Review Article

Anti-aging role of Chinese herbal medicine: an overview of scientific evidence from 2008 to 2018

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Abstract: The aging of the population has become a global health problem. It is an important risk factor for major diseases such as cardiovascular disease, Alzheimer's disease, Parkinson's disease, and cancer. Presently, there is no definite and effective anti-aging treatment. Chinese herbal medicine has a long history of application and is often used for aging-related diseases in China. A large number of clinical and preclinical studies on the anti-aging effect of Chinese herbal medicine has been performed. Through literature research, we reviewed the anti-aging clinical research of Chinese herbal medicine and preclinical research of Chinese herbal medicine monomers, components, extracts, and compounds, and their mechanisms. Results from preclinical studies have shown that Chinese herbal medicines have beneficial anti-aging effects. The mechanism mainly includes anti-oxidative stress, anti-inflammatory, neuroprotection, apoptosis and mitochondrial function regulation, etc. However, more detailed high-quality clinical trials are required for future investigation of the anti-aging effects of Chinese herbal medicines.

Keywords: Chinese herbal medicine (CHM); evidence; mechanism; review; anti-aging

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Introduction

With the improvement of science and technology and living conditions, mankind is gradually moving towards an aging society. According to the United Nations World Population Ageing Report released in 2015 (1), the number of aged people (60 and over) is expected to increase to nearly 2,100 million over the next 35 years. As age increases, the physiological function of the body gradually deteriorates, which is characterized by the decline in the structure and function of organs, cells, and tissues (2). Aging-related diseases are becoming one of the biggest challenges faced by developed and developing countries (3). López-Otínput forwarded nine pathological features of aging, including genomic instability, telomere loss, epigenetic changes, protein homeostasis imbalance, deregulated nutrient sensing, mitochondrial damage, cell senescence, stem cell exhaustion, and intercellular communication changes (4).

Presently, anti-aging methods mainly include diet restriction, gene reprogramming, and drugs (5). A growing number of research data shows that adequate dietary restrictions (DR) have a strong protective effect on obesity, type 2 diabetes, inflammation, hypertension, and cancer-related risk factors under sufficient nutrition (6). In fact, for most people, the duration and degree of the DR program needed for the best benefit are unfeasible and may lead

to related side effects. Short term partial reprogramming of Oct4, Sox2, Klf4, and c-Myc (OSKM) improves physiological markers in mice, prolongs their life span, and improves the muscle regeneration ability of the normal old mice (7). However, the feasibility and safety of these two methods need further studies.

Drug therapy is an anti-aging method, and rapamycin, metformin, and spermidine are the typical drugs. Rapamycin, an mTOR inhibitor, can reduce downstream production of mTOR c1 and S6K by inhibiting the mTOR pathway; the life span of mice can be prolonged by up to 60% with 3 months of rapamycin treatment (8). A study was performed to assess whether the mTOR inhibitor RAD001, could improve immune senility to influenza vaccination in elderly volunteers. The results showed that RAD001 enhanced immune response to influenza vaccines and also reduced the percentage of $CD4^+$ and $CD8^+$ T lymphoblastic cells that expressed the programmed death-1 receptor (PD-1) (9). Metformin, a usual drug used in type 2 diabetes mellitus (T2DM) treatment, has been proven to prolong the life span of nematodes (10). Spermidine, a natural polyamine, can prolong the life of mice and play a protective role in the heart by reducing myocardial hypertrophy and protecting the diastolic function of the heart in aged mice (11). Additionally, low dose lithium can prolong the life span of Drosophila melanogaster by 16%; the mechanism may be related to its glycogen synthetase kinase-3 (GSK-3) inhibition and transcription factor nuclear factor erythroid 2-related factor (NRF-2) activation (12).

However, sufficient clinical evidence of the effects of theses drugs on humans is unavailable. In recent years, the anti-aging effect of Chinese herbal medicine (CHM) has been widely and deeply researched. This article is an overview of the progress on elucidating the anti-aging effects of CHM. The research articles of anti-aging CHM published from 2008 to 2018 were retrieved from PubMed. The Clinical Trials (https://clinicaltrials.gov/) and Chinese Clinical Trial Registry (http://www.chictr.org.cn/) databases were searched for registered clinical trials.

The anti-aging role of CHM

Evidence from clinical studies in humans

Nine clinical trials published from 2008 to 2018 were included (*Table 1*). The types of studies include randomized controlled trials, crossover trials, cohort studies, etc. Resveratrol was the most studied medicine, followed by curcumin. The main outcome indicators of these clinical studies were as follows: general signs, muscle function and structure, cardiovascular and metabolic indicators, cognitive function, aging-related protein or gene, and safety indicators.

