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REVIEW ARTICLE

Anti-ageing active ingredients from herbs and nutraceuticals used in traditional Chinese medicine: pharmacological mechanisms and implications for drug discovery

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Ageing, an unanswered question in the medical field, is a multifactorial process that results in a progressive functional decline in cells, tissues and organisms. Although it is impossible to prevent ageing, slowing down the rate of ageing is entirely possible to achieve. Traditional Chinese medicine (TCM) is characterized by the nourishing of life and its role in anti-ageing is getting more and more attention. This article summarizes the work done on the natural products from TCM that are reported to have anti-ageing effects, in the past two decades. The effective anti-ageing ingredients identified can be generally divided into flavonoids, saponins, polysaccharides, alkaloids and others. Astragaloside, *Cistanche tubulosa* acteoside, icariin, tetrahydrocurcumin, quercetin, butein, berberine, catechin, curcumin, epigallocatechin gallate, gastrodin, 6-Gingerol, glaucarubinone, ginsenoside Rg1, luteolin, icarisid II, naringenin, resveratrol, theaflavin, carnosic acid, catalpol, chrysophanol, cycloastragenol, emodin, galangin, echinacoside, ferulic acid, huperzine, honokiol, isoliensinine, phycocyanin, proanthocyanidins, rosmarinic acid, oxymatrine, piceid, puerarin and salvianolic acid B are specified in this review. Simultaneously, chemical structures of the monomers with anti-ageing activities are listed, and their source, model, efficacy and mechanism are also described. The TCMs with anti-ageing function are classified according to their action pathways, including the telomere and telomerase, the sirtuins, the mammalian target of rapamycin, AMP-activated kinase and insulin/insulin-like growth factor-1 signalling pathway, free radicals scavenging and the resistance to DNA damage. Finally, Chinese compound prescription and extracts related to anti-ageing are introduced, which provides the basis and the direction for the further development of novel and potential drugs.

LINKED ARTICLES

This article is part of a themed section on Principles of Pharmacological Research of Nutraceuticals. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.11/issuetoc

Abbreviations

AMPK, AMP-activated kinase; AST, astragaloside; CAG, cycloastragenol; CCP, Chinese compound prescription; CR, caloric restriction; GSH-Px, GSH peroxidase; INS/IGF-1, insulin/insulin-like growth factor-1; JKSQ, Jinkui Shenqi; LWDH, Liuwei Dihuang; MDA, methane dicarboxylic aldehyde; mTOR, mammalian target of rapamycin; NRF2, nuclear factor erythroid 2-related factor 2; *P. ginseng*, *Panax ginseng*; *R. puerariae*, *Radix puerariae*; Sal B, salvia acid B; SIRTs, sirtuins; SIRT1, sirtuin1; SIRT6, sirtuin6; sMaf, small muscle aponeurotic fibrosarcoma; S6 K, ribosomal protein S6 kinase; TCM, traditional Chinese medicine; TFE, total flavones from *Epimedium brevicornu*; TOR, target of rapamycin; VSMC, vascular smooth muscle cells

DOI:10.1111/bph.13631

Tables of Links

TARGETS	
Enzymes[a]	**Transporters**[b]
AMPK	GLUT4
Mammalian target of rapamycin	
S6K	
Sirtuin 1	
Sirtuin 2	
Sirtuin 6	

LIGANDS	
AMP	Insulin-like growth factor 1
Angiotensin II	Luteolin
ATP	Quercetin
D-galactose	Rapamycin
Epigallocatechin gallate	Resveratrol
6-Gingerol	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.* 2016) and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b]Alexander *et al.*, 2015a,b).

Introduction

Ageing is the major risk factor for several life-threatening diseases. Ageing, a complex molecular process driven by diverse molecular pathways and biochemical events that are influenced by interplay of multiple genetic and environmental factors, could lead to progressive and deleterious changes in the whole organism (Ideker *et al*. 2001; Argyropoulou *et al*. 2013; Wong *et al*. 2003). A myriad of theories including mitochondrial mutation, oxidative damage, carbonyl toxification and free radical theory, which is currently the most widely accepted one, have been used to explain the mechanisms underlying the phenomenon of senescence (Yin and Chen 2005).

