenin can protect human lung cells (A549) from a hemolysin-mediated injury [65].

2.5. Antioxidants against Digestive System Diseases. Several components of Sijunzi soup are also involved in antidiigestive system diseases.

Liquiritigenin has a choleric effect and exhibits the ability to induce hepatic transporters and phase-II enzymes, which are a group of antioxidant systems that function against oxidative stress, carcinogenesis, mutagenesis, and other forms of toxicity [66]. Isoliquiritigenin, which is similar with liquiritigenin, can repress LXR α -dependent hepatic steatosis through JNK1 inhibition and protect hepatocytes from oxidative injury inflicted by fat accumulation [33].

The induction of HO activity by pinocembrin has a protective effect against hepatic damage associated with oxidative stress in rats. Pinocembrin challenges hepatocarcinogens and may exhibit anticarcinogenic effects [59]. Dauricine is subject to oxidative bioactivation in human liver microsomes *in vitro* and in rats *in vivo* [24].

Licoflavone, isobavachalcone, and quercetin are derived from licorice. Licoflavone feeding suppresses gastric mucosa injury and protects and restores injured mucosa in rats with chronic superficial gastritis. These effects are related with the upregulation of serum PGE2 levels [69]. Isobavachalcone shows broad antioxidative activities in rat liver microsomes and mitochondria [70]. Quercetin has beneficial effects on liver fibrosis in rats by enhancing antioxidant enzyme activity and reducing the prooxidant effects [79].

Several studies have demonstrated that isorhamnetin is efficient in protecting hepatocytes against oxidative stress by Nrf2 activation and in inducing the expression of its downstream genes [50].

Paeonol can inhibit HSC proliferation and induce mitochondrial apoptosis by disrupting the NF- κ B pathway, which is probably the mechanism of paeonol reduction of liver fibrosis [20].

2.6. Antioxidants of Antitumors. Natural compounds isolated from Sijunzi decoction, which are rich sources of novel anticancer drugs, have gained increasing interest.

Isoliquiritigenin significantly inhibits the proliferation of C4-2 prostate cancer cells in IEC-6 normal epithelial cells *in vitro*, increases intracellular ROS levels, and causes SKOV-3 and hela cell apoptosis [34–36]. The prodifferentiation effect of isoliquiritigenin on HL-60, particularly the role of redox homeostasis in regulating HL-60 cell differentiation by modulation of the Nrf2/ARE pathway, has been investigated [37, 38].

Licochalcone A and licochalcone B are derived from licorice. Licochalcone A has potent antitumor effects in prostate, breast, and bladder cancer, as well as in leukemia cell lines [74]. A study has shown that the induction of endoplasmic reticulum stress through a PLC γ 1-, Ca²⁺-, and ROS-dependent pathways may be significant when licochalcone A induces apoptosis in HepG2 hepatocellular carcinoma cells [75]. Furthermore, licochalcone B inhibits the concentration-dependent bladder cancer cell proliferation; this antiproliferative effect is caused by the induction of S-phase arrest and apoptotic cell death [77].

Dauricine can inhibit the proliferation activity of urinary tract tumor cells. By inhibiting the NF- κ B signaling pathway in colon cancer cells, dauricine inhibits proliferation and invasion of the cancer [25, 26]. Furthermore, dauricine inhibits human breast cancer angiogenesis by suppressing hypoxia inducible factor-1 α (HIF-1 α) protein accumulation and vascular endothelial growth factor (VEGF) expression [27].

Naringin can induce receptor death and mitochondria-mediated apoptosis in human cervical cancer cells [43]. Naringin reduces the growth potential of human triple-negative breast cancer cells by targeting the β -catenin signaling pathway [44]. Naringin is effective in reducing the number of preneoplastic lesions in rats exposed to 1,2-dimethylhydrazine. Several of these effects may be caused by reduced cellular proliferation and tissue levels of iron and the recovery of antioxidant mineral levels induced by this flavonoid [45].

