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Review Article

A prospective review of the health-promoting potential of Jing Si Herbal Tea

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Abstract

Traditional Chinese medicine (TCM) has gained considerable attention over the past few years for its multicomponent, multitarget, and multi-pathway approach to treating different diseases. Studies have shown that TCMs as adjuvant therapy along with conventional treatment may benefit in safely treating various disorders. However, investigations on finding effective herbal combinations are ongoing. A novel TCM formula, "Jing Si Herbal Tea (JSHT)," has been reported recently for their health-promoting effects in improving overall body and mental health. JSHT is a combination of eight herbs recognized in Chinese herbal pharmacopoeia for their anti-viral, anti-aging, and anti-cancer properties as well as protective effects against cardiovascular, metabolic, neural, digestive, and genitourinary diseases. Thus, to better understand the beneficial effects of the ingredients of JSHT on health, this review intends to summarize the preclinical and clinical studies of the ingredients of JSHT on human health and diseases, and possible therapeutic effects with the related mode of actions and future prospects for their application in complementary therapies.

Keywords: *Health benefits, Jing Si herbal tea, Pharmacological properties, Phytochemical compounds, Traditional Chinese medicine*

Introduction

Recently, there has been a noticeable increase in the prevalence of complementary and alternative medicine (CAM) practice, and 75% of the world's population relies on herbs for their primary health-care requirements [1].

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As CAM use has expanded dramatically, medical professionals should inquire about patients' CAM use concurrently with their medical history. In addition to patients' interest in CAM, researchers have also explored the effectiveness of various therapies and interventions [2].

Traditional Chinese medicine (TCM), an essential category of CAM, is renowned for Chinese herbal medicine and is gaining popularity in many countries. TCM clinics are frequented both by patients looking for therapy for various conditions and those looking to complement, alter, or substitute Western medicine (WM) [3].

Diseases were originally treated using single herbs. However, researchers gained more clinical expertise over time and recognized that ailments were caused by imbalances between the body's various systems. Therefore, to support the dynamic balance between body systems and achieve the best curative results with the most negligible toxicological impact, researchers now prefer the combination of several herbs based on disease severity [4].

Mirroring the pharmaceutical industry, combining TCM to develop new herbal beverages, commonly known as teas, has gained popularity among health-conscious consumers. In addition, herbal tea is a traditional beverage in many cultures around the globe. In general, herbal beverages are composed of natural components derived from various plant parts, including buds, flowers, roots, stems, leaves, and fruits. Scientific evidence shows that herbal teas are rich sources of natural bioactive compounds. These compounds render various biological effects such as anti-viral, anti-oxidant, anti-bacterial, anti-inflammatory, anti-allergic, vasodilatory, anti-mutagenic, anti-carcinogenic, and anti-aging effects, among others [4]. Considering the pharmacological advantages of integrated TCM, the Buddhist Tzu Chi Medical Foundation of Taiwan has recently developed a novel TCM herbal formula known as Jing Si herbal tea (JSHT) by combining eight herbs [5-7]. JSHT is a collective effort to offer TCM as a solution to help citizens improve their overall health and regain balance of the mind and body [5]. The ingredients of JSHT have been reported to exert anti-COVID, anti-aging, and anti-cancer effects, as well as protection against cardiovascular, metabolic, neural, digestive, and genitourinary disease. In the last few decades, substantial studies have been conducted on the effects of JSHT ingredients against different common human diseases. Nevertheless, studies to determine the therapeutic effects of these ingredients are ongoing. However, a review of the fundamental to clinical studies on the potential health benefits of JSHT and its ingredients on various human diseases may provide a useful overview to guide decisions for both consumers and the scientific community. To better understand the beneficial effects of the ingredients in JSHT on health, we searched for relevant articles on *Google Scholar, Web of Science, PubMed, NCBI, Science Direct, ResearchGate*, and *clinicaltrials.gov*. This review first details the individual ingredients of JSHT and their major phytochemical compounds then summarizes its possible therapeutic effects and discusses the mechanism of action and toxicity. In light of this, we hope this review can provide a new foundation for further research on JSHT.

Ingredients of JSHT and their major phytochemical compounds

At the end of 2020, Hualien Tzu Chi Hospital developed JSHT for promoting health and wellness. JSHT, approved by the Taiwan Ministry of Health and Welfare, is the brainchild of a joint effort between WM and TCM professionals. JSHT was prepared with selected local Taiwanese herbs, including leaves of *Anisomeles indica* (L.) Kuntze, *Artemisia argyi*, *Ophiopogon japonicas,* and *Perilla frutescens*; roots of *Houttuynia cordata, Glycyrrhiza glabra*, and *Platycodon grandifloras*; and flowers of *Chrysanthemum morifolium* Ramat. Different authors have extensively investigated the major chemical constituents of each ingredient of JSHT and their diverse bioactivity. Therefore, this section introduces and describes in detail the various ingredients of JSHT and their major phytochemical compounds [Figure 1 and Table 1].

A. indica (L.) Kuntze (family: *Lamiaceae*) is an essential plant for ethnomedicine, with a long history of application in the treatment of various ailments within the context of TCM. The plant can be found across tropical regions, particularly in Southeast Asia, including Taiwan, China, India, Vietnam, Indonesia, Thailand, Philippines, and Australia. The entirety of the plant has a variety of medical applications and currently, multiple phytochemicals have been prepared from the crude extracts of various parts of the plant. The plant contains flavones, alkaloids, arachnoids, and terpenoids such as ovatodiolide, anisomelic acid, iso-ovatodiolide, 4,7-oxycycloanisomelic acid, stigmasterol, and β-sitosterol. The major phytochemicals found in the leaves include tannin, alkaloids, carotenoids, glycosides, and saponin. The seeds contain stigmasterol, β-sitosteroltetracosine, macrocylic diterpenes, and β-tetracoranel-β-amyrin while the flowers contain ovatodiolide, anisomelic acid, and macrocyclic diterpenes [16].

A. argyi (family: *Asteraceae*) is a plant endemic to the northern temperate regions, particularly in Asia. In East Asia, it has a long history of being used as a culinary plant and dietary supplement. *A. argyi* contains a wide range of nutrients, including minerals, polyunsaturated fatty acids, proteins, essential amino acids, dietary fibers, and numerous bioactive compounds such as polysaccharides, flavonoids, organic acids, essential oil, and coumarins. *A. argyi* also contains many essential phytochemical compounds–namely eupatilin, jaceosidin, 5,6-dihydroxy-7,3,4-trimethoxyflavone, 5,6,4-trihydroxy-7,3-dimethoxyflavone,7-O-β-D-glucopyranoside, 5,6,2,4-tetrahydroxy-7,5-dimethoxyflavone, artemisian A-D, isoartemisolide/sesquiterpene dimer (DSF-52), 3,5-dicaffeoylquinic acid, scopoletin, terpenoids, alcohols, ethers, and ketones [17].

C. morifolium Ramat has a wide range of applications, including effective treatments for various ailments in traditional medicine and nutritious herbal tea in the food industry. These perennial plants are prevalent in Asia and northeastern Europe, with most species being indigenous

Figure 1: The main ingredients of Jing Si herbal tea. Image of ingredients adopted from [8-15].

to East Asia. *Chrysanthemum* plants belong to the *Asteraceae* family, which contains low-molecular-weight components, including flavonoids, triterpenes, unsaturated fatty acids, and sesquiterpenes. *Chrysanthemum* spp. leaves contain chlorogenic acid, daucosterol, β-sitosterol, octa-cosyl alcohol, lupeol, ineupatorolide B, syringin, petasiphenol, physcion, acacetin, eupatilin, quercetin, diosmetin, luteolin, apigenin, apigenin-7-O-β-D-glucopyra noside, quercetin-3-O-β-D-glucopyranoside, luteolin-7-O-β -D-glucopyranoside, apigenin-7-O-β-D-neospheroside, and acacetin-7-O-β-D-glucoside. In addition, most *Chrysanthemum* spp. flowers contain anthocyanins, cyanidin 3-glucoside and cyanidin 3-(3”-malonyl) glucoside, and carotenoids—lutein, zeaxanthin, β-cryptoxanthin, 13-cis-β-carotene, trans-β-carotene, and 9-cis-β-carotene [18].

G. glabra belongs to the family Fabaceae (also known as Leguminosae) and has a variety of medicinal uses. Members of this family are also commonly used as feed and food. This species is native to Mediterranean areas but is now also present in Taiwan, China, Russia, and India. Recently, a large number of biological compounds have also been isolated from *G. glabra*, mostly triterpenes, saponins, and flavonoids. Glycyrrhizin, a triterpenoid saponin approximately 50 times sweeter than sucrose, is the principal active component of the roots. The major flavonoids are glycosides of isoliquiritigenin (2′,4,4′- trihydroxychalcone) and liquiritigenin (4′,7-dihydroxyflavanone) such as liquiritin apioside, liquiritin, licuraside, and isoliquiritin. Moreover, five new flavonoids have been isolated from the dried roots: Apioside, glucoliquiritin, shinpterocarpin, shinflavanone, 1-methoxyphaseolin, and prenyllicoflavone A. In addition, licoflavanone and pinocembrin were also isolated from the leaves [19].

H. cordata, a perennial herb belonging to the Saururaceae family, is widely utilized in both Chinese herbal medicine and for food. It prefers moist soil and warm conditions for growth. Its applicability in Taiwan, China, Japan, Korea, India, and other Asian countries has been described. Over the past few 1000 years, local people have eaten as well as used *H. cordata* as medicine, and it is still used as food and medicine. *H. cordata* has several chemical components, with alkaloids being the most abundant; among them, most are phenanthrolactam compounds such as aristololactam and piperolactam. Moreover, *H. cordata* flavonoids include hyperoside, rutin, quercitrin, and quercetin, most of which are glycosides containing rhamnose. However, phenolic acids – including linolenic, stearic, palmitic, oleic, chlorogenic, cryptochlorogenic, and neochlorogenic acid and caffeic and quinic acid derivatives, and other ingredients – are the most isolated components [20].

Ophiopogon japonicus (Ophiopogon genus, Liliaceae family) is both a food and traditional herbal medicine in Taiwan, China, Japan, and some south-eastern Asian