Excessive amounts of free radicals can attack cell membrane, nucleic acids, proteins, enzymes and other biological macromolecules through peroxidation, causing lipid peroxidation of unsaturated fatty acids on the cell membrane, cross linking of nucleic acid and protein molecules, abnormality of DNA mutation or replication, together with decline of enzyme activity, which consequently leads to serious damage on cell function and eventually results in senility and even death (Huang 2007). There are a number of papers and reviews supporting or questioning this theory (Alexeyev 2009; Lapointe and Hekimi 2010; Ristow and Schmeisser 2011). Moreover, a variety of molecular pathways have been identified as the main molecular causes of ageing, such as cellular senescence, mitochondrial dysfunction and telomere attrition, which is considered one of the best known molecular mechanisms of ageing both in humans and mice (Harley *et al*. 1990; Flores *et al*. 2008; Lopez-Otin *et al*. 2013). Telomere attrition could lead to age-related pathologies by resulting in the exhaustion of tissue- and self-renewal capacity of the stem cell compartments (Flores *et al*. 2005; Sharpless and Depinho 2007).

Mitochondrial DNA damage theory is also a research hotspot in recent years. Mitochondrial DNA is exposed to external environments thereby lacking protection from histones and DNA binding proteins and it is also vulnerable to oxygen free radical damage. What is worse, it is not easy to repair because of the lack of repair systems, after the injury (D'Aquila *et al*. 2012). Furthermore, the study found that the senescence of organisms is closely related to the regulation of genes including geronto genes, longevity genes and apoptosis genes. In support, Tom Johnson succeeded in positioning the first 'longevity gene', age-1 (Friedman and Johnson 1988). Micro RNAs (miRNAs), post-transcriptional regulators of gene expression, could lead to inhibition of protein translation by binding inexactly to the 3′-untranslated regions of target mRNAs (Pan *et al*. 2015). In fact, ageing involves not only a myriad of genes and proteins but also changes in endogenous metabolites (Ryazanov and Nefsky 2002; Warner 2005; Panza *et al*. 2007; Yan *et al*. 2009). Metabolomics, the best analysis to fit the holistic concept of traditional Chinese medicine (TCM), has been widely used recently for the discovery of novel biological active compounds and targets, and a series of age-related metabolites were proposed according to exploratory works on aged rats, dogs and humans (Williams *et al*. 2005; Williams *et al*. 2006; Berger *et al*. 2007; Schnackenberg *et al*. 2007; Wang *et al*. 2007; Lawton *et al*. 2008; Cao *et al*. 2015;) including metabolic syndromes, cardiovascular disease, neurodegeneration and diabetes (Li *et al*. 2013a). Therefore, tackling ageing and its vicious spiral would be an effective approach to combat age-related diseases. In fact, research on age-related diseases has become a hot topic recently in the field (Martin 2011).

Reportedly, the most effective intervention in extending longevity in model organisms is caloric restriction (CR), which can not only increases longevity but also reduces risk for most (if not all) age-related diseases. However, CR requires a permanent diet, which makes it difficult for many people to accept, thus limiting its popularity. Although Western medicine with anti-ageing effects has made some progress, side effects, specific targets and multiple drug resistance are worrying. For example, researchers in America found that rapamycin can prolong the lifespan of mice by about 14%; however, its immunosuppressive effect could lead to the invasion of infectious diseases. To the contrary, TCM can exert anti-ageing functions with unique dialectical treatment systems, multi-target mechanisms and few adverse reactions.

For example, it was shown that the extracts obtained from *Rhodiola rosea* could increase longevity of worms and flies without negative effects on reproduction or metabolic rate (Jafari *et al*. 2008; Wiegant *et al*. 2009). Moreover, integration of TCM, as well as Chinese materia medica, into the national healthcare delivery system has become an essential national policy in China, indicating that considerable emphasis has been given to the TCM research and development (Dang *et al*. 2016; Gao *et al*. 2015). Additionally, the popular use of metabolomics in ageing indicated the possibility for reconciliation and integration of Chinese and Western medicine.

Mechanism of anti-ageing by TCM

Although a number of theories on ageing mechanism have been put forward (Linda and David 2002), people know little about ageing compared with that of other areas in biology. Consequently, it is important as well as urgent to explore the mechanism of ageing and strategies of anti-ageing. TCM represents an extraordinary inventory of high diversity structural scaffolds that can offer promising candidate chemical entities in the major healthcare challenge of increasing health span and/or delaying ageing. Referring to the relevant literatures published in the past two decades, the mechanisms of anti-ageing/age-related diseases of active ingredients from TCM are summarized below.