Pancreatistatin is derived from ginseng and may be a novel mitochondria-targeting compound that selectively induces apoptosis in cancer cells and significantly reduces tumor growth [28, 29]. Pancreatistatin treatment in cancer cell lines results in increased ROS production and reduction of mitochondrial membrane potential [30]. Morusin, which is derived from licorice, significantly inhibits the growth and clonogenicity of HT-29 human colorectal cancer cells, as well as the human cervical cancer stem cell growth and migration [72, 73].

Calycosin is an indispensable element in antitumor activities. Calycosin inhibits breast cancer growth and is obtained by estrogen receptor (ER) β -mediated regulation of the IGF-1R signaling pathways and miR-375 expression [56]. Isorhamnetin exhibits antioxidant and antiproliferative activities in a variety of cancer cell lines [51–53].

Glabridin is a novel anticancer agent for treating breast cancer in three different manners, namely, inhibition of migration, invasion, and angiogenesis [49]. Pinocembrin triggers Bax-dependent mitochondrial apoptosis in colon cancer cells [60]. Isobavachalcone induces apoptotic cell death in neuroblastoma through the mitochondrial pathway and is not cytotoxic against normal cells [71]. Paeonol has significant growth-inhibitory and apoptosis-inducing effects in gastric cancer cells, both *in vitro* and *in vivo* [21].

2.7. Antioxidants against Inflammation. The components of Sijunzi soup have a significant role against inflammation.

Naringin is an effective anti-inflammatory compound for attenuating the chronic pulmonary neutrophilic inflammation in CS-induced rats. The oxidative stress caused by cigarette smoke (CS) exposure increases inflammatory cell influxes in the lungs, followed by lipid peroxidation, and increases proinflammatory cytokines, such as the tumor necrosis factor- α [46]. Liquiritigenin has an anti-inflammatory effect, as shown by the inhibition of nitric oxide and tumor necrosis factor-production, which is induced by the lipopolysaccharides in macrophages [67]. Licochalcone A protects BALB/c mice from lipopolysaccharide-(LPS-) induced endotoxin shock by inhibiting the production

TABLE 2

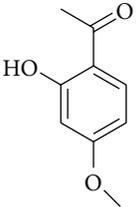
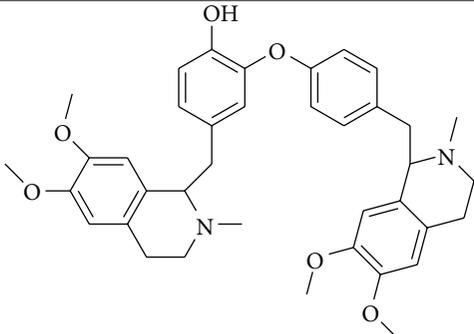
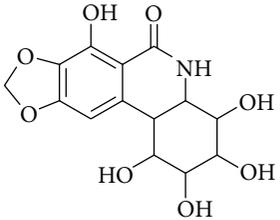
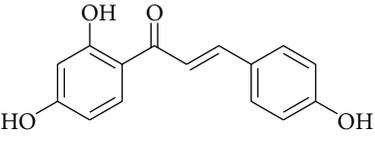
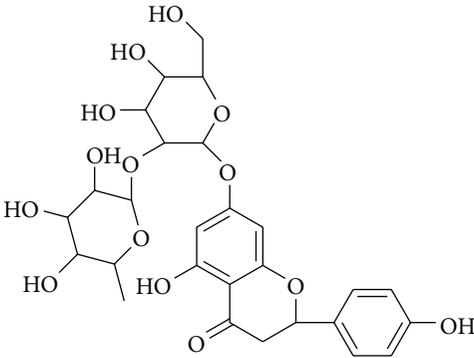
Antioxidant ingredient	Structure of compound	Pharmacological activity	References
Paeonol		(1) Antioxidant and anti-inflammatory properties (2) Treatment for vascular disorders (3) Protection against atherosclerosis. (4) Neuroprotection (5) Protection against hypoxia/reoxygenation damage (6) Growth-inhibitory and apoptosis-inducing effects on cancer cells	[9–12, 18–21]
Dauricine		(1) Inhibition of neuron apoptosis (2) Induction of glutathione depletion and apoptosis in cancer cells (3) Inhibition of tumor cell proliferation (4) Inhibition of cancer angiogenesis (5) Induction of tumor cell apoptosis	[22–27]
Pancreatistatin		(1) Increased reactive oxygen species (ROS) production (2) Induction of mitochondrial membrane collapse (3) Potential induction of tumor apoptosis (4) Reduction of tumor growth	[28–30]
Isoliquiritigenin		(1) Cardioprotection against ischemic injury (2) Decreased blood glucose level (3) Prevention of neurodegenerative diseases (4) Prevention of neuronal apoptotic death (5) Repression of liver X receptor- α -dependent hepatic steatosis (6) Induction of apoptosis (7) Inhibition of cancer cell proliferation (8) Enhancement of HepG2 cell radiosensitivity	[3, 13, 31–38]
Naringin		(1) Inhibition of ROS-activated MAPK pathway (2) Antihypertensive and antithrombotic effects (3) Protection of endothelial function from ROS (4) Protection against myocardial ischemia reperfusion injury (5) Antidiabetic effect (6) Decreased inflammatory cell infiltration (7) Neuroprotective effect (8) Anti-inflammatory effect (9) Protection against pulmonary fibrosis (10) Induction of cancer cell apoptosis (11) Attenuation of chronic pulmonary neutrophilic inflammation (12) Mitigation of erythrocyte aging	[4–6, 14, 15, 39–47]