Some studies reported the following adverse reactions: gastrointestinal reactions, dizziness, diarrhea, constipation, muscle cramps, fatigue, memory loss, allergies, difficulty swallowing, rash, headache, etc. In a randomized, double-blind crossover study of resveratrol, three participants treated with 3 g of resveratrol daily experienced severe gastrointestinal symptoms with one requiring hospitalization, but when the dose was lowered to 2 g/d for the remaining participants, no further gastrointestinal symptoms were reported (13). Resveratrol supplementation at doses of 300 and 1,000 mg/day for 90 days does not adversely affect blood chemistry, and is well tolerated in overweight and older individuals; the incidence of adverse events between the treatment and control groups was not statistically significant (14). This study highlights the safety of short-term and low-dose resveratrol administration. In terms of anti-aging, research shows that resveratrol combined with exercise can reduce or reverse sarcopenia in elderly persons (15). Besides, supplementary resveratrol also improves memory performance and increases hippocampal functional connectivity in healthy older adults; improved glucose metabolism may be an underlying mechanism (16). Another study also showed that a single dose of 75 mg of resveratrol improves neurovascular coupling and cognitive function in patients with T2DM (17). However, a prospective study in 783 older community-dwelling adults showed that there was no association between urinary resveratrol metabolites and longevity; total urinary resveratrol metabolite concentration was not associated with inflammatory markers, cardiovascular disease, cancer, or all-cause mortality (18). Therefore, further clinical research on the anti-aging effect of resveratrol is waranted. On the other hand, curcumin (2,000 mg/day) administration for 12 weeks improves resistance artery endothelial function by increasing vascular nitric oxide bioavailability and reducing oxidative stress (19). A 12-month, randomized, placebo-controlled, double-blind study focused on curcumin and cognition showed that there were no differences in cognitive performance from baseline to the 12-month follow-up between placebo and treatment groups (20). *Ganoderma lucidum* has been used as a traditional medicine to treat a variety of diseases. A randomized, double-blind, placebo-controlled crossover study on *Ganoderma lucidum* shows its antioxidation and hepatoprotective efficacy, but the subjects were healthy middle-aged (40–54 years old)

Table 1 Published clinical trials of CHM for slowing aging in humans from 2008 to 2018

Age	Medicine	Dose	Duration	Case	Main outcomes	Adverse events	References
≥65	Resveratrol	300, 1,000 mg/d	90 days	22/10	Blood chemistries, weight, waist circumference, BP, and blood glucose	Diarrhea, constipation, muscle cramps, fatigue, memory loss, allergies, difficulty swallowing, rash, and headache	(14)
≥65	Resveratrol	NA	9 years	783	All-cause mortality, CRP, TNF-α, IL-6, IL-1β, prevalent and incident cancer, and cardiovascular diseases	No reports	(18)
50–80	Resveratrol	2–3 g/d	6 weeks	30	Cardiometabolic, endothelial function, and skeletal muscle gene expression	Gastrointestinal symptoms	(13)
65–80	Resveratrol	500 mg/d	12 weeks	15/15	Mitochondrial density, muscle fatigue resistance, and cardiovascular function	No reports	(15)
50–75	Resveratrol	200 mg/d	26 weeks	23/23	Hippocampal functional connectivity, HbA1c, body fat, and leptin	No reports	(16)
40–80	Resveratrol	75, 150, and 300 mg/d	NA	36	Neurovascular coupling capacity	No reports	(17)
45–74	Curcumin	0.2 mg/d	12 weeks	20/19	Artery endothelial function, vascular nitric oxide bioavailability, and oxidative stress	Diarrhea, dizziness, and nausea gastrointestinal	(19)
40–90	Curcumin	0.15 g/d	12 months	80/80	Montreal cognitive assessment	Gastrointestinal	(20)
40–54	Ganoderma lucidum	225 mg/d	6 months	21/21	Anthropometric measurements, oxidative index, antioxidative enzymes, and hepatic marks	No reports	(21)

BP, blood pressure; CRP, C-reactive protein; IL-6, interleukin-6; IL-1β, interleukin-1β; HbA1c, glycated hemoglobin.

volunteers (21), therefore, its efficacy in the elderly should be further studied.

Additionally, we found 10 registered clinical trials (*Table 2*) from Clinical Trials (https://clinicaltrials.gov) and Chinese Clinical Trial Registry (http://www.chictr.org.cn), the recruiting locations are mainly China and the United States. Generally, large-scale clinical research on the anti-aging effect of CHM remains unavailable. Presently, there are still some shortcomings in clinical research such as fewer cases, short follow-up time, etc.

Evidence from Preclinical Studies

In this section, we summarize the known effects, and mechanisms of single herbs and their components or extracts in preclinical studies (*Tables 3* and *4*).

Monomers and Components of CHM

Resveratrol

Resveratrol is a natural polyphenolic compound found in several plants, including grapes and Polygonum cuspidatum (79). Studies have shown that it indirectly activates SIRT1 *in vivo* (80). The life-prolonging metabolic roles of SIRT1 include gluconeogenesis regulation, fatty acid oxidation reduction, fat production reduction, insulin secretion upregulation, and autophagy regulation (81). Additionally, resveratrol can alleviate H_2O_2-induced oxidative stress injury in endothelial cells, thereby slowing aging (82). Resveratrol can also protect against arterial aging, and this effect is associated with reduced activity of