Table 1: Major phytochemical compounds of the ingredients of Jing Si herbal tea

Ingredients	Major phytochemical compounds	Reference
A. indica (L.) Kuntze	Ovatodiolide, Alpha-Humulene, 2TCH2H, 4DHNT, Stigmasterol, Bicyclo [8.1.0] undecane, 2-(4-Methylphenyl) ethynylaniline, Vitamin E, E12TD	[16]
A. argyi	Eupitalin, Jaceosidin, 5,6-dihydroxy-7,3,4-trimethoxyflavone, 5,6,4-trihydroxy-7,3-dimethoxyflavone, 7-O-β-D-glucopyranoside, 5,6,2,4-tetrahydroxy-7,5-dimethoxyflavone, Artemisian A-D, Isoartemisolide/ DSF-52, 3,5-dicaffeoylquinic acid, Scopoletin, Terpenoids, Alcohols, Ethers, Ketones	[17]
C. morifolium Ramat	Chlorogenic Acid, Luteolin-7-O-β-Glucoside, 3,5-Dicaffeoyl QuinicAcid, Apigenin-7-O-β-Glucoside, Linarin, Acacetin-7-O-β-Glucoside, Luteolin, Apigenin, Cyanidin-3-O-Glucoside, Cyanidin-3-O-(6-MalonylGlucoside), Cyanidin, Carotenoids, dendranlignan A	[18]
G. glabra	Liquiritin, Isoliquiritin, Glycyrrhizin, Liquiritigenin, Isoliquiritigenin, 18-β-Glycyrrhetinic acid, Liquiritin apioside, Glycyrrhetic acid, Licochalcone A, Glabridin, Glycycoumarin	[19]
H. cordata	Sodium houttuyfonate, Houttuynin, Houttyunoid, Houttuynoside, Bornyl acetate, β-myrcene, Ethyl caprate, Ethyl dodecanoate, 2-undecanone, 2-tridecanone, Quercetin, Linolenic acid, Oleic acid, Palmitic acid, Stearic acid, Neochlorogenic acid, Chlorogenic acid, 4-dicaffeoylquinic acid, Aristololactam, Rutinum, Hyperoside	[20]
O. japonicus	Saponins, DT-13, Ophiopoganin, Ophiopogoside, Ophiopogonanoe, Ruscogenin, β-d-fructan, FOJ-5, Methylophiopogona, Nolinospiroside, Pulullan, lectin, liposomes, 8-Formylophiopogonanone B	[21]
P. frutescens	Phenolic acids (rosmarinic acid, rosmarinic acid-3-O-glucoside, caffeic acid, caffeic acid-3-O-glucoside, ferulic acid), Flavonoids (catechin, apigenin, apigenin 7-O-glucuronide, apigenin 7-O-diglucuronide, luteolin, luteolin 7-O-glucuronide, luteolin 7-O-diglucuronide, scutellarein, scutellarein 7-O-glucuronide, scutellarein 7-O-diglucuronide), Anthocyanins (shisonin, malonylshisonin, cyanidin 3-O-caffeoylglucoside-5-O-glucoside, cyanidin 3-O-caffeoylglucoside-5-O-malonylglucoside), triterpene acids, Fatty acids (palmitic acid, stearic acid, lauric acid, oleic acid, linoleic acid, linolenic acid), Tocopherols (α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol), Phytosterols (campesterol, stigmasterol, β-sitosterol, β-amyrin), Perillaldehyde	[22]
P. grandiflorus	Triterpenoid saponins, platyconin, taxifolin, platycoside, quercetin-7-Oglucoside, quercetin-7-O-rutinoside, luteolin-7-Oglucoside, apigenin-7-Oglucoside, luteolin, apigenin, palmitic, oleic acids, caffeic acid, 3,4-dimethoxycinnamic acid, ferulic acid, isoferulic acid, m-coumaric acid, p-coumaric acid, p-hydroxybenzoic acid, αresorcylic acid, 2,3-dihydroxybenzoic acid, 2-hydroxy4-methoxybenzoic acid, homovanillic acid, chlorogenic acid, lobetyol, lobetyolin, lobetyolinin, spinasterol, α-spinasteryl-3-O-β-D-gluc oside, betulin, β-sitosterol, and δ-7-stigmastenone-3, platycodin D	[23]

2TCH2H: 2,6,10,14,18,22-Tetracosahexaene, 2,6,10,15,19,23-hexamethyl-, (all-E)-, 4DHNT: 4-Dehydroxy-N-(4,5-methylenedioxy-2- nitrobenzylidene) tyramine, E12TD: Ethane, 1-(4,4,4-trifluro1,3-dithiobutyl)-2-(3,3,3-trifluoro-1,2-dithiopropyl), DT-13: Ruscogenin 1-O-[β-D-glucopyranosyl- (1→2)]-[β-D-xylopyranosyl-(1→3)]-β-D-fucopyranoside, FOJ-5: Fructosan with an average molecular weight of 5 kDa from *O. japonicus, A. indica: Anisomeles indica, A. argyi: Artemisia argyi, C. morifolium: Chrysanthemum morifolium, G. glabra: Glycyrrhiza glabra, H. cordata: Houttuynia cordata, O. japonicus: Ophiopogon japonicus, P. frutescens: Perilla frutescens, P. grandiflorus: Platycodon grandiflorus*

countries. Roots of *O. japonicas* are considered an effective clinical tonic and strengthening drug for treating various disorders. Several substances, including saponins, DT-13 (ruscogenin 1-O-[β-D-glucopyranosyl-(1→2)]-[β-D-xylopyranosyl-(1→3)]-β-D-fucopyranoside), ophiopoganin, ophiopogoside, ophiopogonanoe, ruscogenin, β-d-fructan, FOJ-5 (fructosan with an average molecular weight of 5 kDa), methylophiopogonanone A/B, nolinospiroside, pulullan, lectin, liposomes, and 8-formylophiopogonanone B, have been identified from various parts of *Ophiopogon japonicus*. The primary active components of *Ophiopogon japonicus* are steroidal saponins and homoisoflavonoids, which have various pharmacological actions [21].

P. frutescens is an annual herbaceous, aromatic, edible, and attractive plant, a member of the Lamiaceae family. In East Asian countries (Taiwan, China, Korea, Japan, India, and Vietnam), it has been used as a culinary and medicinal herb for thousands of years. In addition, folk medicine uses the leaves, seeds, and stems of *P. frutescens* for a variety of therapeutic purposes. Perilla seeds, stems, and leaves contain 271 identified and documented phytochemical substances. These active compounds may be categorized either as hydrophilic (flavonoids, anthocyanins, and phenolic acids) or lipophilic (volatile compounds, policosanols, tocopherols, triterpenes, phytosterols, and fatty acids). The primarily identified phytochemicals are phenolic acids (rosmarinic acid: Rosmarinic acid-3-O-glucoside; caffeic acid: Caffeic acid-3-O-glucoside; and ferulic acid), flavonoids (catechin, apigenin, apigenin 7-O-glucuronide, apigenin 7-O-diglucuronide, luteolin, luteolin 7-O-glucuronide, luteolin 7-O-diglucuronide, scutellarein, scutellarein 7-O-glucuronide, and scutellarein 7-O-diglucuronide), anthocyanins (shisonin, malonylshisonin, cyanidin 3-O-caffeoylglucoside-5-O-glucoside, and cyanidin 3-O-caffeoylglucoside-5-O-malonylglucoside), triterpene acids, fatty acids (palmitic, stearic, lauric, oleic, linoleic, and linolenic acid), tocopherols (α-, β-, γ-, and δ-tocopherol), phytosterols (campesterol, stigmasterol, β-sitosterol, and β-amyrin), and perillaldehyde [22].

Platycodon grandiflorus, the sole species in the family Campanulaceae, has long been used coventionally as herbal medicine. In addition to its usage as a legal medicine and nutritional supplement, it is a common element in healthy foods and vegetable meals in Northeast Asia (including Taiwan, China, Korea, and Japan). Natural products extracted from Platycodon grandiflorus can be classified into different classes and display different structural characteristics. In the past few decades, at least 100

compounds have been isolated from Platycodon grandiflorus, including triterpenoid saponins, platyconin, taxifolin, platycoside, quercetin-7-Oglucoside, quercetin-7-O-rutinoside, luteolin-7-Oglucoside, apigenin-7-Oglucoside, luteolin, apigenin, palmitic, oleic acids, caffeic acid, 3,4-dimethoxycinnamic acid, ferulic acid, isoferulic acid, m-coumaric acid, p-coumaric acid, p-hydroxybenzoic acid, αresorcylic acid, 2,3-dihydroxybenzoic acid, 2-hydroxy4-methoxybenzoic acid, homovanillic acid, chlorogenic acid, lobetyol, lobetyolin, lobetyolinin, spinasterol, α-spinasteryl-3-O-β-D-glucoside, betulin, β-sitosterol, and δ-7-stigmastenone-3, and platycodin D [23].

Therapeutic effects of JSHT and its ingredients

The ingredients of JSHT have been documented to have multiple biological impacts on health promotion and treatment of various diseases. Several studies have reported various pharmacological activities, including anti-COVID,-aging,-cancer,-diabetic,-obesity,and-inflammatory activities, and cardio-, hepato-, nephro-, and neuroprotective effects [Figure 2]. To explain the nature of individual JSHT ingredients, this review intends to summarize their pharmacological and therapeutic effects and potential mechanisms against various disorders based on the relevant research for future clinical use and experimental reference.

Anti-COVID-19 activity

Since the outbreak of COVID-19, health-care professionals worldwide have concentrated on devising methods to combat the virus, and TCM experts have joined the endeavor. Therefore, several anti-coronavirus health products based on TCM formulas have arrived in the market due to the latter's efforts. At the end of 2020, Hualien Tzu Chi Hospital developed JSHT for health and wellness. In a clinical trial, researchers from the Buddhist Tzu Chi Medical Foundation investigated the efficacy and safety of JSHT combined with standard treatment for patients with mild-to-moderate COVID-19 [Table 2] [5]. The results demonstrated that in adult patients with mild-to-moderate COVID-19, the combination of JSHT and standard therapy significantly improved C-reactive protein level, reverse transcription-polymerase chain reaction threshold value, and Brixia score–most notably in males and older patients (aged >60). The patients also experienced 51, 70, and 100% lower risks of intubation, Medisave Care Unit admissions, and mortality, respectively, compared to those receiving standard management alone. This suggests that supplemental JSHT treatment can avert critical status and fatality. Li *et al*. [30] performed a retrospective cohort study on severe COVID-19 patients to investigate the impact of JSHT-incorporated treatment strategy on death and hospital course. The study recruited 10 patients divided into two groups: >70 years and <70 years and each group contained five patients. In all patients, JSHT was co-treated with death as the primary outcome. Laboratory tests, computed tomography (CT) values, clinical course, and hospital stays were considered secondary outcomes. Study results indicate that older patients (>70 years) have higher Charlson Comorbidity Index scores and Veterans Health Administration COVID-19 scores, as well as lower hemoglobin levels than <70 years old. Moreover, CT values, lymphocyte count, lactate dehydrogenase, and D-dimer were inconsistent among nonsurvivors. The death rate was 20%, and the recovery rate for mild illness in 14 days was 40%. Another research team from the Buddhist Tzu Chi Medical Foundation reported that JSHT demonstrated anti-viral activity in Calu-3 and Caco-2 cells and mice pretreated for 3 days when exposed to distinct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants [6]. Intriguingly, JSHT significantly inhibited 3cL and RdRp activity, demonstrating the multitargeting nature of JSHT and making it a possible SARS-CoV-2 infection preventive. In addition, numerous investigations have demonstrated the anti-viral activity of JHST's ingredients during the past decade. Recently, a study showed the potent anti-inflammatory properties of *A. indica* (L.) Kuntze may alleviate the uncontrolled release of pro-inflammatory cytokines (NO, tumor necrosis factor [TNF]-α, and interleukin (IL)-12) in response to COVID-19 infection [31]. Similarly, *A. argyi* may have therapeutic potential for decreasing COVID-19-induced inflammatory-related conditions because of its anti-inflammatory capabilities, which are mediated by inhibiting the nuclear factor kappa B (NF-κB) pathway [32]. *C. morifolium* Ramat contains the

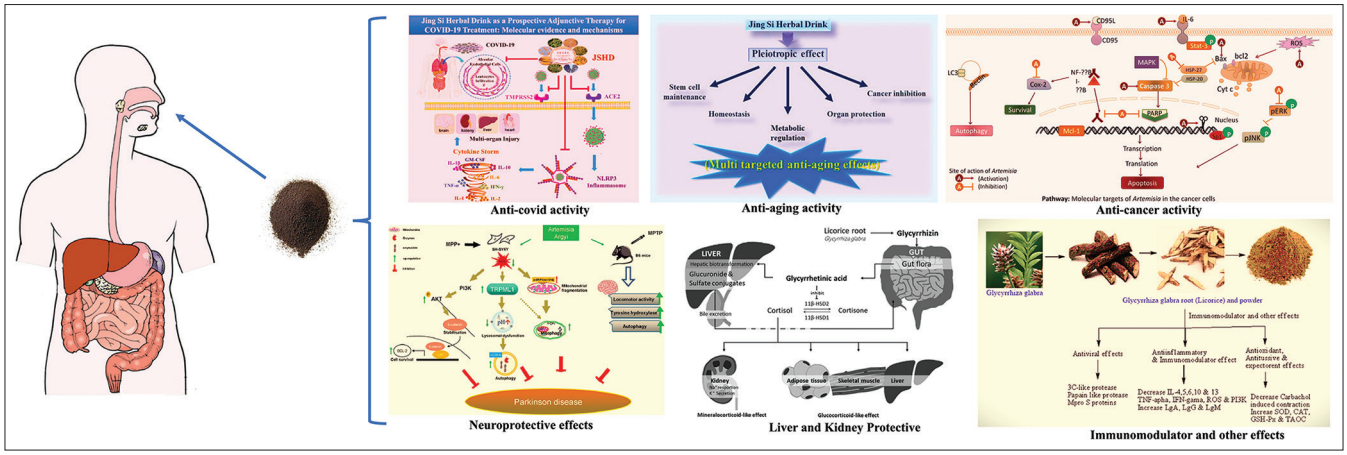

Figure 2: Various pharmacological activities such as anti-covid [24], anti-aging [25], anti-cancer [26], neuroprotective [27], liver and kidney [28], immunomodulator and other effects [29] of the individual ingredients in Jing Si herbal tea