TABLE 2: Continued.

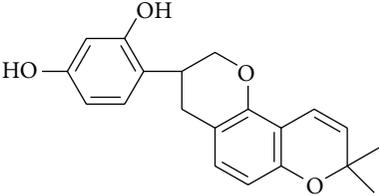
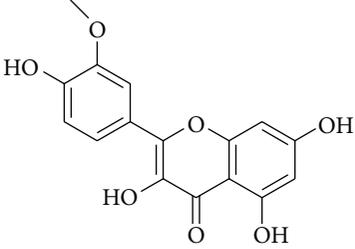
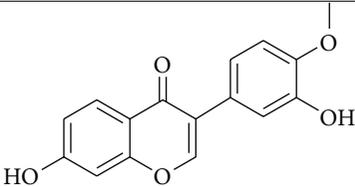
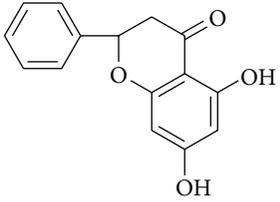
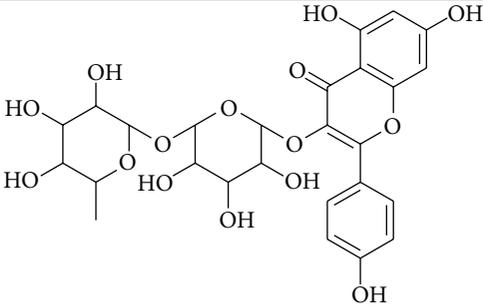
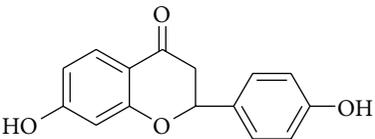
Antioxidant ingredient	Structure of compound	Pharmacological activity	References
Glabridin		(1) Antioxidation (2) Protection against obesity-related metabolic disorders (3) Neuroprotective effect (4) Anti-inflammatory effect (5) Anticancer effect	[7, 16, 17, 48, 49]
Isorhamnetin		(1) Inhibition of ROS-induced apoptotic pathway (2) Anti-ROS-induced cardiomyopathy (3) Protection of hepatocytes against oxidative stress (4) Antioxidant and antiproliferative effects (5) Modulation of the peroxisome proliferator-activated receptor pathway in gastric cancer	[8, 50–54]
Calycosin		(1) Neuroprotection (2) Inhibition of breast cancer growth	[55, 56]
Pinocembrin		(1) Neurovascular protection (2) Protection of cerebral ischemia (3) Increased viability and mitochondrial membrane potential of cultured rat cerebral microvascular endothelial cells (4) Protection of rat brain against oxidation and apoptosis (5) Abrogation of neurotoxin effects (6) Improvement of rat cognitive impairments (7) Anticarcinogenic effects (8) Triggering mitochondrial apoptosis in cancer cells	[57–60]
Nicotiflorin		(1) Improvement of brain infarct volume and neurological deficits (2) Protection against memory dysfunction, energy metabolism failure, and oxidative stress (3) Protection against cerebral ischemic damage	[61–63]
Liquiritigenin		(1) Improvement of behavioral performance and attenuation of neuronal loss in the brain (2) Protection of human lung cells (A549) (3) Choleric effect and induction of hepatic transporters and phase-II enzymes (4) Induction of apoptosis in the mitochondrial pathway (5) Anti-inflammatory effect (6) Protection of osteoblast against cytotoxicity	[64–68]