Table 2 The ongoing RCTs of CHM for slowing aging from 2008 to 2018

Trial number	Objectives	Interventions	Primary outcomes	Subjects (age)
NCT03085680	To examine whether dietary supplementation with curcumin affects cognitive and physical function in older adults	I: Curcumin and C: microcrystalline cellulose	Walking and handgrip	24 [70–99]
NCT01968564	To assess the ability of curcumin to improve the function of arteries with age	I: Curcumin 500–2,000 mg/d and C: Placebo	Arterial stiffness and NO-Mediated endothelium-dependent dilation	118 [45–80]
NCT01811381	To test the clinical benefits of curcumin and the effect of adding physical exercise program on memory function or brain imaging and blood-based markers associated with AD	I: Curcumin; aerobic yoga; non-aerobic yoga: and C: Placebo	The levels of blood biomarkers for mild cognitive impairment	80 [50–90]
NCT01126229	To determine whether resveratrol is safe and improves memory and physical performance in older adults	I: Resveratrol 300, 1,000 mg/d and C: Placebo	Safety outcomes	32 [65–100]
NCT02123121	To evaluate whether Resveratrol improves physical function	I: Resveratrol 1,000 and 1,500 mg/d; C: Placebo	Mitochondrial respiration; cytochrome oxidase; citrate synthase enzymes; and mitochondrial DNA content	60 [≥65]
NCT02523274	To evaluate the effect of combining physical exercise with resveratrol supplementation on physical function	I: Resveratrol 250, 1,000 mg/d and C: Placebo	Walking speed	60 [≥65]
NCT01504854	To determine whether daily resveratrol is beneficial in delaying or altering the deterioration of memory and daily functioning.	I: Resveratrol; C: Placebo	Number of Adverse Events; MRI	119 [≥50]
ChiCTR-IPR-16007802	To observe the safety and synergistic effects of Kangshuailao tablet adjuvant chemotherapy for lung cancer	I: chemotherapy + Kangshuailao tablet; C: chemotherapy	Bone marrow suppression and safety	120 [18–75]
ChiCTR1800014814	To evaluate the clinical efficiency of Jianpi Yangwei paste in Frailty syndrome treatment	I: Jianpi Yangwei and C: Nothing	Fried frailty phenotype/ MBI-C/TCM Syndromes/ Routine blood test	60 [60–90]
ChiCTR-IOR-16008394	To evaluate the efficacy and safety of Cong Rong jing in treating early-stage Parkinson's disease	I: Sifrol/XI Ning + Cong Rongjing; C: Sifrol/XI Ning + placebo	Unified Parkinson's disease rating scale	144 [50–70]

the PRR-ACE-Ang II axis and stimulation of the ACE2-Ang-(1-7)-ATR2-MasR axis (83).

Curcumin

Curcumin is a bioactive substance extracted from the rhizome of Curcuma longa L (84). Curcumin supplementation can increase the survival rate of Drosophila, which may be related to its antioxidant activities and the mitigating effect of heat shock responses (85). Another study showed that curcumin suppresses vascular aging and inflammation triggered by long-term administration of a high-fat diet, which might be a prophylactic food against arteriosclerotic disease (86). Aging is the major risk factor for osteoarthritis and studies have found that curcumin can treat it by inducing autophagy via the Akt/mTOR signaling pathway (87).

Ginsenoside Rg1

Ginsenoside Rg1, an active ingredient of Panax ginseng, can improve the cognitive ability of the D-galactose-induced aging rat model; its mechanism may be related to neural stem/progenitor cell protection, and antioxidant and anti-inflammatory capacity enhancement in the hippocampus (88).

Table 3 The slowing aging effects of CHM monomers and components in animal and cell models

Components	Animal/cell	Dose	Duration	Main effects	Mechanism	References
Acteoside	D-gal- and $AlCl_3$-induced mice	30, 60, and 120 mg/kg/d	30 days	Memory enhancement	NOS, NO, and caspase-3↓; Nissl bodies↑	(22)
Acteoside	D-gal- and $AlCl_3$-induced mice	30, 60, and 120 mg/kg/d	30 days	Memory enhancement	nerve growth factor and tropomycin receptor kinase A↑	(23)
ASP	D-gal-induced mice	200 mg/kg	35 days	Prevented HSCs Senescence	T-AOC↑; ROS, 8-OHDG, p16, Rb, p53, p21, β-catenin, p-GSK-3β, TCF-4↓	(24)
ASP	D-gal-induced mice	120 mg/kg	35 days	Protective effect against liver injury	ALT, AST, TBIL, MDA, and AGEs↓; SOD and GSH-Px↑	(25)
ASP	X-ray-induced mice	200 mg/kg	80 days	Delayed aging of HSCs	SA-β-Gal positive cells, ratio of G1 stages, and P53↓; length of telomere↑	(26)
ASP	X-ray-induced mice	200 mg/kg	80 days	Delayed aging of HSCs	SA-β-Gal positive cells, ratio of G1 stages, ROS, and p16 mRNA↓; T-AOC↑	(27)
Baicalin	UVB-induced cytotoxicity in HaCaT cells	50, 100, and 200 ug/mL	24 h	Inhibited UVB-induced damage	Cell viability↑; CPDs, IL-6, TNF-α, Apoptosis, p53/p21, c-fos mRNA p53, PCNA, and RPA↓	(28)
Berberine	PHDFs by UVB irradiation	1, 5, 10, and 20 μM	72 h	Anti-skin aging	MMP-1↓; type I procollagen↑	(29)
Berberine	H_2O_2-induced Senescent HDFs	6, 12, and 20 μM	12 h	Suppressed H_2O_2-induced Senescence	SIRT1↑; ROS, and Chk2↓	(30)
CMP	D-gal induced mice	40, 80, and 160 mg/kg/d	7 weeks	Inhibited mitochondrial injury and anti-aging	TBARS↓; CAT, SOD, GPx↑	(31)
CSP	D-gal induced mice	20, 40, and 80 mg/kg	56 days	Delayed the aging process	Relative length of telomere↑	(32)
Curcumin	Drosophila	0.5, and 1.0 mg/L	2-3 weeks	Increased mean lifespan	dInR, ATTD, Def, CecB, DptB, and MDA↓; Mn-SOD, and Cu-SOD↑	(33)
Curcumin	Drosophila	10, 50, 100, 125, 250, 500, and 1,000 uM	14/8 weeks	Extended Life Span↑	Mitigate the expression levels of age-associated genes	(34)
Deoxyschisandrin	HaCaT cells by UVB	100 μM	24 h	Protected cells from UVB-induced cell damage	ROS, apoptosis, and cleaved caspase-3/8/9↓	(35)
Echinacoside	C. elegans	2, 20, 200, and 1,000 μM	36 h	Extended lifespan	sod-3 and hsp-16.2↑	(36)
Ginsenoside Rg1	D-gal induced rats	20 mg/kg	27 days	Slowed brain aging and increased learning and memory abilities	Senescent cells, IL-1, IL-6↓; SOD, GSH, telomerase activity and length↑	(37)