Table 2: Anti-COVID and anti-aging effects of the Jing Si herbal tea and its ingredients

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
Anti-COVID effects	Jing Si herbal tea	*In vitro* and animal model	Inhibited viral replication	Inhibited viral entry into Calu-3 and Caco-2 cells. Decreased 3cL and RdRp activity	[6]
	-	Clinical study	Reduced the SARS-CoV-2 viral load and systemic inflammation and alleviated lung infiltrates in the patients with mild-to-moderate COVID-19	Improved the reverse transcription-polymerase chain reaction cycle threshold value, C-reactive protein level, and Brixia score	[5]
	-	Clinical study	The death rate was 20% and recovery rate to mild illness in 14 days was 40%	Older patients (>70 years) have higher Charlson Comorbidity Index scores and VACO scores as well as lower hemoglobin levels than <70 years patients	[30]
	A. indica (L.) Kuntze	Animal model	Inhibited pro-inflammatory mediators and tumor cell proliferation	Inhibited NO, TNF-α and IL-12	[31]
	A. argyi	Animal model	Attenuated airway inflammation	Decreased iNOS expression and NF-κB phosphorylation	[32]
	C. morifolium Ramat	*In vitro* and animal model	Showed anti-platelet and anti-thrombosis activity	Suppressed TXA2, NF-κB, and iNOS. Decreased serum levels of TNF-α, IL-1β, IL-6, and CRP and reduced macrophages, neutrophils, and white blood cells	[33]
	G. glabra	*In vitro*	Protected against coronavirus	Replication of the virus was inhibited by inducing oxide synthase in Vero cells	[34]
	H. cordata	Bedside-to-bench (*in vitro* and clinical trial)	Inhibited SARS-CoV-2 pathogenesis in anti-viral and -inflammatory assays	Block binding between ACE2 and spike protein of SARS-CoV-2	[35]
	O. japonicus	Animal model	Inhibited venous thrombosis	Secured endothelial cells from anoxic injury and decreased leukocytes adhesion and inflammation of the vein wall	[36]
	P. frutescens	*In vitro*	Inhibited SARS-CoV-2 replication by inactivating the virion	Inactivate SARS-CoV-2 spike protein Decrease viral protein/RNA synthesis and the levels of TNF-α, IL-1, and IL-6	[37]
	P. grandiflorus	*In vitro*	Platycodin D showed a protective effect against SARS-CoV-2 infection	Blocked lysosome and TMPRSS2-driven viral entry	[38]
Anti-aging effects	Jing Si herbal drink	*In vitro* and animal model	Displayed pleiotropic effects against aging-associated disorders	Maintained stem cell homeostasis and provided cytoprotection. Regulated blood glucose metabolism, enhanced neurons' autophagic clearances, and suppressed cancer growth and migration	[25]
	A. indica (L.) Kuntze	*In vitro*	Ovatodiolide compound showed inhibitory effects on melanogenesis	Inhibited mushroom tyrosinase activity (IC_{50}=0.253 mM), suppressed intracellular tyrosinase activity (IC_{50}=0.469 mM), and decreased the amount of melanin (IC_{50}=0.435 mM)	[39]
	A. argyi	Animal model	Exerted ameliorative effects on DNCB-induced ADlike lesions by exerting antiallergenic skin inflammatory effects related to the recovery of skin barrier dysfunction	Suppressed cytokine abundance via the regulation of crucial factors, including Lyn, Syk, MAPKs, PI3K/Akt, and IκBα, during the process of AD pathogenesis	[40]
	C. morifolium Ramat	Clinical study	Significantly improved erythema and overall rosacea severity in patients with moderate rosacea, with mild adverse reactions observed in both the treatment and placebo groups		[41]
	-	Clinical study	Inhibited mushroom tyrosinase activity. Reduced facial melanin levels. No moisture, elasticity, wrinkles, evenness, and pore size changes		[42]
	G. glabra	Clinical study	Lightened hand solar lentigines		[43]

Contd...

Table 2: Contd...

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
	H. cordata	*In vitro*	Inhibited UVB-irradiated skin aging through regulation of the MAPK signaling pathway by attenuating the activation of JNK/ERK/c-Jun in human dermal fibroblasts	Inhibited intracellular ROS production and inflammatory cytokine secretions (IL-6 and IL-8) while increasing collagen type I synthesis along with downregulating MMP-1 gene and protein expressions	[44]
	O. japonicus	Animal model	Extended lifespan in *C. elegans*	Slightly increased the pharyngeal pumping rate of *C. elegans* and reduced the accumulation of lipofuscin	[45]
	P. frutescens	*In vitro* and clinical study	Improved skin elasticity and reduced skin pigmentation	Reduced retraction time and melanin content	[46]
	-	Clinical study	Increased skin hydration and skin elasticity	The sulcus cutis was narrower with the effect of the test serum, and the number of equilateral triangles was increased than the baseline	[47]
	P. grandiflorus	Animal model	Alleviated DNCB-induced atopy-like dermatitis	Reduced the elevation of serum total IgE or cytokine mRNA. Suppressed Th1 and Th2 responses	[48]

VACO: Veterans Health Administration COVID-19, ACE2: Angiotensin-converting enzyme 2, IL-1β: Interleukin 1 beta, IL-6: Interleukin 6, iNOS: Inducible nitric oxide synthase, TXA2: Thromboxane A2, NF-κB: Nuclear factor kappa B, NO: Nitric oxide, RdRP: RNA dependent RNA polymerase, TNF: Tumor necrosis factor, DNCB: 1-chloro-2, 4-dinitro benzene, AD: Atopic dermatitis, Lyn: Lck/Yes novel tyrosine kinase, SyK: Spleen tyrosine kinase, MAPKs: Mitogen-activated protein kinases, PI3K/Akt: Phosphatidylinositol-3-kinase and protein kinase B, IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, UVB: Ultraviolet B, JNK: Jun N-terminal kinase, ERK: extracellular regulated kinase, ROS: Reactive oxygen species, MMP-1: Matrix metalloproteinase-1, IgE: Immunoglobulin E, mRNA: Messenger RNA, Th1: T helper cell type 1, Th2: T helper cell type 2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, CRP: C-reactive protein, IC_{50}: Half maximal inhibitory concentration, *C. elegans: Caenorhabditis elegans, A. indica: Anisomeles indica, A. argyi: Artemisia argyi, C. morifolium: Chrysanthemum morifolium, G. glabra: Glycyrrhiza glabra, H. cordata: Houttuynia cordata, O. japonicus: Ophiopogon japonicus, P. frutescens: Perilla frutescens, P. grandiflorus: Platycodon grandiflorus*

flavonoids luteolin and apigenin, which have antithrombotic properties. These compounds effectively suppressed the production of thromboxane A2 and collagen-induced platelet aggregation in an *in vitro* human investigation, suggesting their potential use in treating or preventing blood clots [33]. Moreover, casticin from *C. morifolium* Ramat, another polymethylflavone, may inhibit tissue damage and cytokine storms during COVID-19 infection by inhibiting the NF-κB and inducible nitric oxide synthase (iNOS) pathways and reducing serum levels of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6) and C-reactive protein. Further, glycyrrhizic acid, the active component of *G. glabra*, efficiently inhibits the entry and replication of the SARS virus [34]. Furthermore, it can inhibit entry, replication, and inflammation of SARS-CoV-2 by regulating steroid metabolism, blocking the main protein of SARS-CoV-2, and inhibiting the release of inflammatory agents that lead to cytokine storms. Tsai *et al*. [35] devised NRICM101, a new TCM formulation, as a COVID-19 treatment for a bench-to-bedside study. *H. cordata*, one of the constituents of NRICM101, can reportedly block the SARS-CoV-2 spike RBD protein from binding to ACE2 and reduce TNF-α production. COVID-19 mortality is associated with thrombotic complications such as pulmonary emboli, venous thromboembolic disease, and stroke. In a recent study, *O. japonicas* remarkably reduced venous thrombosis [36]. Anoxic injury to endothelial cells was prevented by ethanol extracts of *O. japonicas*, which also reduced leukocyte adhesion to the endothelium and suppressed inflammation of the vein walls in rat and mouse models, further supporting its therapeutic potential for COVID-19. Another recent *in vitro* study using Calu-3 cells showed that *P. frutescens* leaf extract (PLE) could inhibit virus protein/RNA synthesis as well as virus-induced cytokines such as IL-1, IL-6, and TNF-α [37]. In addition, PLE prevents viral entry by inactivating the SARS-CoV-2 virus, i.e., the spike protein. Notably, the combination of PLE and remdesivir has a synergistic impact against SARS-CoV-2. Platycodin D (a bioactive compound of *P. grandifloras*) is capable of redistributing membrane cholesterol to block the main infectious routes for SARS-CoV-2, including lysosomes and TMPRSS2 [38]. Considering the pharmacological effects mentioned above, JSHT has excellent therapeutic potential to prevent and improve the clinical outcomes of COVID-19. However, due to the lack of studies on human subjects, more clinical trials focused on patient groups, efficacy, and doses are required. Furthermore, the effects of JSHT on anhedonia and depressive symptoms linked to long COVID were assessed in a recent study using mice models subjected to unpredictable chronic mild stress [49]. The study's results demonstrate that JSHT mitigates the cytokine storm by inhibiting NF-κB cascades, offering protective effects against symptoms connected with long-term COVID-19 infection.

Anti-aging activities

Aging can be defined as the progressive loss of cells, tissues, and organs throughout a person's lifetime. The loss of tissue homeostasis and normal function increases susceptibility to age-related illnesses by reducing adaptation to varied stress circumstances. Consequently, aging is one of the critical risk factors for various disorders. To promote healthy aging, pharmacological interventions must target a variety of factors associated with aging disorders and simultaneously promote adult stem cell rejuvenation. TCM has demonstrated rejuvenation potential in a variety of experimental models. In this context, JSHT and its constituent compounds obtained from natural sources with potential properties, which could achieve similar benefits as synthesized compounds, are of