Regulation of telomeres and telomerase

Telomeres, composed of tandem repeats of the TTAGGG bound to an array of proteins, are specialized nucleotide sequences at the ends of chromosomes (Blackburn 2001; Chan and Blackburn 2004; Finkel *et al*. 2007). Telomere length is demonstrated to be related to the replicative lifespan of normal somatic cells. Indeed, the replication of normal somatic cells is limited by telomere shortening, which proceeds incrementally with each round of cell division, resulting in the loss of 50–200 terminal base pairs of the telomere in humans both *in vitro* and *in vivo*; thus, the telomeres become shorter (Watson 1972; Olovnikov 1973; Allsopp *et al*. 1992; Allsopp and Harley 1995). Telomere length mainly depends on telomerase, a ribonucleoprotein enzyme that can elongate telomeric repeats in the 5′-to-3′ direction, thus mitigating the end-replication problem (Blackburn 1991; Chan and Blackburn 2004).

Recently, a growing number of results have demonstrated that some active ingredients and prescriptions of TCM could play distinct roles in anti-ageing via improving telomerase activity or suppressing telomere shortening (Table 1). For example, astragaloside (AST) cycloastragenol (CAG) (Figure 1) could exert anti-ageing effects in human embryonic lung fibroblasts by affecting activity of telomerase and expression of the klotho gene (Guo *et al*. 2010), a novel gene closely related to human ageing. AST, a macromolecular saponins, has poor bioavailability when taken orally. Specifically, Liu *et al*. studied the physicochemical property of AST and CAG and their metabolism *in vivo* and *in vitro*. The experimental data showed that AST was easily transformed by the intestinal flora into metabolites with strong pharmacological activity, especially CAG which was the potent component of AST, exerting most of its efficacy (Liu 2013). Moreover, telomerase activity in testicular tissues of mice, which were gavaged with *Cynomorium songaricum* (*C. songaricum*) polysaccharide at 40 or 80 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$, was clearly higher than that of mice treated with D-galactose, indicating that *C. songaricum* polysaccharide could exert anti-ageing effect by improving telomerase activity (Ma *et al*. 2009). In addition, flavonoids of *Epimedium brevicornu* (*E. brevicornu)* could significantly extend the population doublings of human diploid fibroblast cells from 53 to 64 generations, decrease the expression of p16 mRNA, increase the content of phosphorated Rb protein and protect the telomere length without activating telomerase (Hu *et al*. 2004). Meanwhile, metabonomic studies using liquid chromatography coupled with MS-investigated the anti-ageing effects of total flavones from *E. brevicornu* (TFE) on 4, 10, 18 and 24-month-old rats. Clearly, the TFE-treated group had smoother fur, more locomotor activities and better appetite compared with the untreated 24-month-old rats. The results indicated that the anti-ageing effects exerted by TFE might be related to the intervention on lipid metabolism and its anti-oxidation activity, as most of the age-related metabolites, such as saturated fatty acids, unsaturated fatty acids, ergothioneine, carnosine and deoxycholic acid, were reset to a younger level (Yan *et al*. 2009).

Great attention has been paid to telomere and telomerase by the medical community in recent years. With the rapid development of molecular biology, more and more drugs with anti-ageing features through controlling telomere length and telomerase activity will continue to be found and fully explored..

Regulation of sirtuins

Sirtuins (SIRTs), a group of NAD^+-dependent deacetylases belonging to a class of highly conserved proteins, are widely distributed across the range of organisms from bacteria to humans and play distinct roles in regulating some cellular functions, such as gene repair, cell cycle, metabolism and oxidative stress, via deacetylation of histones and non-histones (Oberdoerffer and Sinclair 2007; Westphal *et al*. 2007). Notably, overexpression of SIRTs could extend lifespan in yeast, *Drosophila and Caenorhabditis elegans* (*C. elegans*) (Rogina and Helfand 2004; Viswanathan *et al*. 2005). Sirtuin1 (SIRT1) has been investigated most thoroughly and deeply among the SIRTs in mammals (Pillarisetti 2008). The possible mechanism involves two aspects. On one hand, SIRTs could increase stress resistance by activating negative regulation of pro-apoptotic factors such as p53 and forkhead box-O (FOXO) (Luo *et al*. 2001; Brunet *et al*. 2004). In fact, SIRT1 induced the deacetylation of p53 and subsequently reduced its binding capacity with cis-DNA components, thereby preventing it from inducing DNA damage and apoptosis and suppressing cell proliferation. Meanwhile, SIRT1 could deacetylate FOXO1 and enhance nuclear ectopic transcriptional activity, thus increasing the expression of antioxidant enzymes such as SOD (Marfe *et al*. 2011). On the