Table 3 (*continued*)

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Components	Animal/cell	Dose	Duration	Main effects	Mechanism	References
Glycoproteinof FPZ	D-gal induced mice	1, 4, and 10 mg/g	6 weeks	Anti-aging	Bodyweight, kidney index, MDA↓; SOD, CAT, and klotho↑	(38)
Icariin	C57BL/6 mice	Standard diet plus 0.02%	12 months	Extended healthspan and mean lifespan	γ-H2AX t, MDA↓; bone mineral density, SOD↑	(39)
Icariin	BALB/c mice; TNF-α induced ECs	Feed pellets in 0.02%/10^{-8} mol/L	3 months; 36 h	Intervened in Cardiac Inflammaging	SIRT6 and SIRT6 mRNA↑; NF-κB, SA-β-Gal, TNF-α, ICAM-1, IL-2, and IL-6↓	(40)
Icariside II	C. elegans	15, 45, and 75 μM	4 days	Extended lifespan	Insulin/IGF-1 signaling; daf 16 and hsf-1↑	(41)
LBPS	Zebrafish	1.0, 2.0, 3.0, and 4.0 mg/mL	3 days	Inhibited cell apoptosis and senescence	p53, p21, and Bax↓; Mdm2 and TERT↑	(42)
Ligustilide	D-gal-induced mice	80 mg/kg/d	8 weeks	Prevented cognitive impairment and attenuated neurotoxicity	MDA, cleaved caspase-3, GFAP↓; Na^+-K^+-ATPase, and GAP-43↑	(43)
MLP	C. elegans	25 mg/L	24 h	Delayed aging and regulated fat metabolism	Fat-6, lipl-4, sod-3, unc-51, and fard-1↑	(44)
PSG-1	D-gal-induced mice	50, 100, and 150 mg/kg/d	4 weeks	Attenuated oxidative stress	GSSG and MDA↓; SOD, CAT, GPx, GSH-Rd, and GSH↑	(45)
PSG-1	D-gal induced mice	50,100,150 mg/kg/d	4 weeks	Improved oxidative stress and immune impairment	T and B cell proliferation and interleukin-2↑	(46)
Ot B	C.elegans	50 μM	50 days	Extended the lifespan	Body movement, DAF-16↑	(47)
Paeonol	H_2O_2-induced senescent HUVECs	10, 30, 60, 120, and 360 μM	24 h	Protected against premature senescence	Sirt 1↑; p53, H3K14, and H4K14↓	(48)
Resveratrol	High glucose-induced MCs	1 ug/mL	72 h	Arrested senescence	$p27^{kip1}$and $p21^{cip1}$ ↓; Sirt 1↑;	(49)
Resveratrol	AA + iron-induced HepG2 cells	3, 10, 30, and 60 μM	1 h	Protected mitochondria against oxidative Stress	Cell viability, p-ACC, p-AMPK, p-LKB1, and GSH↑; ROS and MitoSOX↓	(50)
Resveratrol	Senescent ECs; WKY rats	10 umol/L	1 h	Improved endothelial function	S6K1, Akt, MitoSox, and DHE↓; NO↑	(51)
Salidroside	UVB-induced senescentHDFs	1, 5, and 10 uM	24 h	Protected against premature senescence	Cell viability↑; p53, p21, p16, MDA, MMP-1, IL-6, TNF-α↓	(52)
Salidroside	D-gal-induced mice	1 g/kg	8 weeks	Anti-aging	AGEs, GFAP, and NT-3↓; Lymphocyte proliferation and IL-2↑	(53)
SFPS	D-gal-induced mice	100 and 300 mg/kg	8 weeks	Activated antioxidant defense	CAT, SOD, Nrf2, and JNK1/2↑; MDA↓	(54)

Table 3 (*continued*)

Table 3 (*continued*)

Components	Animal/cell	Dose	Duration	Main effects	Mechanism	References
TFE	SD Rats	0.06 g/kg/day	3 months	Retards aging	Lymphocyte apoptosis and apoptosis promoting genes↓; apoptosis inhibiting genes↑	(55)
TFE	SD Rats	0.06 g/kg/day	3 months	Intervention on lipid metabolism and antioxidation	Weight, TG, TC, and MDA↓; SOD↑	(56)
TFE	SD Rats	0.06 g/kg/day	3 months	Anti-aging	Age-related metabolites	(57)
TSG	C57BL/6 mice and C2C12 and Hela cells	40.6 mg/kg/d; 25, 50, and 100 μM	30 weeks/24 h	Delayed senile symptoms	Motor function, bone mineral density, organ pathology, and mitochondrial function↑; AMPK/SIRT1/PGC-1α	(58)
Yam dioscorin	HUVEC; D-gal-induced mice	10–1,000 ug/mL; 20 and 80 mg/kg	24 h/6 weeks	Attenuated oxidative status and learning dysfunction	iNOS, MDA, and AGEs↓; GSH and ORAC↑	(59)
YLSP	D-gal-induced mice	0.15, 0.3, and 0.6 g/kg	8 weeks	Improved redox homeostasis and immune impairment	SOD, GSH-Px, CAT, and IL-2↑; IL-6, MDA, AGE, p53, and p21↓	(60)
β-asarone	SAMP8	34 mg/kg/day	2 months	Prevented autophagy and synaptic loss	ROCK↓; GAP43, MAP2, and SYN↑	(61)

ASP, Angelica Sinensis Polysaccharide; CMP, cordyceps militaris polysaccharide; CSP, cynomoriumsongaricum polysaccharide; PSG-1, ganoderma atrum polysaccharide; LBPS, lycium barbarum polysaccharides; MLP, mulberry leaf polyphenols; Ot B, otophylloside B; TFE, total flavone of epimedium; TSG, tetrahydroxystilbene glucoside; SIRT, silent information regulator; SFPS, sargassum fusiforme polysaccharides; YLSP, Yulangsan polysaccharide.