great interest. In search of a promising pleiotropic medicine for aging treatment, a research team from the Buddhist Tzu Chi medical foundation tested JSHT for its anti-aging benefits using relevant *in vitro* and *in vivo* models [25] [Table 2]. Their findings indicated that JSHT preserved stem cell homeostasis and offered cytoprotection. In addition, it inhibited the growth and migration of cancer cells, promoted autophagic clearing in neurons, and affected blood glucose metabolism. A research team concluded that JSHT is a possible pleiotropic agent for healthy aging since it acts on multiple sites and provides a cumulative protective effect against numerous age-associated diseases. Several other studies also showed the potential anti-aging effects of the ingredients in JSHT. For instance, Huang *et al*. studied the antioxidative properties of *A. indica* (L.) Kuntze methanol extract and the inhibitory effect of its active component, ovatodiolide, on melanogenesis in B16F10 melanoma cells [39]. The results revealed that mushroom tyrosinase activity (IC_{50} = 0.253 mM) was inhibited by purified ovatodiolide. In addition, the compound effectively decreased the amount of melanin (IC_{50} = 0.435 mM) due to suppressed intracellular tyrosinase activity (IC_{50} = 0.469 mM) in a dose-dependent manner. Atopic dermatitis (AD) is a prevalent recurrent inflammatory skin condition. In one study, *A. argyi* extract ameliorated DNCB-induced AD-like lesions by exerting anti-allergenic restorative skin inflammatory actions after skin barrier failure [40]. These effects are thought to be related to suppressing cytokine abundance through regulating various factors involved in AD pathogenesis–including IκBα, Syk, Lyn, MAPKs, and PI3K/Akt. Similarly, *Platycodon grandiflorus* showed potential effects on AD in DNCB-treated NC/Nga mice [48]. Oral treatment of PG is considered to reduce the elevated levels of serum total IgE or cytokine mRNA. *Platycodon grandiflorus* probably alleviates AD-like skin lesions by inhibiting both Th1 and Th2 cytokines. Similar to AD, rosacea is an inflammatory dermatosis with a complex etiology involving systemic or local, endogenous, and environmental factors. Rosacea is considered a disease characterized by vascular changes. As an herbal extract containing a potent combination of saponins, phenylpropenoic acids, and flavonoids, *C. morifolium* Ramat is well-known for improving capillary mechanical resistance and decreasing vascular wall permeability. Clinical trial findings showed that, compared to baseline and placebo, treatment with *C. morifolium* Ramat extract-based cream significantly reduced the rosacea and erythema severity and overall severity efficacy assessment scores (P = 0.046 and P = 0.001, respectively) [41]. In addition, another clinical study assessed the effects of *C. morifolium* Ramat extract in cosmetic formulations on biophysical skin parameters in healthy people [42]. Dose-dependent inhibition of tyrosinase activity was observed with *C. morifolium* Ramat extracts. Furthermore, time-dependent reductions in facial melanin levels were also observed in the faces of human volunteers who were exposed to daily cosmetic formulations with 0.5% *C. morifolium* Ramat water extract. Benign hyperpigmentation, another age-related, often occurs on sun-exposed skin in adults (face, hands) due to photoaging, postinflammatory, or chronoaging processes. Age-related blemishes are caused by a limited, benign proliferation of melanocytes at the dermo-epidermal interface, producing aesthetic issues. Grippaudo and Di Russo [43] conducted a clinical trial to evaluate the efficacy of glycyrrhetinic acid (extracted from *G. glabra*) monotherapy combined with fractional CO_2 laser for benign hand hyperpigmentation treatment. The hand solar lentigines of all participants, investigators, and blinded dermatologists improved. *P. frutescens*, another ingredient of JSHT, can effectively reduce the effects of skin aging and hyperpigmentation disorders. An *in vitro* and clinical study by Mungmai *et al*. [46] revealed that the anti-melanogenic effects of *P. frutescens* on B16F10 cells occur without cytotoxicity or death. In addition although skin elasticity improved slightly in the 4th week compared to the third, it was found that the amount of melanin in the skin significantly decreased (P < 0.05) without any irritation in the 4th week. The same research team conducted another clinical trial on the efficacy of cosmetic formulation containing PLE (PLES) for aging skin [47]. No skin irritation or allergic reaction was reported during application and following PLES treatment, skin hydration and elasticity could increase. However, frequent exposure to UV radiation generates changes in an individual's skin characterized by tanning, burning, elastin fibers, loosening collagen, and diminished skin integrity, known as photoaging. A fraction enriched in hyperosides produced by *H. cordata* Thunb was tested for photoprotection against UVB-induced aging of human fibroblasts [44]. Activation of JNK/ERK/c-Jun in human dermal fibroblasts was attenuated by the hyperoside-enriched fraction obtained from *H. cordata*. Recently, there has been an increasing interest in *O. japonicas* as an anti-aging agent. Yu *et al*. [45] reported that *O. japonicas* is capable of extending the lifetime of nematodes as well as reversing the age-related drop in pharyngeal pumping and decreasing the formation of the age pigment lipofuscin in the animals.

Anti-cancer activities

Cancer is a complex disease characterized by either increased or decreased cell proliferation, resulting in apoptosis. Exogenous and endogenous causes might contribute to excessive reactive oxygen species (ROS) generation. Thus, DNA is broken or mutated, chromosomes rearranged, DNA cross-links formed, nucleic acids degrade, the cell membrane becomes damaged due to lipid peroxidation, and tumors can form. JSHT ingredients have shown anti-cancer properties in both *in vitro* and *in vivo* studies [Table 3]. Ovatodiolide, which is present in the plant *A. indica* (L.) Kuntze, reportedly has an anti-proliferative effect on several cancer cells. In AGS cells, the pure ovatodiolide reduced cell proliferation and triggered cell death in a dose-dependent manner, accompanied by G2/M cell cycle arrest and nuclear condensation and fragmentation [50]. Activation of Bax and reduction in Bcl-2 mRNA levels could be potential causes, at the very least in part, of the apoptotic effects of ovatodiolide on AGS cells. Moreover, ovatodiolide can effectively suppress oral tumorigenesis and stemness properties through JAK2/STAT3 signaling [51]. *A. argyi* polysaccharide fraction reportedly prevents tumor cell-induced platelet aggregation by inhibiting the interaction of podoplanin with C-type lectin-like receptor 2 [52]. Furthermore, computational tools

Table 3: Anti-cancer and cardiovascular protective effects of the ingredients of Jing Si herbal tea

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
Anti-cancer	*A. indica* (L.) Kuntze	*In vitro*	Ovatodiolide compound significantly inhibited cell proliferation and induced cell apoptosis of human gastric cancer cells	Activated *Bax* and the reduction in *Bcl-2* mRNA levels	[50]
	-	*In vitro*	Ovatodiolide effectively suppressed oral tumorigenesis and stemness properties of oral cancer stem-like cells	Suppressed oral-sphere formation, reduced clonogenicity, enhanced cisplatin sensitivity and dysregulated JAK2/STAT3 signaling pathway	[51]
	A. argyi	*In vitro*	Prevention of tumor cell metastases	Suppressed PDPN- and tumor cell-induced platelet aggregation by irreversibly blocking the interaction between PDPN and CLEC-2	[52]
	C. morifolium Ramat	*In vitro*	Inhibited the proliferation of MCF7 cells	Regulates the biological processes of their protein targets	[53]
	G. glabra	*In vitro*	18 β-glycyrrhetinic acid potently inhibited the migration and invasion of colorectal cancer cells and reduced MMP expression as well	Suppressed PI3K and STAT3 signaling pathways	[54]
	-	*In vitro* and animal model	Glycycoumarin exerted anti-liver cancer activity	Inactivated oncogenic kinase TOPK, which in turn led to activation of its binding partner p53, followed by cell cycle arrest and cell death induction	[55]
	-	Animal model	Glycyrrhizin exerted anti-cancer action in lung cancer cell lines	Suppressed the TxA2 pathway	[56]
	H. cordata	*In vitro*	Showed anti-carcinogenic activity against breast cancer	Induced cell cycle arrest via the modulation of cyclin D1, CDK4, and p21protein expressions. Suppressed cell migration and invasion by inhibiting MMP-1 and MMP-9 secretion	[57]
	-	*In vitro*	Induced apoptosis in human HepG2 hepatocellular carcinoma cells	Promoted the activation of HIF-1a-FOXO3 and MEF2A pathways	[58]
	O. japonicus	*In vitro*	Ophiopogonin-B decreased proliferation and induced apoptosis of human gastric cancer cells	Anti-cancer mechanisms are associated with the JNK1/2 and ERK1/2 signaling pathways	[59]
			O-D inhibited cell proliferation and induced apoptosis in human breast carcinoma MCF-7 cells	O-D-induced G_2/M cell cycle arrest was associated with down-regulation of cyclin B1. Activation of caspase-8 and caspase-9 was associated with ophiopogonin D-induced apoptosis	[60]
	P. frutescens	*In vitro* and animal model	Synergistically suppressed proliferation of A549 human lung adenocarcinoma	Induced two-stage cell cycle arrest at G_1 and G_2/M phases	[61]
	P. grandiflorus	*In vitro*	Induced cell apoptosis and inhibited cell proliferation	Inhibited the expression of p-Akt and p-STAT3	[62]
	-	*In vitro*	Induced cancer cell death is associated with cytoplasmic pinocytic and autophagic vacuolation	Activated AMP-activated protein kinase	[63]
Cardioprotective	*A. argyi*	Animal model	Showed antihypertensive activity in spontaneously hypertensive rats	The underlying mechanism appears to involve, at least in part, an increase in urine and electrolyte output	[64]
	C. morifolium Ramat	Animal model	Alleviated hypertensive cardiac hypertrophy in rats	Inhibited HIF-1a expression and modulated PPARa-mediated CPT-1a, PDK-4, and GLUT-4 expressions	[65]
	G. glabra	Animal model	18 β-glycyrrhetinic acid showed cardioprotective effects on acute myocardial infarction	Inhibited oxidative stress, inflammation, apoptosis via the PI3K/Akt pathway, and reduced cell contractility and Ca^{2+} concentration via L- type Ca^{2+} channels	[7]

Contd...

Table 3: Contd...

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
	-	*In vitro* and animal model	*G. glabra* extracts showed cardioprotective effects against doxorubicin-induced cardiotoxicity	Decreased serum LDH and CK-MB levels, improved heart morphology, and increased GSH-PX activity and GSH level	[66]
	H. cordata	*In vitro* and animal model	2-undecanone protected against fine particle-induced heart inflammation	Modulated Nrf2/HO-1 and NF-κB pathways	[67]
	O. japonicus	Animal model	8-Formylophiopogonanone B antagonized doxorubicin-induced cardiotoxicity	Suppressed heme oxygenase-1-dependent myocardial inflammation and fibrosis	[68]
	P. frutescens	*In vitro*	Protected endothelium against vascular inflammation	Inhibited ICAM-1 expression and IL-6 production, adherence of leukocytes to endothelial cells, and EMPs generation	[69]
	-	Animal model	Perillaldehyde prevented the formation of atherosclerotic plaques	Increased tetrahydrobiopterin levels and subsequent eNOS recouping	[70]
	P. grandiflorus	Animal model	Platycodin D provided myocardial protection in spontaneously hypertensive rats	Downregulated the expression of FGF2, uPA, MMP2, MMP9, and CTGF and decreased TGF-β1expression	[71]

Bax: B-cell lymphoma protein 2, *Bcl-2*: BCL2-Associated X Protein, mRNA: Messenger RNA, JAK2/STAT3: Janus kinase 2/signal transducer and activator of transcription 3, PDPN: Podoplanin, CLEC-2: C-type lectin-like receptor 2, MMP: Matrix metalloproteinase, PI3K: Phosphatidylinositol-3-kinase, TOPK: T-lymphokine-activated killer-cell-originated protein kinase, TxA2: Thromboxane A2, CDK4: Cyclin-dependent kinase 4, HepG2: Hepatoma G2, HIF-1a-FOXO3: Hypoxia-inducible factor 1-alpha- Forkhead Box O3, MEF2A: Myocyte enhancer factor 2A, JNK: Jun N-terminal kinase, ERK: extracellular regulated kinase, p-Akt: Phospho-protein kinase B, p-STAT3: Phospho-signal transducer and activator of transcription 3, AMP: Adenosine monophosphate, PPARa: Peroxisome proliferator activated receptor alpha, CPT-1a: Carnitine palmitoyltransferase -1a, PDK-4: Pyruvate dehydrogenase kinase 4, GLUT-4: Glucose transporter type 4, PI3K/Akt: PI3K and protein kinase B, LDH: Lactate dehydrogenase, CK-MB: Creatine kinase-myoglobin binding, GSH-PX: Glutathione peroxidase, Nrf2/HO-1: Nuclear factor erythroid 2-related factor transcription factor/Hemoxygenase 1, NF-κB: Nuclear factor kappa B, ICAM-1: Intercellular adhesion molecule 1, IL-6: Interleukin 6, EMPs: Endothelial microparticles, eNOS: Endothelial nitric oxide synthase, FGF2: Fibroblast growth factor-2, uPA: Urokinase-type plasminogen activator, CTGF: Connective tissue growth factor, TGF-β1: Transforming growth factor-β1, O-D: Ophiopogonin-D, A. indica: Anisomeles indica, *A. argyi: Artemisia argyi, C. morifolium: Chrysanthemum morifolium, G. glabra: Glycyrrhiza glabra, H. cordata: Houttuynia cordata, O. japonicus: Ophiopogon japonicus, P. frutescens: Perilla frutescens, P. grandiflorus: Platycodon grandiflorus*, MCF: Michigan cancer foundation