Table 1

Mechanisms of anti-ageing/age-related diseases via regulation of telomere and telomerase by TCM

Active ingredients/ source	Experimental model	Efficacy	Mechanism	Reference
Polysaccharide				
Cistanche deserticola Ma	D-galactose-induced subacute ageing model mice	Significantly decreases MDA content in heart and brain, enhances telomerase activity, lymphocyte proliferation, phagocytosis of peritoneal macrophages and peripheral blood IL-2 content	Antagonizes free radical injury and enhances telomerase activity and the immunity of ageing mice	(Zhang *et al.*, 2011a)
Cynomorium songaricum Rupr.	D-galactose-induced ageing of mice	Exerts the anti- ageing effect on the ageing mice	Significantly increases the activity of telomerase in testicle	(Ma *et al.*, 2009)
Angelica sinensis Oliv. Diels	D-galactose and sodium nitrite-induced subacute senile dementia mice	Improves the ability of learning and memory, delays ageing	Might by increasing SOD and telomerase activity	(Li *et al.*, 2013)
	X-ray irradiation-induced ageing of murine haematopoietic stem cell	Significantly inhibits the cell ratio of in HSC G1 stage and the increase in the number of SA-β-Gal positive cells, down-regulates the expression of p53 protein and increases the length of telomere and the vitality of telomerase in HSCs	May be related to the increase in the length of telomere and the activity of telomerase, as well as the down-regulation of the expression of p53 protein	(Zhang *et al.*, 2013a)
Astragalus membranaeus Fisch. Bge.	Senile human embryonic lung diploid fibroblasts	Improves cell viability of HDF cells, reduces expression of SA-β-gal and shortening velocity of TRF	Modulates telomerase activity, regulates or changes telomere binding protein	(Zhu *et al.*, 2012)
Flavonoid				
Euphorbia humifusa Willd.	D-galactose-induced ageing mice	Improves telomerase content and SOD activity in testes and brain tissues of aged mice, decreases MDA content	Antioxidant and regulation of telomerase activity	(Cao *et al.*, 2011)
Epimedium brevicornu Maxim.	Senescent human diploid fibroblasts (2BS)	Significantly extends the population doublings of 2BS cells, decreases the expression of p16 mRNA, increases the content of phosphorylated Rb protein and improves the telomere length of 2BS cells rather than activates telomerase activity	Protects telomere length probably through inhibiting the p16 gene expression, promoting the production of phosphorylated Rb protein but not activating the telomerase	(Hu *et al.*, 2004)
Acteoside				
Cistanche tubulosa Schenk Wight	D-galactose-induced ageing mice	Decreases MDA content, obviously enhances telomerase activity in heart and brain, lymphocyte proliferation, phagocytosis of peritoneal macrophages and peripheral blood IL-2 content	Antagonizes free radical injury and enhances telomerase activity and the immunity of ageing mice	(Zhang *et al.*, 2008b)
C21 steroidal glycoside				
Cynanchum bungei Decne.	D-galactose-induced ageing mice	Prompts the ability of anti-oxidation, anti-fatigue and anti-stress	Increases SOD activity and telomerase activity, decreases MDA level	(Zhang *et al.*, 2007)

(Continues)

Table 1 (Continued)