Table 4 The slowing aging effects of CHM extracts in animal and cell models

Extracts of herb	Animal/Cell	Dose	Duration	Main effects	Mechanism	References
Akebia quinata fruit extract	HDFs	10, 25, 50, 100, 200, and 500 ug/mL	0.5 h	Antioxidation and antiglycation	AGEs, CML, and ROS↓; fibrillin-1↑	(62)
A. cochinchinensis root extract	D-gal-induced aging mice	2.66 g/kg	15 days	Slowed aging	Spleen index and SOD↑; MDA↓	(63)
BSPO	C. elegans	500 ug/mL	2 days	Extended lifespan	GST-4 and HSP-16.2↑; ROS and lipofuscin↓	(64)
Centella asiatica water extract	Mice	2 mg/mL	2 weeks	Enhanced cognition	Mitochondrial, antioxidant, and synaptic genes↑	(65)
Codonopsis pilosula decoction	D-gal-induced aging mice	5 and 15 g/kg/d	32 days	Enhanced immune function in aging mice	Spleen and thymus index, CD138, IgG, IgM, C3, and C4↑	(66)
CXE	C. elegans	25 mg/L	2,6 days	Anti-aging	Age-1, daf-2, and let-363↓; ins-18, let-60, sir-2.1, and sod-3↑	(67)
Dandelions extracts	HDFs	30, 100, and 300 ug/mL	24 h	Anti-senescence	MMP ↓; GSH, GR mRNA, and UV absorption↑	(68)
ECD	SAMP8	50, 100, 150, 450, 500, and 2,500 mg/kg	4 weeks	Antagonized immunosenescence and extended lifespan	Naive T and natural killer cells↑; necrosis in peripheral lymphocytes, IL-6↓	(69)
G.lucidum extract	BALB/c mice	50 and 250 mg/kg/d	15 days	Improved antioxidation status	GSH, MnSOD, GPx, and GST↑; lipid peroxidation, AOPP, and ROS↓	(70)
G.lucidum extract	Rats	50 and 250 mg/kg/d	15 days	Ameliorated decline of cellular energy status.	ICDH, αKGDH, SDH, MDH, Complex II, and Complex IV↑	(71)
G.lucidum extract	Rats	50 and 250 mg/kg/d	15 days	Improved mitochondria function	PDH, αKGDH, SDH, complex I and II↑; lipid peroxidation↓	(72)
Paeonia extracts	D-gal-induced aging mice	100, 200, and 400 mg/kg	3 weeks	Antioxidant	SOD and GSH ↑; 8-iso PGF2α, MDA, and carbonyl protein ↓	(73)
Pine pollen	2BS and D-gal-induced aging mice	1.2 mg/mL; 500, 1,000, and 1,500 mg/kg	24 h and 8 weeks	Anti-aging	SA-β-Gal, p53, p21, p16, PTEN, p27, AGEs, TNF-α, IL-6, and MDA↓; SOD↑	(74)
Pine pollen	Mice	750 mg/kg	60 days	Anti-aging	Depletion of kidney mtDNA and MDA↓; SOD↑	(75)
PME	C. elegans	10, 100, and 1,000 ug/mL	48 and72 h	Anti-aging	Lipofuscin↓; oxidative and thermal stress resistance↑	(76)
P.oleracea phenolic extract	D-gal/$NaNO_2$-induced mice	360 and 720 mg/kg/day	8 weeks	Prevention of aging and cognitive dysfunction	SOD and CAT↑; hippocampal morphological damage and MDA↓	(77)
Siraitia grosuenorii	Mice	3 g/day	10 months	Anti-aging	ROS, p21, p53 and p16↓; p57↑	(78)

BSPO, n-butanol extract from seeds of Platycladus orientalis; C. songaricum, Cynomorium songaricum; CXE, Chuan Xiong Extract; ECD, Cistanche deserticola extracts; PME, polygonum multiflorum extracts; G.lucidum, ganoderma lucidum; A. cochinchinensis, asparagus cochinchinensis; P.oleracea, portulaca oleracea

Later studies showed that its protective effect may be achieved via downregulation of the p19/p53/p21 signaling pathway (89). Hematopoietic stem cell (HSC) senescence is an important hypothesis accounting for organismal aging; Ginsenoside Rg1 can improve the resistance of Sca-1$^+$ hematopoietic stem/progenitor cells (HSC/HPCs) in aging mice by reducing DNA damage and inhibiting excessive activation of the Wnt/β-catenin signaling pathway (90). The function of the spleen and thymus decreases with aging; Ginsenoside Rg1 can protect the spleen and thymus of D-galactose-induced aging rats via reducing oxidative stress injury and downregulating the expression of aging-related proteins (91).

Salidroside

Salidroside, a phenylpropanoid glycoside, is a potent component isolated from the root of Rhodiola rosea, which can resist immune aging by enhancing humoral and cell-mediated immune responses in aged rats after antigen activation (92). Besides, salidroside can also play a therapeutic role in learning and memory decline by stimulating cAMP response element binding protein (CREB)-dependent functional neurogenesis during aging (93). Aging is the major risk factor for cardiovascular diseases, especially coronary atherosclerosis, which is mainly attributed to the aging of vascular structure and function. Studies showed that salidroside can prevent oxidized low-density lipoprotein (ox-LDL)-induced endothelial cell senescence by promoting the cell cycle and reducing intracellular lipid deposition, inhibiting the expression of senescence-related molecules (94).