demonstrated that phytochemical substances extracted from *C. morifolium* Ramat flower extracts had a potent inhibitory effect on breast cancer cell lines (MCF-7 cells) [53]. According to gene ontology analysis, *Chrysanthemum*'s active compounds inhibit the growth of breast cancer through the regulation of the biological processes of their protein targets. 18-β-glycyrrhetinic acid, glycycoumarin, and glycyrrhizic acids present in *G. glabra* showed anti-cancer action in colon, liver, and lung cancer cell lines. The anti-cancer activity of 18-β-glycyrrhetinic acid was evaluated against colorectal cancer cells LoVo, SW480, and SW620 [54]. The findings revealed that 18-β-glycyrrhetinic acid might reduce PI3K and STAT3 signaling pathways as it regulates the apoptosis, invasion, and migration of colorectal cancer cells. Song *et al*. [55] reported that glycycoumarin is highly effective against liver cancer in both cell culture and HepG2 xenograft models. The anti-cancer effect of glycycoumarin is related to its capacity to directly inactivate T-lymphokine-activated killer-cell-originated protein kinase, resulting in the p53-dependent reduction of cell growth and induction of apoptosis. In an animal model of lung cancer, glycyrrhizin provided anti-cancer activity with low toxicity through inhibition of thromboxane A2 [56]. However, few studies investigated the effects of anti-proliferation, anti-invasion, anti-migration, and apoptosis induction by *H. cordata* extracts on different breast cancer cell types. For instance, the research by Subhawa *et al*. [57] showed that *H. cordata* Thunb extracts promoted breast cancer cell cycle arrest by modulating the expressions of CDK4, cyclin D1, and p21 proteins. Moreover, by reducing matrix metalloproteinases release, the extracts reduced breast cancer cell migration and invasion. Furthermore, *H. cordata* Thunb induces apoptosis in human HepG2 hepatocellular cancer cells by activating the HIF-1A-FOXO3 and MEF2A signaling pathways [58]. Two important steroid glycosides, ophiopogonin B and D, isolated from *O. japonicas* exerted anti-cancer effects against human gastric cancer cells and breast carcinoma MCF-7 cells. Zhang *et al*. [59] reported that ophiopogonin B treatment resulted in increased phosphorylation levels of JNK1/2 and ERK1/2 in SGC-7901 cells. The anti-cancer mechanisms of ophiopogonin B may involve the JNK1/2 and ERK1/2 pathways. Another compound, ophiopogonin-D, reduced cell growth and promoted apoptosis in MCF-7 human breast cancer cells [60]. Ophiopogonin D-induced G_2/M cell cycle arrest was associated with downregulation of cyclin B1, and apoptosis was associated with the activation of caspase-8 and caspase-9. A study by Abd El-Hafeez *et al*. [61] showed a synergistic tumor-suppressive potency of *P. frutescens* and anti-cancer tyrosine kinase inhibitors on A549 cells, both *in vitro* and *in vivo*. The synergistic anti-tumor effect results from the activation of a two-stage cell cycle arrest at the G1 and G2/M phases. Another study showed that metabolites of *Platycodon grandiflorus*-induced cell apoptosis and inhibited cell proliferation by affecting the Akt and STAT3 signaling pathways [62]. Furthermore, a bioactive component of *Platycodon grandiflorum* called Platycodin D

causes cancer cell death associated with severe vacuolation through AMPK activation when cellular energy levels are low [63].

Cardiovascular protection

The JSHT ingredients and their phytochemical compounds demonstrate interventional activity in the process of cardiac remodeling and functional deterioration [Table 3]. In spontaneously hypertensive rats, *A. argyi* aqueous extract demonstrated antihypertensive activity, and a part of the mechanism appears to involve an increase in urine and electrolyte production [64]. With further research, *C. morifolium* Ramat showed similar antihypertensive activity [65]. The polyphenol-rich extract of *C. morifolium* Ramat ameliorated hypertension-induced cardiac hypertrophy in rats by lowering blood pressure and decreasing HIF-1a expression, followed by regulation of PPAR-mediated PDK-4, GLUT-4, and CPT-1a expressions. Furthermore, 18 β-Glycyrrhetinic acid (extracted from *G. glabra*) demonstrated protective effects against myocardial infarction [7], indicating that it might have cardioprotective effects against acute myocardial infarction by suppression of inflammation, oxidative stress, and apoptosis via the PI3K/Akt pathway and reduction of Ca^{2+} concentration and cell contractility through L-type Ca^{2+} channels. A similar cardioprotective effect of *G. glabra* extract (GBE) was found in the DOX-induced cardiotoxicity mice model [66]. Mice treated with GBE were significantly protected from DOX-induced cardiotoxicity, as seen by lower creatine kinase isoenzyme and blood lactate dehydrogenase levels, improved heart morphology, and elevated glutathione levels and glutathione peroxidase activity. Similarly, 8-formylophiopogonanone B, a natural isoflavone in *O. japonicas*, protected against DOX-cardiotoxicity by reducing heme oxygenase-1-dependent myocardial inflammation and fibrosis [68]. Another compound, Platycodin D from *P. grandifloras*, considerably attenuates cardiac fibrosis [71]. A recent study revealed that the administration of *P. grandifloras* under conditions of spontaneous hypertension leads to a reduction in myocardial collagen content and fibrosis (downregulated the expression of fibroblast growth factor-2, urokinase-type plasminogen activator, matrix metalloproteinase-2, matrix metalloproteinase-2, and connective tissue growth factor and decreased transforming growth factor-β1 expression). It is worth mentioning that some cardiovascular diseases, such as $PM_{2.5}$-mediated heart injury, have been linked to exposure to air pollution. Interestingly, by activating the Nrf2 transcription factor, 2-undecanone extracted from *H. cordata* can reduce the NF-κB pathway and the inflammatory damage to mouse myocardium caused by exposure to $PM_{2.5}$ [67]. In addition, inflammation of the blood vessels is critical to the development of cardiovascular diseases, including atherosclerosis. Paradee *et al*. showed that ethanol extracts of *P. frutescens* had a protective effect on endothelium against vascular inflammation by inhibiting intracellular adhesion molecule-1 expression and IL-6 production, adherence of leukocytes to endothelial cells, and endothelial microparticle generation [69]. Furthermore, another study demonstrated that Perillaldehyde, one of the principal oil components in *P. frutescens*, inhibits atherosclerosis progression by endothelial nitric oxide synthase recovery and boosts tetrahydrobiopterin production [70].

Anti-diabetic activities

Globally, diabetes is one of the major chronic diseases, and approximately 10% of the world's population has a blood glucose metabolic abnormality characterized primarily by hyperglycemia. This condition is defined by either insufficient insulin secretion from β-cells of pancreatic islets, known as type 1 diabetes, or the inability of cells to react in response to secreted insulin, known as type 2 diabetes. A prolonged state of hyperglycemia causes increased ROS formation and dyslipidemia, resulting in extensive cellular damage and associated problems. Previous literature showed the potential effects of the ingredients of JSHT for diabetes management [Table 4]. The anti-diabetic effects of the flavonoids and phenolic compounds of *A. indica* (L.) Kuntze has been reported in experimental diabetic rats [72]. The results showed that ethyl acetate and hexane fraction of *A. indica* (L.) Kuntze improved fasting blood glucose, hemoglobin, and plasma insulin levels, and insulin sensitivity/resistance indicators such as quantitative insulin sensitivity check index, homeostasis model assessment of β-cell dysfunction, homeostasis model assessment of insulin resistance, and glucose tolerance. However, the aqueous extract of *A. argyi* exhibited marked anti-hyperglycemic effects in ALX-induced diabetic rats [73]. The aqueous extract showed marked improvements in serum insulin, total proteins, C peptide, and total hemoglobin, as well as decreases in glycosylated hemoglobin. Recently, Yamashita *et al*. reported the anti-hyperglycemic activity of *G. glabra* flavonoid oil (GFO) in diabetic KK-A^y mice [75], revealing that GFO improves hyperglycemia by targeting glucose transporter type-4 translocation in skeletal muscles through AMPK and Akt activation. Kumar *et al*. [76] also recorded the anti-hyperglycemic activity of *H. cordata* Thunb. extract in STZ-induced diabetic rats. The anti-diabetic effects of *H. cordata* are attributable to an increased expression of glucose transporter type-2 and GLUT-4 proteins, potentiating insulin secretion from pancreatic β-cells. Kim *et al*. [78] showed the anti-hyperglycemic effects of *P. frutescens* and proposed that *P. frutescens* can modulate the AMPK pathway and inhibit gluconeogenesis in the liver to prevent and treat type 2 diabetes. Besides, Zheng *et al*. found *Platycodon grandiflorum* aqueous-ethanol extract to have hypoglycemic effects without stimulating insulin secretion in STZ-induced diabetic ICR mice [79]. In obese diabetic KK-A^y mice, the hot water extract of *C. morifolium* Ramat showed hypoglycemic effects [74]. The mechanism involved suppression of chronic inflammation in adipose tissues, decreased adipocyte sizes, and increased peroxisome proliferator-activated receptor γ expression. Long-term hyperglycemia has been well documented as the primary cause of numerous diabetic complications, such as nephropathy and neuropathy. Diabetic nephropathy (DN) is a gradual consequence of diabetes, which may initially lead to nephrotic syndrome and subsequently evolve into chronic kidney disease and end-stage renal disease. Recently, Qiao *et al*. [77] showed the protective effect of ophiopogonin

Table 4: Anti-diabetic and anti-obesity effects of Jing Si herbal tea ingredients

Property	Sample/ingredients	Experimental model	Outcomes	Mode of action	Reference
Anti-diabetic	*A. indica* (L.) Kuntze	Animal model	Showed anti-diabetic activity in STZ-induced diabetic rats	Improved FBG, HbA1c, plasma insulin levels and HOMA-IR, HOMA-β and QUICKI	[72]
	A. argyi	Animal model	Showed anti-diabetic activity in ALX-induced diabetic rats	Marked improvements in serum insulin, total proteins, C peptide, and total hemoglobin, and decreases in HbA1c	[73]
	C. morifolium Ramat	Animal model	Exerted antidiabetic effects in obese diabetic KK-A^y mice	Increased PPARγ expression decreased the adipocyte sizes, suppressed chronic inflammation in adipose tissues, and elevated adiponectin levels	[74]
	G. glabra	Animal model	Exerted anti-hyperglycemic effect in diabetic KK-A^y mice	Promoted GLUT4 translocation in skeletal muscle through AMPK and Akt activation	[75]
	H. cordata	Animal model	Exhibited anti-hyperglycemic effect in STZ-induced diabetic rats	Reversed the expression patterns of GLUT-2, GLUT-4, and caspase-3 levels	[76]
	O. japonicus	Animal model	Ophiopogonin D showed a protective effect against STZ-induced diabetic nephropathy	Increased serum albumin and creatinine clearance. Decreased serum creatinine, blood urea nitrogen, TGF-β1, and kidney hypertrophy	[77]
	P. frutescens	Animal model	Exerted beneficial effects on hyperglycemia, dyslipidemia, glucose, and insulin intolerance	Modulated the AMPK pathway and inhibited gluconeogenesis in the liver	[78]
	P. grandiflorus	Animal model	Induced hypoglycemic effects without stimulating insulin secretion	Decreased blood glucose levels	[79]
Anti-obesity	*A. argyi*	Animal model	Improved dyslipidemia in HFD-induced obese rat	Reduced TG, TC, LDL-c, serum ALT, and AST levels	[80]
	C. morifolium Ramat	Animal model	Attenuated obesity-associated inflammation	Modulated the muscle AMPK-SIRT1 pathway	[81]
	G. glabra	Clinical study	Efficiently improve the lipid profile in overweight and obese subjects	Decreased TC, LDL-c levels, TC/HDL-c, LDL-c/HDL-c ratios, and log of TG/HDL-c	[82]
	H. cordata	Animal model	Showed anti-obesity effect and reduced dyslipidemia in HFD-induced obese rats	Decreased TC, TG, and LDL	[83]
	O. japonicus	Animal model	β-d-fructan prevented HFD-induced obesity and increased energy expenditure in mice	Ameliorated plasma lipid profiles, decreased leptin secretion, attenuated hepatic lipid accumulation, and increased the expressions of genes related to lipid and energy metabolism in the liver	[84]
	P. frutescens	*In vitro* and animal model	Showed anti-obesity effects in HFD-induced obese rats	Prevented body weight gain, improved serum lipids and hepatic lipids, and reduced epididymal fat	[85]
	P. grandiflorus	Animal model	Suppressed HFD-induced obesity in mice	Increased allobaculum and the production of SCFAs (butyrate and propionate) and other carbohydrate-related metabolites	[86]