TABLE 2: Continued.

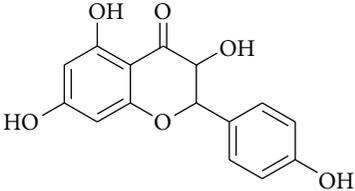
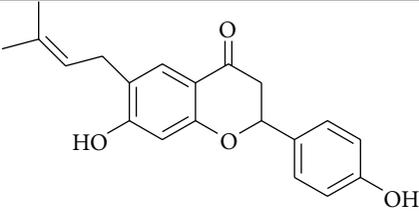
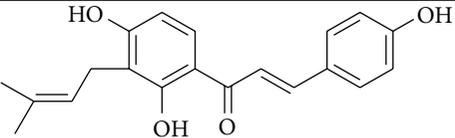
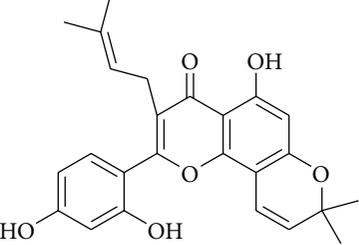
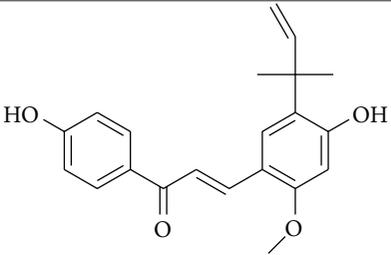
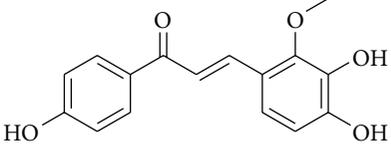
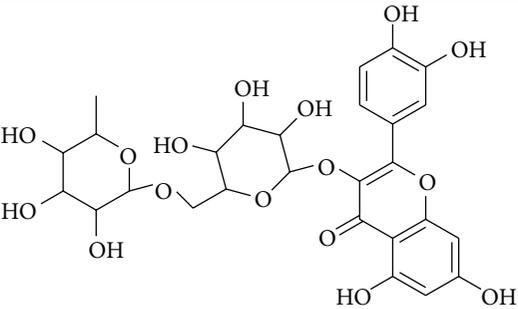
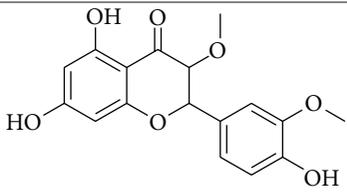
Antioxidant ingredient	Structure of compound	Pharmacological activity	References
Kaempferol		(1) Attenuation of neuronal toxicity (2) Inhibition of monoamine oxidase and excessive NO production	[63]
Licoflavone		(1) Suppression of gastric mucosa injury	[69]
Isobavachalcone		(1) Antioxidant effects on rat liver microsomes and mitochondria (2) Induction of neuroblastoma apoptosis	[70, 71]
Morusin		(1) Anticancer properties	[72, 73]
Licochalcone A		(1) Antitumor and antimetastatic properties (2) Apoptosis-promotion (3) Inhibition of inflammatory cytokines and ROS production	[74-76]
Licochalcone B		(1) Inhibition of cancer cell proliferation	[77]
Rutin		(1) Inhibition of primary humoral immune response	[78]

TABLE 2: Continued.