Active ingredients/ source	Experimental model	Efficacy	Mechanism	Reference
Astragaloside				
Astragalus membranaeus Fisch. Bge.	Aged human embryonic lung fibroblast	Reduces β- galactosidase activity, increases cell viability, telomerase activity and klotho mRNA expression	Regulates telomerase activity and klotho gene expression	(Guo *et al.*, 2010)
Ginsenoside Rg1				
Panax ginseng C. A. Meyer	Tert-butylhydroperoxide-induced Sca-1+ haemopoietic stem cell ageing in mice	Reduces the percentage of positive cells expressed SA-β-Gal and the number of cells entered G1 phase, increases the number of colony of mixed haematopoietic progenitor, markedly decreases telomere shortening, reinforces telomerase activity	Activates telomerase activity, reduces the shortening of telomere length	(Zhou *et al.*, 2011)
	Tert-butylhydroperoxide (t-BHP)-induced senescence in WI-38 cells	Attenuates t-BHP-induced cell senescence, markedly reduces the RTF shortening, promotes telomerase expression	Probably by activating telomerase activity and preventing terminal restriction fragment shortening	(Zhao *et al.*, 2005)
Alkaloid				
Uncaria rhynchophylla Miq. Miq. ex Havil.	D-galactose-induced ageing model of rats aortic endothelial cells	Improves cell morphology and inhibits cell ageing	Reduces expression of β-galactosidase and relative expression quantity of telomerase	(Jiang *et al.*, 2011)
Allicin				
Allium sativum Linn.	t-BHP-induced senescence in fibroblast cells	Significantly attenuates t-BHP-induced sencscence, markedly decreases RTF shortening and results in telomerase activation	Activates telomerase activity and prolongs terminal restriction fragment length	(Ke *et al.*, 2006)
Pine pollen				
Pinus massoniana Lamb.	Human embryonic lung fibroblasts of ageing	Increases cell population doubling level and enhances telomerase activity	By activating telomerase activity	(Zhao and Yu, 2004)

other hand, SIRTs might regulate body's energy metabolism to suppress fat accumulation and increase insulin secretion from islet beta cells via stimulating metabolism-related genes such as PPARγ coactivator-1α (Schilling *et al*. 2006), thus leading to an increase in stress resistance and extension in lifespan.

Various studies have demonstrated that TCM can exert anti-ageing effects through the regulation of SIRTs (Table 2). One such example is resveratrol, which is a polyphenol particularly found in red wine, red grapes and tea and is the most potent regulatory factor of SIRT1 (Howitz *et al*. 2003; Li *et al*. 2016). Resveratrol can mimic the anti-ageing effect of CR, thus being able to regulate the average lifespan of the organism (Baur *et al*. 2006; Mouchiroud *et al*. 2010). Accumulating data published have confirmed that resveratrol can prolong the lifespan of yeast, nematodes, fruit flies and fishes (Bass *et al*. 2007; Mouchiroud *et al*. 2010; Wood *et al*. 2004a). Moreover, icariin (Figure 2), a principal active ingredient of *Epimedium* in berberidaceae is another active compound that exerts anti-ageing effects (Lee *et al*. 1995). Icariin could improve the expression of SIRT6 and reduce the expression of NF-κB protein and the inflammatory response of old mice, indicating that the anti-ageing mechanism of icariin was likely to be closely related to NF-κB signalling pathway and SIRT6 histone deacetylase (Chen *et al*. 2012). It is likely that SIRT6 was up-regulated after treatment with icariin, specifically combined with the RELA subunit of NF-κB dimer, then attached to the downstream gene promoter of NF-κB, leading to H3K9 histone deacetylation. As a result, the chromosome configuration was changed and coiled tightly, thereby silencing the downstream target genes of NF-κB. Therefore, target gene transcription was reduced, and the cell senescence was diminished (Chen *et al*. 2012; Li *et al*. 2015). Additionally, Li *et al*. found that *Cornus officinalis* (*C. officinalis*) polysaccharide could slow the progression of age-related cataracts by significantly increasing the activity of SOD, the expression of

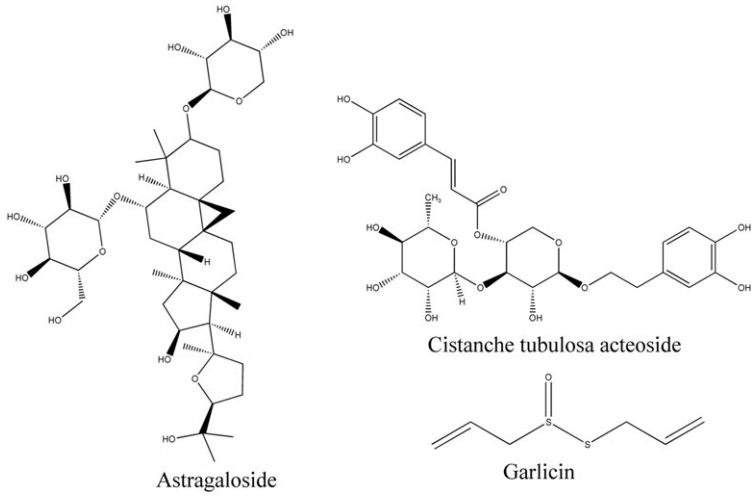

Figure 1

Structural formula of *Cistanche tubulosa* acteoside, garlicin and astragaloside with anti-ageing/age-related diseases effects from traditional Chinese medicine by regulating telomeres and telomerase.