FBG: Fasting blood glucose, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, HOMA-β: Homeostasis model assessment of β-cell dysfunction, QUICKI: Quantitative insulin sensitivity check index, STZ: Streptozotocin, ALX: Alloxan, PPARγ: Peroxisome proliferator-activated receptor-gamma, GLUT: Glucose transporter type, AMPK: 5-Prime-Amp-activated protein kinase, Akt: Protein kinase B, TGF-β1: Transforming growth factor-β1, HFD: High-fat diet, TG: Triglycerides, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein-cholesterol, ALT: Alanine aminotransferase, AST: Aspartate transaminase, AMPK-SIRT1: AMPK-silent information regulator T1, SCFAs: Short-chain fatty acids, *A. indica: Anisomeles indica, A. argyi: Artemisia argyi, C. morifolium: Chrysanthemum morifolium, G. glabra: Glycyrrhiza glabra, H. cordata: Houttuynia cordata, O. japonicus: Ophiopogon japonicus, P. frutescens: Perilla frutescens, P. grandiflorus: Platycodon grandiflorus*

D extracted from *O. japonicas* against renal damage in an STZ-induced DN rat model. Ophiopogonin D treatment decreased TGF-β1, serum creatinine, kidney hypertrophy, and blood urea nitrogen. Furthermore, serum albumin and creatinine clearance were increased by ophiopogonin D treatment in DN rats. Thus, the literature shows that *O. japonicas* could alleviate the development and progression of DN.

Anti-obesity activities

Over the past few decades, obesity has become a major health issue worldwide. Metabolic syndrome symptoms linked to obesity include hypertension, glucose intolerance, insulin resistance, and dyslipidemia. Obesity in humans can be prevented and managed through various approaches, and efforts have been made to identify new materials since obesity cannot be entirely cured or prevented, and the vast majority of anti-obesity drugs can lead to adverse effects. The ingredients of JSHT are recognized to have an anti-obesity impact and are thus used to treat obesity [Table 4]. Investigating the anti-obesity activity of *A. argyi* in high-fat diet (HFD)-induced obese rats, a study found that *A. argyi* extracts significantly lower the levels of TG, TC, LDL-c, serum ALT, and AST levels [80]. These results imply that

by increasing lipid metabolism, *A. argyi* extracts may aid in weight loss and dyslipidemia treatment. A similar study was also conducted on *H. cordata* extract by Thunb *et al*. [83] < which showed that the extract decreased the levels of TC, TG, and LDL in HFD-induced obese rats. Correspondingly, rodents treated with *P. frutescens* also showed reduced obesity through prevention of body weight gain, improvement of hepatic lipids and serum lipids, and reduction of epididymal fat [85]. Furthermore, Mirtaheri *et al*. [82] conducted a double-blind, randomized, controlled clinical trial to investigate the effects of GBE on the lipid profile and atherogenic indices in 64 overweight and obese subjects. Their findings revealed that after 8 weeks, GBE decreased the levels of TC, LDL-c levels, TC/HDL-c, LDL-c/HDL-c ratios, and log of TG/HDL-c. Decreased energy expenditure and chronically positive energy balance contribute to the prevalence of obesity and associated metabolic dysfunctions such as dyslipidemia, hepatic fat accumulation, inflammation, and muscle mitochondrial defects. Wang *et al*. asserted that β-d-fructan, a water-soluble polysaccharide extracted from *Ophiopogon japonicus*, is a promising candidate drug for the treatment of obesity-related metabolic diseases due to its ameliorative effect on lipid profile, attenuation of hepatic lipid accumulation, and upregulation of 12 genes involved in lipid and energy metabolism in the liver [84]. Lee *et al.* [81] examined the effects of *C. morifolium* Ramat flower extract on obesity-induced inflammation. By regulating the AMPK-SIRT1 pathway in muscles, the extract reduces the inflammation associated with obesity. Recently, gut microbiota has been a potential target for anti-obesity dietary interventions. A diet rich in bioactive compounds, including polyphenols and dietary fiber, can regulate gut flora and promote healthy weight maintenance. A study by Ke *et al.* [86] showed that *Platycodon grandiflorus* altered the gut metabolome and gut microbiota in HFD-fed mice; it primarily increased allobaculum and the production of SCFAs (butyrate and propionate) and other carbohydrate-related metabolites.

Hepatoprotective properties

Chronic liver disease, such as nonalcoholic steatohepatitis, nonalcoholic liver disease, liver fibrosis, cirrhosis, and many other conditions, can be caused by a wide range of chemicals, including drugs, dietary components, alcohols, and other environmental pollutants. Excessive alcohol consumption can cause liver dysfunction and alcoholic liver disease, resulting in liver damage. Researchers have proven that AST, AST, ALP, and bilirubin can be expressed in the liver and that their abnormally high levels can cause damage and necrosis in liver tissues [Table 5]. A recent study showed that the aqueous and ethanolic extracts of *A. indica* (L.) Kuntze decreased ALT, AST, and ALP levels in STZ-induced diabetic rat models [87]. Liver cells are sensitive to oxidative stress, and it was reported that *A. argyi* extract exhibited protective activity against chemically and immunologically induced acute liver injuries in a CCl_4-induced liver injury mouse model of [88]. According to the findings, *A. argyi* may help prevent oxidative liver damage, maintain intracellular levels of antioxidant enzymes, reduce levels of ALT, AST, ALP, TNF-α, IL-1, and MDA, and improve SOD and GPx activities. In an APAP-induced liver injury mouse model, the ethyl acetate extract of *C. morifolium* Rama, which protects against liver injury, showed significant anti-oxidant activity [89]. Mechanistically, *C. morifolium* Rama might reduce apoptosis through PI3K–Akt pathway and suppress excessive oxidative stress through the GSK3 β–Nrf2 pathway. In a laboratory experiment, licorice total flavonoids (LTF) were isolated from *G. glabra,* and three different types of liver damage mice models were used to study its hepatoprotective effects, including tetrachloromethane, Chinese liquor, and a high-fat emulsion [90]. Their findings suggested that LTF can reduce hepatic injury and repair liver tissue by reducing the levels of AST, ALT, ALP, TG, cholesterol, hepatic MDA, and increasing hepatic SOD and GPx of hepatic injury mice. Furthermore, a recent report from Kang and Koppula [91] claimed the hepatoprotective effects of *H. cordata* ethyl acetate extract in CCl_4-treated mice due to its significant reduction in the levels of increased serum and regulation of the altered levels of serum cholesterol. Recently, there has been a surge in interest in the polysaccharides derived from *O. japonicas* roots, which exhibit antioxidant properties and protect the liver from the detrimental effects of diabetes. Chen *et al*. [92] showed that OJP1, a polysaccharide isolated from the roots of *Ophiopogon japonica*, significantly reduced the levels of TG, TC, LDL-C, HDL-C, and MDA while increasing the activities of SOD and GPx in diabetic rats. Furthermore, the hepatoprotective effects of rosmarinic and caffeic acid, two primary compounds of *P. frutescens*, against *t*-BHP-induced oxidative liver damage were reported by Yang *et al*. [93]. Both compounds reduced MDA, ALT, and AST levels and increased GSH, GPx, and SOD activity. Moreover, the attenuative effects of *Platycodon grandiflorus* on hepatic insulin resistance and oxidative stress in HFD-induced nonalcoholic fatty liver diseases were investigated [94]. By modulating fatty acid synthase expression and phosphorylation of acetyl-CoA carboxylase, *Platycodon grandiflorus* significantly decreased HFD-induced liver damage, hyperlipidemia, and hepatic steatosis. *Platycodon grandiflorus* also improves insulin sensitivity by regulating the PI3K/Akt/GSK3 β signaling pathway and alleviating oxidative stress by increasing glutathione content and antioxidant activities.

Anti-inflammatory activities

The anti-inflammatory activity of JSHT ingredients has been tested both *in vitro* and *in vivo* [Table 5]. Nasrin *et al*. [16] investigated the *in vitro* anti-inflammatory potential of a methanol extract of *A. indica* (L.) Kuntze (MeOH-AI), revealing that MeOH-AI significantly inhibited protein denaturation and hemolysis induced by heat and hypotonic solution. Computer-aided analyses and molecular docking indicated anti-inflammatory activity through binding with COX-2. Moreover, inflammatory bowel diseases (IBD), like ulcerative colitis, have become more prevalent globally. Shin *et al*. [95] reported that in a dextran sulfate sodium-induced colitis mouse model, *A. argyi* ethanol extracts mediated IBD symptoms and enhanced immunomodulatory responses in lymphoid tissues through the activation of Nrf2 and

Table 5: Hepatoprotective and anti-inflammatory effects of Jing Si herbal tea ingredients

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
Hepatoprotective	*A. indica* (L.) Kuntze	Animal model	Aqueous and ethanolic extracts showed hepatoprotective effects STZ-induced diabetic rat models	Reduced the levels of ALT, AST, ALP	[87]
	A. argyi	Animal model	Protected against oxidative liver injury	Reduced the levels of ALT, AST, ALP, TNF-α, IL-1, and MDA. Restored the activities of SOD and GPx	[88]
	C. morifolium Ramat	Animal model	Showed protective effect from APAP-induced liver injury	Reduced the levels of AST, ALT, and ROS. Upregulated SOD and GSH. Increased levels of p-AMPK, p-GSK3β, HO-1, and NQO1, and promoted Nrf2	[89]
	G. glabra	Animal model	Reduce hepatic injury in mice	Reduced ALT, AST, and ALP, hepatic MDA, TG, and cholesterol levels. Increased SOD and GPx activities	[90]
	H. cordata	Animal model	Exhibited significant hepatoprotective property in carbon tetrachloride-induced hepatotoxicity in mice	Reduced the elevated serum levels and regulated the altered levels of serum cholesterol	[91]
	O. japonicus	Animal model	Showed liver-protective effects from the injurious effects of diabetes	Reduced the levels of TG, TC, LDL-C, HDL-C, and MDA. Increased the activities of SOD and GPx in the serum	[92]
	P. frutescens	Animal model	Showed hepatoprotective effect against oxidative liver injury	Reduced the levels of AST, ALT, and MDA and increased the activities of GSH, GPx, and SOD	[93]
	P. grandiflorus	Animal model	Exerted profound effects on hepatic insulin sensitivity and oxidative stress	Regulated phosphorylation of acetyl-CoA carboxylase, expression of fatty acid synthase, and PI3K/Akt/GSK3β signaling pathway	[94]
Anti-inflammatory	*A. indica (L.)* Kuntze	*In vitro*	Anti-inflammatory studies produced remarkable responses	Inhibited protein denaturation and hemolysis induced by heat and hypotonic solution	[16]
	A. argyi	*In vitro* and animal model	Mediated IBD symptoms and enhanced immunomodulatory responses in lymphoid tissues	Activated Nrf2, and HO-1, inhibited NF-κB, and upregulated IL-10	[95]
	C. morifolium Ramat	*In vitro*	Inhibited the production of inflammatory mediators	Inhibited TLR4 signaling	[96]
	G. glabra	Animal model	Diammonium Glycyrrhizinate reduced inflammatory injury	Suppressed NF-κB, TNF-α, and ICAM-1 in colonic mucosa	[97]
	H. cordata	*In vitro* and animal model	Showed anti-inflammation potential	Reduced NO production and suppressed the expression of PGE2, iNOS, IL-1β, TNF-α, and IL-6	[98]
	O. japonicus	*In vitro*	Showed anti-inflammation potential	Inhibited the phosphorylation of ERK1/2 and JNK in MAPK signaling pathways	[99]
	P. frutescens	Animal model	Protected against dextran sulfate sodium-induced murine colitis	Inhibited the activation of NF-κB and STAT3 and elevated the accumulation of Nrf2 and HO-1	[100]
	P. grandiflorus	*In vitro*	Showed anti-inflammation potential	Suppressed NF-κB and activated HO-1	[101]