Total Flavonoid of Epimedium and Icariin

Epimedium is the dry leaf of Epimedium brevicornu Maxim (95). Its main constituents are the Total Flavonoid of Epimedium (TFE) and Icariin. Oxidative stress is one of the main causes of aging and can induce oxidative DNA damage, causing cell cycle arrest and apoptosis; however, TFE can effectively reduce oxidative stress-induced DNA damage in aging rats by inhibiting p-p53/p21 and chk1/chk2 expression, increasing superoxide dismutase (SOD) activity and decreasing malondialdehyde (MDA) content (96). Icariin alleviates the age-dependent deficit in cognitive function, which may be via activation of neural stem cells (NSCs) in the hippocampus (97). Parkinson's disease (PD) is one of the most common neurodegenerative diseases. Two different damage models of dopamine neurons in rat midbrain induced by neurotoxins of 6-hydroxydopamine (6-OHDA) and lipopolysaccharide (LPS) were employed to investigate the neuroprotective effects of Icariin. The result showed that it could protect dopamine neurons both *in vivo* and *in vitro*, and the mechanism may be related to the inhibition of microglia-mediated neuroinflammation (98).

Angelica Sinensis Polysaccharide

Angelica Sinensis (Dang gui) is the dry root of an umbelliferous plant *Angelica sinensis* (Oliv.) Diels (95). Angelica Sinensis Polysaccharide (ASP) is a major ingredient in Angelica Sinensis. ASP ameliorated stress-induced premature senescence of hematopoietic cells by protecting bone marrow stromal cells against chemotherapeutic injury via alleviating the oxidative damage of stromal cells and improving their hematopoietic function (99).

Astragalus polysaccharides (APS)

APS is a major active ingredient of Astragalus membranaceus. Bone marrow mesenchymal stem cell (BMSCs) dysfunction under pathological stimulation is involved in the development of aging-related diseases such as osteoporosis (100). APS treatment may attenuate apoptosis and senescence in BMSCs, inhibiting the reduction of Nanog, Sox2, and Oct4 expression caused by ferric ammonium citrate (FAC) (100).

Echinacoside (ECH)

ECH is a phenylethanoid glycoside isolated from Cistanche tubulosa, found to extend the life span of worms, increase their tolerance to heat shock and oxidative stress, and modulate the nuclear localization and transcriptional activities of daf-16 (101).

Tetrahydroxystilbene glucoside and emodin

2,3,5,4'-tetrahydoxystilbene-2-O-β-D-glucoside (TSG) is a major bioactive constituent of *Polygonum multiflorum* Thunb. Several studies have indicated that TSG exerts a marked neuroprotective effect against glutamate-induced hippocampal damage by decreasing ROS production and stabilizing mitochondrial membrane potential (MMP) (102). TSG enhanced hippocampal-dependent contextual fear memory and novel object recognition probably via promoting phosphorylation of ERK1/2, CaMKII, and CREB, upregulation of silent information regulator 1 (SIRT1), and downregulation of miR-134 (103). Emodin, an active component of *Polygonum multiflorum* Thunb, may exert a significant neuroprotective effect by activating the PI3K/Akt signaling pathway against glutamate-induced apoptosis and improving behavioral function in cerebral ischemia (104). However, attention should be paid to its toxicity, especially hepatic adverse reactions (105).

Others

Other preclinical studies on the anti-aging effects of the

monomers and components of CHM are shown in *Table 3*.

Extracts of CHM

Ganoderma lucidum (Ling Zhi)

Ganoderma lucidum is the dried fruiting body of *Ganoderma lucidum* (Leyss. ex Fr.) Karst. or *Ganoderma sinense* (95). *Ganoderma lucidum* extracts play a role in ameliorating DNA damage (106), which is a major causes of aging. Since oxidative stress also plays an important role in the aging process, researchers accessed its ability to protect bladder function from ischemia/reperfusion (I/R)-mediated oxidative damage, and found that *Ganoderma lucidum*, prior to I/R, can completely inhibit the negative effects of I/R (107).

Cistanches herba (Rou Cong Rong)

Cistanches is the dry-sliced fleshy stem of *Cistanche deserticola* Y.C. Ma or Cistanche tubulosa (Schenk) Wight. *Cistanche deserticola* can improve the age-related behavioral decline and pathological manifestations of cataract and retinopathy in rats (108). Cistanche tubulosa extends the lifespan and increases the flies' resistance to oxidative stress, and enhances memory formation in young flies (109).

Cynomorium songaricum (Suo Yang)

Cynomorium songaricum (CS) is a dry fleshy stem of *Cynomorium songaricum* Rupr (95). Research shows that it extends both the mean and maximum lifespan of adult female flies by improving antioxidant stress ability (110). The ethyl acetate fraction of CS attenuated staurosporine-induced SK-N-SH neuroblastoma cell death (111). The flavonoid extract of CS shows antioxidant and anti-fatigue effects on the swimming endurance of rats; free radical scavenging enzymes increase after treatment with the flavonoid extract (112).