Antioxidant ingredient	Structure of compound	Pharmacological activity	References
Quercetin		(1) Antiliver fibrosis properties (2) Modulation of degranulation and oxidative burst	[54, 69, 79]

of inflammatory cytokines and ROS [76]. Quercetin and kaempferol can modulate the degranulation and oxidative burst of stimulated human neutrophils. Rutin, which is derived from licorice, inhibits the primary humoral immune response in mice [78]. The induction of HO-1 by isorhamnetin may reduce ROS production, and the antioxidant property of isorhamnetin might inhibit the COX-2 expression in response to inflammation [54].

2.8. *Others.* The Sijunzi soup has a significant role in other aspects, such as the mitigation of musculoskeletal diseases and the progression of hematological system diseases.

The modulation of PI3K antioxidant effects and the attenuation of mitochondrial dysfunction by liquiritigenin represent an important mechanism for the protection of osteoblasts against cytotoxicity, which results from mitochondrial oxidative stress [68].

Naringin mitigates erythrocyte aging induced by paclitaxel (PTX), which suggests that naringin inhibits PTX-induced aging by reducing the PTX-induced oxidative stress [47].

3. Antioxidants List

See Tables 1 and 2.

4. Conclusion

The oxidative products of organisms cause several diseases. Several studies have been conducted on the effects of antioxidant-scavenging free radical. Sijunzi decoction contains a variety of antioxidants. The effects of these antioxidants have gained attention from scholars at home and abroad. Various research results have been obtained. The antioxidants in Sijunzi decoction decrease free radical content and enhance the free radical scavenging activities in the body by adjusting the activity of the antioxidative enzyme system when spleen deficiency occurs. The antioxidants in Sijunzi decoction eliminate the peroxidation damage in tissues, cells, and various types of biological macromolecules and protect the normal structure and function of the cell membrane. Sijunzi decoction improves the pathological changes of tissues and cells in the cardiovascular and respiratory systems, corrects the nerve and endocrine functions, strengthens digestion, and induces tumor cell apoptosis. Revealing mainly the antioxidant of Sijunzi decoction is

necessary to understand its antioxidant effects. Research to discover the antioxidant components of Sijunzi decoction and their target research are areas of future study in this field.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

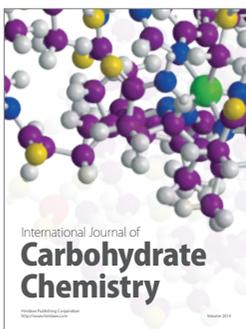
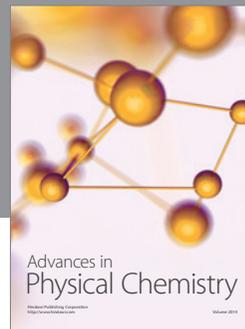
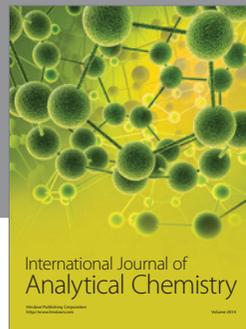
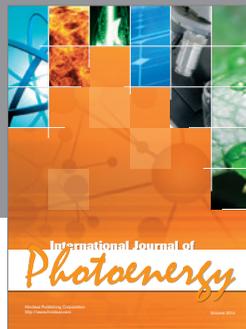
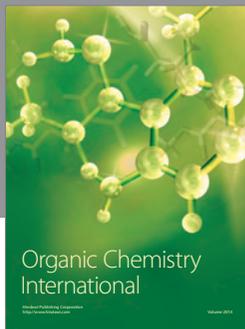
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