STZ: Streptozotocin, ALT: Alanine aminotransferase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, TNF-α: Tumor necrosis factor-alpha, IL: Interleukin, MDA: Malondialdehyde, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, ROS: Reactive oxygen species, GSH: Glutathione, p-AMPK: Phosphorylated - 5-prime-amp-activated protein kinase, p-GSK3β: Phosphorylated-glycogen synthase kinase 3 Beta, HO-1: Hemoxygenase 1, NQO1: NAD (P) H quinone dehydrogenase 1, TG: Triglyceride, TC: Total cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein cholesterol, PI3K/Akt/GSK3β: Phosphatidylinositol-3-kinase and protein Kinase B/glycogen synthase kinase 3 Beta, IBD: Inflammatory bowel diseases, Nrf2: Nuclear factor erythroid 2-related factor 2, TLR4: Toll-like receptor 4, ICAM-1: Intercellular adhesion molecule 1, NO: Nitric oxide, PGE2: Prostaglandin E2, iNOS: Inducible nitric oxide synthase, IL-1β: Interleukin 1 beta, ERK1/2: Extracellular-regulated kinase 1/2, IL-6: Interleukin 6, JNK: Jun N-terminal Kinase, MAPK: Mitogen-activated protein kinase, STAT3: Signal transducer and activator of transcription 3, NF-κB: Nuclear factor kappa B, *A. indica: Anisomeles indica, A. argyi: Artemisia argyi, C. morifolium: Chrysanthemum morifolium, G. glabra: Glycyrrhiza glabra, H. cordata: Houttuynia cordata, O. japonicus: Ophiopogon japonicus, P. frutescens: Perilla frutescens, P. grandiflorus: Platycodon grandiflorus*, APAP: Acetaminophen

HO-1, inhibition of NF-κB, and upregulation of IL-10. Similar result were also reported by Park *et al*. [100] for *P. frutescens* extracts. *P. frutescens* treatment prevented the activation of NF-κB and STAT3 produced by dextran sulfate sodium, although it increased the accumulation of Nrf2 and HO-1 in the colon. Correspondingly, the anti-inflammatory mechanism of *P. grandifloras* ethanol extract was associated with the inhibition of NF-κB translocation and the activation of HO-1 production [101]. Further, to explore a possible anti-inflammatory effect of diammonium glycyrrhizinate (extracted from *G. glabra*) in ulcerative colitis, the suppressive expression of TNF-α, ICAM-1, and NF-κB in colonic mucosa was detected by immunohistochemistry in a rat model [97]. Furthermore, in LPS-stimulated RAW264.7 cells, the methanolic and aqueous extracts of *H. cordata* fermentation product inhibited the generation of PGE2, NO,

and inflammatory cytokines (TNF-α, IL-1, IL-6) [98]. Later, a carrageenan-induced rat paw edema model also confirmed the anti-inflammatory activities of fermented *H. cordata*. Zhao *et al*. isolated thirteen homoisoflavonoids compounds from *O. japonicas* [99]. Among these isolated compounds, 4'-*O*-demethylophiopogonanone E exhibited anti-inflammatory effect through suppressing the phosphorylation of JNK and ERK1/2 in MAPK signaling pathways, hence reducing the generation of pro-inflammatory cytokines and NO. Recently, a new bisepoxylignan called dendranlignan A, isolated from *C. morifolium* Ramat flowers, inhibited LPS-induced inflammation in H9c2 cardiomyocytes via the TLR4 pathway [96].

Kidney protective activities

Chronic kidney disease is typically caused by oxidative damage, inflammation, and other factors that interfere with the water and salt metabolism in the body [Table 6]. Antioxidative compounds can protect against contrast agent-induced cytotoxicity in renal proximal tubular cells and preserve renal function during the pathogenesis of an acute kidney injury. For instance, Kim *et al*. isolated 14 phenolic compounds from *A. argyi*. Their findings indicated that the anti-oxidant and antiapoptotic effects of methyl caffeate, an isolated phenolic compound from the *A. argyi*, protect LLC-PK1 cells from iodixanol-induced cell death. This action is attributed to MAPK (P38, JNK, and ERK) inhibition as well as KIM-1 and caspase-3 activities [102]. Xia *et al*.[103] found that total flavonoids from *C. morifolium* Ramat exerted kidney protective effects against lead-induced oxidative damage in mice by increasing CAT and GSH-Px activity and decreasing MDA concentration. Furthermore, ophiopogonin A, an active compound of *O. japonicas*, alleviated hemorrhagic shock-induced renal injury via the p-ERK/ERK signaling pathway [106]. Inflammation also contributes significantly to kidney disease. Zhang *et al.* [108] showed that saponins extracted from the roots of *Platycodon grandiflorum* protect mice kidneys from cisplatin-induced damage by modulating PI3K/Akt/apoptosis signaling pathways and suppressing NF-κB activation. Notably, most kidney damage or nephrotoxicity occurs as a result of drug use and is much more common in hospitalized patients. *G. glabra,* another important component of JSHT, demonstrated an ameliorative impact against nephrotoxicity induced by gentamicin in mice [104]. Gentamicin increased tissue levels of Bax, and Cox-2 and decreased expression of Nrf-2, and HO-1, but these levels recovered to normal in the *G. glabra* -treated group. Interestingly, rats treated with *H. cordata* exhibited a considerable improvement in renal function, most likely due to lowered biochemical indices and oxidative stress parameters (decreased levels of MDA, BUN, and creatinine and increased levels of CAT, SOD, and GSH) associated with gentamicin-sulfate-induced nephrotoxicity [105]. Multiple studies support the notion that renal ROS mediates kidney damage in patients with diabetes. *P. frutescens* sprout extract reportedly prevents high-glucose-induced renal mesangial cell dysfunction by modulating AMPK and NADPH oxidase signaling [107].

Neuroprotective activities

An alarming rise has been observed in the prevalence of neurodegenerative diseases. Despite advances in the treatment of Alzheimer's, Parkinson's, and Huntington's diseases, the pathophysiology of these conditions is not yet entirely understood. The provision of neuroprotective agents may delay the onset and reduce the symptoms of neurodegenerative diseases by decreasing inflammation, apoptosis, immune dysfunction, and oxidative stress. Numerous studies have established the potential neuroprotective properties of JSHT's ingredients [Table 6].

One experimental study suggested that Alzheimer's disease (AD) may benefit from the ethyl acetate extract of *A. indica (L.)* Kuntze, which may have anti-oxidant and acetylcholinesterase (AChE) inhibitory properties due to its phenolic components [109]. AD results from chronic inflammation of certain parts of the brain and its development could be attributed to oxygen-free radicals in elderly individuals. JSHT's ingredients may provide protective effects through their antioxidant properties, resulting in a reduced risk of brain damage and improved neurological function. It has been suggested that a combination of anti-inflammatory and antioxidant activities with neuroprotective effects might result in memory improvement. In a test of animal behavior, 3,5-dicaffeoylquinic acid (3,5-diCQA)–the primary phenolic ingredient in *A. argyi* –dramatically ameliorated learning and memory deficits by boosting the levels of AChE and SOD while decreasing the levels of AChE, MDA, and GSH [111]. In addition, 3,5-diCQA may prevent neuronal death by protecting mitochondrial functions and inhibiting apoptotic signaling molecules such as p-Akt, Bax, and p-tau (Ser 404). Similarly, a study showed that *H. cordata* water extracts improved symptoms of cognitive impairment in cholinergic dysfunction AD's disease models due to cholinergic dysfunction and inhibited cholinergic antagonists and tauopathies [120]. Furthermore, glycyrrhizic acid, another important phytochemical compound isolated from *G. glabra,* significantly improved copolamine-induced cognitive impairment in a mouse model [117]. Administration of *G. glabra* increased phosphorylation of ERK and JNK proteins, SOD, and CAT enzyme activities, and decreased the activity of AChE. Aβ is well established as one of the initiators that causes the progression of AD by accumulation and aggregation, which can be caused by Aβ overproduction or clearance failures. Wang *et al*. [114] isolated luteolin, a flavonoid compound of *C. morifolium* Ramat and found that it exhibited a neuroprotective effect in an STZ-induced AD rat model by dispersing Aβ plaques and inhibiting free radical products. Furthermore, the ethyl acetate fraction of the methanol extract of *Ophiophogon japonicas* displayed significant protective effects against Aβ-induced cytotoxicity to PC12 cells and was a potent inhibitor of β-secretase activity, resulting in decreased Aβ production [121]. Similarly, in 5XFAD mice, the ethanol extract of leaves of *P. frutescens* inhibited and disassembled Aβ aggregation, lowering lipid peroxidation and bad cholesterol [123]. However, Nam *et al*. [125] suggested

Table 6: Nephron- and neuroprotective effects of Jing Si herbal tea ingredients

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
Nephroprotective	*A. argyi*	*In vitro*	Protected kidney epithelium cells against apoptotic damage caused by iodixanol	Inhibited the activities of MAPKs (JNK, P38 and ERK), caspase-3, and KIM-1	[102]
	C. morifolium Ramat	Animal model	Showed kidney protective effects against lead-induced oxidative damage in mice	Increased the activity of GSH-Px, and CAT and decreased MDA concentration	[103]
	G. glabra	Animal model	Showed ameliorative impact against nephrotoxicity induced by gentamicin	Increased the levels of SOD and GSH-Px, promoted the expression of Nrf2 and COX-2, and inhibited IL-1β and IL-6 production	[104]
	H. cordata	Animal model	Showed protective effects against nephrotoxicity and oxidative stress	Decreased the levels of creatinine, BUN, and MDA. Increased the levels of GSH, SOD, and CAT	[105]
	O. japonicus	*In vitro* and animal model	Alleviated hemorrhagic shock-induced renal injury	p-ERK/ERK signaling pathway	[106]
	P. frutescens	*In vitro*	Protected renal mesangial cell dysfunction against high glucose	Modulated AMPK and NADPH oxidase signaling	[107]
	P. grandiflorus	Animal model	Exerted kidney protection effects against cisplatin-induced kidney injury	Inhibiting the activation of NF-κB and regulated PI3K/Akt/apoptosis signaling pathways	[108]
Neuroprotective	*A. indica* (L.) Kuntze	*In vitro*	Showed potential effect on AD treatment	Inhibited cholinesterase activities	[109]
	-	Animal model	Ovatodiolide prevented rats from brain I/R damage	Hampered neuronal apoptosis and microglial inflammation via the SIRT1-NF-κB pathway	[110]
	A. argyi	Animal model	Ameliorated the cognitive impairment induced by TMT	Prevent neuronal apoptosis by protecting mitochondrial activities and repressing apoptotic signaling molecules such as p-Akt, BAX, and p-tau (Ser 404)	[111]
	-	*In vitro*	Showed protective effects against PD	Reduced ROS, cell apoptosis, and MDA levels. Increased GSH and SOD levels	[112]
	-	*In vitro*	Eupatilin showed neuroprotective effects against focal cerebral ischemia	Reducing IKKα/β phosphorylation, IκBα phosphorylation, and IκBα degradation	[113]
	C. morifolium Ramat	Animal model	Luteolin showed a protective effect on learning defects and hippocampal structures in AD	Inhibited free radical products and dispersing Aβ plaques	[114]
	-	Animal model	Showed protective effects against PD	Increased the levels of SOD and GSH-Px and decreased MDA levels	[115]
	-	Clinical trial	Showed neuroprotective effect on ischemic stroke patients	Increased the levels of BDNF, SOD, and TAC and decreased the levels of the NIHSS, serum NSE, S100, and MDA	[116]
	G. glabra	Animal model	Showed neuroprotective effect on cognitive function	Increased phosphorylation of ERK and JNK proteins. Decreased activity of AChE and increased activity of SOD and CAT enzymes	[117]
	-	Clinical trial	Improved the symptoms in PD patients	Improved total UPDRS scores, daily activities and tremors along with motor test and rigidity scores	[118]
	-	Clinical trial	Improved the symptoms in patients with acute ischemic stroke	Declined in NIHSS scores and MRS	[119]
	H. cordata	Animal model	Improved cognitive deficits in cholinergic dysfunction AD's disease-like models	Inhibited cholinesterase activities	[120]
	O. japonicus	*In vitro*	Exhibited a neuroprotective effect on Aβ toxicity	Inhibited β-secretase activity and decreased MDA content	[121]
	-	Animal model	Methylophiopogonanone A showed therapeutic potential against cerebral I/R injury	Regulated the expression of MMP-9 and tight junction proteins	[122]
	P. frutescens	Animal model	Inhibited Aβ aggregates induce memory deficit	Inhibited and disassembled Aβ aggregation, lowered the lipid peroxidation and bad cholesterol	[123]

Contd...