Alpiniae oxyphyllae fructus (Yi Zhi)

Alpiniae oxyphyllae fructus is the dried and ripe fruit of Zingiberaceae plant *Alpinia oxyphylla* Miq. (95). Cardiac hypertrophy is a pathophysiological phenomenon associated with aging. Research has proven that Alpiniae oxyphyllae fructus (AOF) can improve aging-related cardiovascular diseases such as myocardial remodeling and cardiac hypertrophy. It inhibits apoptosis in the cardiac tissue of SD rats by regulating apoptosis-related genes and activating the longevity factor SIRT1 (113). Further research shows that AOF protects against cardiac hypertrophy in the D-galactose-induced senescent rat model via downregulation of both concentric and eccentric hypertrophy signaling pathways such as ERK1/2/JNK (114).

Others

Other preclinical studies on the anti-aging effect of CHM extracts are shown in *Table 4*.

CHM compounds

Researchers studied the anti-aging effect and mechanism of eight kinds of CHM compounds (Liu Wei Di Huang Wan, Qi Bao Mei Ran Dan, Shi Quan Da Bu Wan, Sheng Mai Yin, Er Chen Wan, Huan Shao Dan, Qin Jiao Wan, and Tian Ma Wan) on *Caenorhabditis elegans* and found that their mechanism was partially related to antioxidative and thermal stress effect (115). Researchers firstly focused on the expression of related proteins (STUB1, CaMKIIα, AMFR) in Alzheimer's disease (AD), and then studied the effect of CHM compounds on their expression (116-118).

Liu Wei Di Huang

Liu Wei Di Huang (LW) is a typical traditional Chinese medicine (TCM) prescription, consisting of six herbs. It has long been clinically used to treat many kinds of aging-related diseases. It was demonstrated to ameliorate the decline of learning and memory in senescence-accelerated mouse/prone 8 (SAMP8); improvement of the synaptic plasticity via inhibiting voltage-dependent calcium channels and promoting N-Methyl-d-aspartate receptor function may be one of the mechanisms (119). Senescence-accelerated mouse/prone 8 (SAMP8) is considered a robust experimental model for AD. LW-AFC was prepared from Liu Wei Di Huang decoction and included polysaccharides, glycosides, and oligosaccharides. Research shows it can ameliorate cognitive impairment by altering gene expressions and regulating pathways in the hippocampus (120). Aqueous LW extract shows potential benefits for PD treatment in both primary mesencephalic neuron cells and MPTP-treated C57BL/6 mice (121).

Dang Gui Shao Yao San

Dang Gui Shao Yao San (DSS) was originally described in Dong Han Dynasty, ancient China. JD-30 is a fraction extracted from DSS and is able to improve synaptic plasticity and ameliorate deterioration of cognition by blocking and disrupting Aβ aggregation (122). Simultaneously, the elevation of estradiol, NO, and glycine levels in blood plasma may contribute to the cognitive improvement effects of DSS (123). Systems pharmacology research indicated that DSS treats neurodegenerative diseases and other diseases, as determined through research on the same pathological proteins involved in these diseases (124). Additionally, DSS has been proven to promote angiogenesis and neurogenesis after ischemic stroke (125). In conclusion, DSS has great potential in the treatment of neurodegenerative diseases, especially AD, and needs further study.

Zuo Gui Yin

Zuo Gui Yin/Wan is one of the TCM prescriptions from a classical TCM book named "Jing Yue Quan Shu". Bone mineral density was enhanced markedly in ovariectomized mice and naturally aged mice after Zuo Gui Wan administration. This result shows that it has an anti-aging activity (126). In terms of neuroprotection, Zuo Gui Wan promoted the recovery of neurological function by abrogating inflammation via regulating NogoA, NgR, and RhoA levels, and other neurotrophic factors (127).

Bu Shen Yi Zhi formula

Bu Shen Yi Zhi (BSYZ) formula, a traditional CHM compound composed of Fructus Cnidii (She Chuang Zi), Panax ginseng (Ren Shen), Polygonum multiflorum (Shou Wu), Cortex moutan (Mu Dan Pi), Ligustrum lucidum (Nv Zhen Zi), and Fructus lycii (Gou Qi Zi), has been well-researched by Chinese research teams, especially its neuroprotection effect. Neuroinflammation is considered to be an important mediator in the pathogenesis and progression of PD. BSYZ is thought to alleviate 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced neuroinflammation by inhibiting the activation of NLRP3 inflammasome in microglia (128). Additionally, the acetate extract components of BSYZ provide neuroprotection against scopolamine (SCOP)-induced cognitive dysfunction by inhibiting oxidative stress and apoptosis (129). In a recent study, the team used a systems pharmacology approach to investigate the active ingredients of BSYZ and potential targets in AD, and on this basis established the APPswe/PSEN1dE9 transgenic mouse model to validate the proposed mechanisms for BSYZ. The results showed that the effects of BSYZ on cognitive dysfunction may be related to the regulation of amyloid-β metabolism and neuronal apoptosis (130).

Others

Other preclinical studies on the anti-aging effect of CHM compounds are shown in *Table 5*.

Concluding remarks

In summary, no theory can fully explain the complex process of aging as it is multifactorial. In recent years,