Table 6: Contd...

Property	Sample/ ingredients	Experimental model	Outcomes	Mode of action	Reference
	-	Animal model	Counteract VaD-associated structural and functional deterioration	Attenuated proinflammatory mediators, including NO, TNF-α, and IL-6, downregulated the upstream MAPKs/NFκB/iNOS pathway	[124]
	P. grandiflorus	Animal model	Improved cognitive deficits	Decreased Aβ-related pathology and ameliorated Aβ-induced cognitive impairment	[125]
	-	Animal model	Improved learning and memory by enhancing synaptogenesis	Activated the MAPK/ERK signaling pathway	[126]

MAPKs: Mitogen-activated protein kinases, KIM-1: Kidney injury marker-1, JNK: Jun N-terminal kinase, ERK: extracellular regulated kinase, GSH-Px: Glutathione peroxidase, CAT: Catalase, MDA: Malondialdehyde, SOD: Superoxide dismutase, Nrf2: Nuclear factor erythroid 2-related factor 2, COX-2: Cyclooxygenase-2, IL-1β: Interleukin 1 beta, IL-6: Interleukin 6, BUN: Blood urea nitrogen, AMPK: Adenosine monophosphate-activated kinase, NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen, NF-κβ: Nuclear transcription factor-kappa B, AD's: Alzheimer's disease, STRT1: Sirtuin-1, TMT: Trimethyltin, *BAX*: B-cell lymphoma protein 2, PD: Parkinson's disease, ROS: Reactive oxygen species, IKKα/β: Inhibitory kappa B kinase α, Aβ: Amyloid-beta, BDNF: Brain-derived neurotrophic factor, TAC: Total antioxidant capacity, NIHSS: National Institutes of Health Stroke Scale, NSE: Neuron-specific enolase, AChE: Acetylcholinesterase, UPDRS: Unified Parkinson's disease rating scale, MRS: Modified Rankin scale, MMP-9: Matrix metalloproteinase-9, NO: Nitric oxide, TNF-α: Tumor necrosis factor-alpha, iNOS: Inducible nitric oxide synthase, PI3K/Akt: Phosphatidylinositol-3-kinase and protein kinase B, IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, *A. indica: Anisomeles indica, A. argyi: Artemisia argyi, C. morifolium: Chrysanthemum morifolium, G. glabra: Glycyrrhiza glabra, H. cordata: Houttuynia cordata, O. japonicus: Ophiopogon japonicus, P. frutescens: Perilla frutescens, P. grandiflorus: Platycodon grandiflorus*

that as a potential therapeutic agent for AD, *Platycodon grandiflorum* root extract may be able to decrease Aβ-related pathology and ameliorate Aβ-induced cognitive impairment. Hippocampal synaptogenesis is a key process for cognitive function, which involves the formation of synapses between neurons in the hippocampus and adult hippocampal neurogenesis. Kim *et al*. [126] found that the root extract of *Platycodon grandiflorus* improved learning and memory by increasing synaptogenesis via activation of the ERK1/2 signaling pathway in the hippocampus of mice. Another neurodegenerative disorder, vascular dementia (VaD) is defined by time-dependent memory loss and is essentially accompanied by neuroinflammation. In a recent study, polyphenol-rich PLE exerted therapeutic efficacy against VaD via decreasing proinflammatory mediators, including NO, TNF-α, and IL-6, and downregulating the upstream MAPKs/NF-κB/iNOS pathway [124].

The etiology of Parkinson's disease (PD), the second most prevalent age-related neurodegenerative disease, remains to be clarified. Inflammation and oxidative stress are crucial factors in the development and progression of PD. The ingredients of JSHT have been shown to protect cells from oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction. One study evaluated the neuroprotective effects of *A. argyi* against PD on 6-hydroxydopamine-induced toxicity in SH-SY5Y cells [112], revealing that the ethanolic extracts of *A. argyi* significantly reduced ROS, cell apoptosis, and MDA levels, as well as increased GSH and SOD levels. Similar results were also recoded for *C. morifolium* Ramat extracts against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD in C57BL/6 mice [115]. In a clinical trial, the ingestion of licorice root (*G. glabra*) could alleviate the symptoms of PD without causing major adverse effects [118]. Four months following licorice consumption, total Unified PD Rating Scale scores, daily activities, tremor, motor test, and rigidity scores improved significantly.

Cerebral ischemia–including stroke–is the leading cause of disability and death worldwide. It causes irreversible damage to the brain and loss of neural function. Ischemia results in an increase in ROS, mitochondrial dysfunction, and neuronal death as a result of a lack of oxygen, impaired blood flow, and calcium accumulation. Hu *et al*. [110] demonstrated the ability of ovatodiolide (extracted from *A. indica* [L.] Kuntze) to attenuate neurological apoptosis and deficits following cerebral ischemia in a dose-dependent manner. Mechanistically, OVA prevented brain I/R damage in rats by inhibiting neuronal apoptosis and microglial inflammation through the SIRT1-NF-κB pathway. Another compound, eupatilin—a substance isolated from *A. argyi*—was found to have neuroprotective benefits against focal cerebral ischemia by reducing NF-κB signaling activity in the ischemic brain by decreasing IKKα/β phosphorylation, IκBα phosphorylation, and IκBα degradation [113]. Furthermore, a homoisoflavonoid compound of *O. japonicas* known as methylophiopogonanone A, showed therapeutic potential for the treatment of cerebral I/R injuries in a rat model due to its ability to mitigate blood–brain barrier damage via modulation of tight junction proteins and MMP-9 expression [122]. In the treatment of ischemic stroke, reducing oxidative stress and increasing neuroprotection can play a critical role. In a clinical trial, Zhu *et al*. [116] evaluated the protective effect of *C. morifolium* Ramat extract on patients with ischemic stroke (60 patients). They found that compared to the levels on the 2st day, the levels of TAC, BDNF, and SOD were increased, and the MDA, serum NSE, NIHSS, and S100 levels were decreased in the *C. morifolium* Ramat group on the 4th day. In another clinical trial, Ravanfar *et al*. [119] evaluated the efficacy of the whole extract of licorice (extracted from *G. glabra*) in the neurological improvement of 75 patients after acute ischemic stroke. Results demonstrated that patients who ingested 450 mg and 900 mg of licorice extracts after 24 h of an ischemic stroke

had significantly better neurologic improvement (based on NIHSS scores) after 3 months.

Toxicity of the ingredients of JSHT

Despite well-established application, products derived from any herb require not only efficacy but also safety evidence. Several investigations on the toxicological effects of JSHT ingredients have been published, and surprisingly, most studies have shown weak potential toxicity. Basappa *et al*. [127] conducted a study to evaluate the toxicity of *A. indica* (L.) Kuntze leaf flavonoid fraction (ALFF) in mice, human lymphocytes, and human cancer cell lines. Under the experimental conditions, acute and subacute exposures to ALFF are nontoxic to mice, with the maximum tolerated dose exceeding 5000 mg/kg body weight. ALFF reportedly does not influence the hematological system, is not clastogenic or mutagenic, and inhibits the multiplication of cancer cells. Studies on the acute toxicity of hexane leaf extract of the *Artemisia* species were carried out by Ogbole *et al.* [128] on rats administered doses of 1000, 2000, and 2500 mg/kg intraperitoneally. They monitored and observed various parameters, such as the rats' decreased intake of food and fluids, in contrast to their increased output of urine and feces. Moreover, few significant changes were observed in the hematological system, and the extract was shown to have a lethal dose (LD50) of 2750 mg/kg body weight. Overall, studies showed low toxicity in short-term treatment. In a long-term toxicity study, Li *et al*. [129] treated the rats with *C. morifolium* Ramat daily by oral gavage at dose levels of 320, 640, and 1280 mg/kg body weight for 26 consecutive weeks followed by a 4 weeks recovery period. The data demonstrated no toxicological changes in food, water consumption, body weight, microscopic histopathologic examination, hematologic examination, organ weight, and blood biochemical examination were found in any treatment group. According to our assessments of the scientific literature, *G. glabra* is not a prominent teratogen and exhibits mild mutagenicity, genotoxicity, carcinogenicity, and developmental toxicity. Based on the scientific evidence, Nazari *et al*. [130] claimed that *G. glabra* is moderately toxic. Having said that, they also mentioned that since oral dispensation reduces absorption and first-pass metabolism of *G. glabra*, there is a lower risk of toxicity after oral administration than after intravenous or IP administration. However, the use of *G. glabra* and its components is contraindicated in pregnancy and neonates. As an edible plant, *H. cordata*'s potential toxicity is typically overlooked. There are no reports of its toxicity in long-term consumption as a vegetable or for medicinal use alone in certain regions of Asia, and the National Health Commission of China listed it in 2013 as one of the plants that can be used as both food and medicine, suggesting that *H. cordata* is relatively safe for oral administration in humans [20]. Although *O. japonicas* is well-known as both food and a therapeutic herb, the toxicity and safety assessments for this plant remain lacking. Few investigations on the toxicity of *O. japonicas* decoction have been conducted. Zhang *et al*. [131] evaluated the possible development of *O. japonicas* -induced toxicity in Sprague Dawley (SD) rats, and found that *O. japonicas* decoction (26.9 g/kg) had no significant effects on maternal body weight, fetal weight, viability, or fetal malformations in SD rats. The results showed that *O. japonicas* had no harmful effects on the fetuses or on the pregnant female SD rats that were treated. Interestingly, there are very few studies that have reported on the toxicological aspects of materials originating from *P. frutescens*. The inhalation of smoke from roasted perilla seeds caused occupational asthma via an IgE-mediated mechanism. In addition, a single instance of anaphylaxis due to perilla seed has been documented [22]. Regarding the *P. grandifloras*, Lee *et al*. [132] reported that at doses up to 2000 mg/kg, playtcodin D did not cause treatment-related mortality, significant changes in body weight, substantive histopathological changes, or abnormal clinical signs in 14 principal organs in male and female mice.

Conclusions and future perspectives

The eight ingredients of JSHT are potentially rich sources of phytochemicals that may help reduce disease risk conditions and, therefore, manage several noncommunicable diseases. Based on current evidence, this review summarized the therapeutic activities of JSHT's individual ingredients. It is clear from the reported evidence that the pharmacological activities of the eight ingredients in JSHT strengthen the promotion of JSHT as a health-care product. Thus, the review will provide a new foundation for consumers and the scientific community to better understand the health promotional benefits of JSHT.

Nevertheless, it is still noteworthy that our understanding of JSHT use has numerous limitations. The first gap is that research on the chemical composition of JSHT is currently lacking. Although several researchers have studied the individual ingredients of JSHT and identified numerous phytochemical compounds, structural modifications of the phytochemical compounds after combining all the ingredients may need to be taken into consideration. Moreover, the majority of research done on JSHT's ingredients focused on crude extracts and their abundant bioactive secondary metabolites; however, the results of these investigations are still ambiguous and inadequate. Thus, additional systematic studies on JSHT are required to identify the particular phytochemical compounds in the extracts and determine their pharmacological effects with greater precision. Further, the current health-related information on JSHT is insufficient, and its clinical value has not been sufficiently explored. Therefore, a deep and systematic phytochemical investigation of JSHT and its pharmacological properties, especially the mechanism of action, to illustrate its ethnomedicinal use and support further efficacy and safety should undoubtedly be the focus of further research.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

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