Table 5 The slowing aging effects of CHM compounds in animal and cell models

Compound	Model	Dose	Duration	Effects	Mechanism	References
Bu Shen Yi Zhi formula	SCOP-induced senescent mice	1.46, 2.92, and 5.84 g/kg/d	2 weeks	Improved cognitive ability; ameliorated oxidative stress and neuronal apoptosis	Bax, caspase-3, and MDA↓; Bcl-2, SOD, and GSH↑	(131)
Bu Shen Yi Zhi formula	SAMP8	1.46, 2.92, and 5.84 g/kg/d	4 weeks	Ameliorated cognitive dysfunction, neuronal apoptosis, and ER stress	AChE, Caspase-3, Bax/Bcl-2, Perk, BIP, PDI, and CHOP↓; ChAT, Ach, and SIRT1↑	(132)
Bu Shen Yi Zhi formula	SAMP8	1.46, 2.92, and 5.84 g/kg/d	30 days	Attenuated cognitive impairment and inflammation, oxidative stress, and neuronal apoptosis	PPAR-γ, Bcl-xl, SOD, and GSH-Px↑; GFAP, COX-2, NF-kB, IL-1β, and IL-6↓	(133)
Cerebralcare granule	D-gal-induced aging mice	7.5, 15, and 30 g/kg/d	8 weeks	Attenuated memory impairment and oxidative stress	CAT, SOD, and ACh↑; AChE, NO, MDA, GSH, GPx NF-kB, TNF-α, COX-2, and caspase-3↓	(134)
Dang Gui Shao Yao San	D-gal-induced aging mice	1.8, 3.6, and 7.2 g/kg	6 weeks	Ameliorated cognition deficits	SOD, GSH, and Bcl-2↑; NO, NOS, Bax, and caspase-3↓	(135)
Dang Gui Shao Yao San	SAMP8	0.7, 1.4, and 2.8 mg/mL	8 weeks	Improved spatial learning and memory	LTP and Nissl-positive cell densities↑; Aβ↓	(136)
Fu Zhi San	SAMP8	0.3, 0.6, and 1.2 g/kg/day	8 weeks	Ameliorated memory deficits	Aβ, BACE1, β-CTF, p-Tau, and p-25↓	(137)

Table 5 (*continued*)

Table 5 (*continued*)

Compound	Model	Dose	Duration	Effects	Mechanism	References
Geng Nian Chun	C. elegans	3.94 mg/mL	48 h	Enhanced oxidative stress, resistance, and lifespan	ROS↓; sod-3, mtl-1, hsp-12.6, and hsp-16.2↑	(138)
He Shou Wu Yin	Natural aging rat	4.8 g/100 g	30 and 60 days	Inhibited spermatogenic cell apoptosis	14-3-3σ, DR6, Bax, Caspase-3, and Cytc↓	(139)
Huang Lian Jie Du decoction	SAMP8	15g/kg/d	1 month	Ameliorated cognitive impairment	Regulation of gene expression patterns	(140)
Kun Tai capsule	Accelerated aging ovary model	0.4, 0.8, and 1.6 g/kg	4 weeks	Regulated the estrous cycles, increased hormone secretion and fertility, and decreased atretic follicles	AMH, SOD2, and Bcl-2↑; Bax↓	(141)
LWDH ethanol extract	C. elegans	0.1-2mg/mL	36 h	Alleviated β-amyloid-induced toxicity	ROS↓; heat shock protein↑	(142)
LWDH	SAMP8	1.6 g/kg/d	5 months	Improved cognitive impairment	Modulation of N-glycan patterns	(143)
LWDH	SAMP8	1.6 g/kg/d;	5.5 months	Improved cognitive impairments	Modulating intestinal microbiome	(144)
RRF	Natural aging rat	141, 282, and 564 mg/kg/d;	16 weeks	Ameliorated perimenopause	FSH↓; estradiol, hypothalamic dopamine, and norepinephrine↑	(145)
Shi Quan Da Bu Tang	C. elegans	100 ug/mL	48 h	Increased life span	Heat shock protein↑; Aβ-induced toxicity and H_2O_2↓	(146)
Tian Gui Geng Nian	Natural aging rat	0.72, 1.80, and 4.5 g/kg/d	180 days	Neuroprotection and anti-aging	ERβ, TH positive neuron, and VEGF↑; G-CSF↓	(147)
Tiao Geng Tang	Ovariectomized rats	3.87 g/d	8 weeks	Anti-aging and antioxidative	Estradiol, Erα, Erβ, SOD, and T-AOC↑; follicle-stimulating hormone and MDA↓	(148)
Yi Fu Ning	Natural aging rat	1 and 2 g/kg	6 weeks	Delayed ovarian aging	Ovarian and uterine index↑; SOD, CAT↑; MDA, 8-OHDG, p19, p53, p21, and Rb↓	(149)
Zuo Gui Yin	Natural aging rat	13.78, 20.67, and 31 g/kg/d	8 weeks	Promoted estradiol production	VEGF mRNA↓; SPARC mRNA↑	(150)
Zuo Gui Yin	Natural aging rat	13.78, 20.67, and 31.00 g/kg/d	8 weeks	Promoted estradiol production	FSHR, LRH-1, and ERα↑	(151)

LWDH, Liu Wei Di Huang; RRF, a TCM Recipe Composed of Radix Astragali, Radix Angelicae Sinensis, and Folium Epimedii.

research on the anti-agining effect of CHM has developed rapidly, but no CHM has been proven to have a clinically effective anti-aging effect. In this review, CHM has been shown to have several anti-aging biological activities *in vivo* and *in vitro*, beneficial neuroprotective effects in neurodegenerative diseases like AD, PD, and skin photoaging, and cardiovascular disease protective effects. Research has mainly focused on the components, extracts, and compounds of CHM, whose mechanisms include clinical symptom improvement, anti-oxidation, free radical scavanging, neuroendocrine level regulation, vascular endothelial function improvement, immunity and apoptosis regulation, DNA damage prevention, etc.. Among these, anti-oxidation and free radical scavenging are the most

common. However, compared with a large number of preclinical studies, there are relatively few related clinical studies and a lack of long-term follow-up studies for endpoint events. Therefore, more convincing clinical trials are needed to confirm the efficacy of CHM, and elucidate the detailed pharmacokinetics, toxicity, standardization, and therapeutic dosage in humans. In conclusion, as a multitarget anti-aging drug, future research should pay more attention to CHM.

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Footnote

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