SIRT1 mRNA and FOXO1 mRNA and reducing the expression of p53 mRNA, indicating that *C. officinalis* polysaccharides probably regulated the expression of downstream genes p53 and FOXO1 through regulating SIRT1, eventually inhibiting or delaying apoptosis of epithelial cells in the lens (Li *et al*. 2014).

Overall, many active ingredients of TCM can slow down ageing via the activation of SIRTs. So far, much attention has been paid to SIRT1, which is of great importance to anti-ageing. With the in-depth study on SIRT1 and molecular mechanisms of ageing, gene therapies targeted at SIRT1 will surely play a distinct role in extending human lifespan (Ling and Hu 2013).

Regulation of nutrient and energy sensing pathways

The lifespan of many species is controlled by the nutrient and energy sensing signal transduction pathways, including the target of rapamycin (TOR)/ribosomal protein S6 kinase (S6 K), the AMP-activated kinase (AMPK) and the insulin/insulin-like growth factor-1 (INS/IGF-1) signalling pathways (Kenyon 2010; Alic and Partridge 2011).

Regulation of mTOR

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that is evolutionarily highly conserved and can mediate the stress response. mTOR signalling, is emerging as a critical regulator of ageing (Rajapakse *et al*. 2011) and partial inhibition of its downstream targets, such as S6 K or protein synthesis, extends lifespan in yeast, worms, flies and mice (Kapahi *et al*. 2004; Kaeberlein *et al*. 2005; Hansen *et al*. 2007; Syntichaki *et al*. 2007).

It is clearly possible to cure age-related diseases by rapamycin but the side effects (e.g. suppressing the immune system) are inevitable (Wu *et al*. 2015). Fortunately, TCM can function as rapamycin analogues, which are much safer, more effective with fewer side effects. Ginsenoside Rb1, a protopanaxdiol extracted from the roots of *Panax ginseng* (*P. ginseng*), which has been long used as a 'precious tonic' to support vitality and maintain homeostasis in China, was found to have preferable anti-ageing activities (Helliwell *et al*. 2015). Specifically, the natural senile mouse models of 20 months old were prepared and injected with ginsenoside Rb1 (Figure 3) at first. During the experimental period, there was a remarkable reduction of MAO activity in Rb1 group, a decline of PAI-1 protein expression in high-dose Rb1 group and a decrease of mTOR protein phosphorylation levels in low-dose Rb1 group as well as in high-dose group, implying that the anti-ageing effects of ginsenoside Rb1 on mice may be partially or completely related to the mTOR/p70s6k pathway (Peng *et al*., 2014) Similarly, 6-gingerol (Figure 3) extracted from ginger could markedly decrease senescence in vascular smooth muscle cells (VSMCs) induced by angiotensin II, with cell cycle arrestin the G0/G1 phase and decreased protein leveld of mTOR and phosphorylated p70-S6 K, suggesting that 6-gingerol may attenuate VSMCs senescence through inhibition of the mTOR/P70-S6 K pathway (Zhou *et al*. 2014).

Regulation of AMPK

AMPK has been defined as the 'cellular energy regulator', as it can sense the change in the AMP/ATP ratio and keep the balance between cellular carbon use efficiency and ATP yields (Geng *et al*. 2014; Zhang *et al*. 2014a). AMPK activity declines in ageing skeletal muscle of mammals, while overexpression of AMPK directly activates DAF-16/FOXO by phosphorylation (Greer *et al*. 2007) and extends *C. elegans* lifespan even when CR starts in middle age animals (Apfeld *et al*. 2004).

In recent years, studies have found that TCM can fight against ageing and prevent age-related diseases by modulating the activity of AMPK. For example, the total saponins of *Panax notoginseng* inhibited H9c2 apoptosis induced by serum, glucose and oxygen deprivation and prevented reduction of mitochondrial membrane potential, as well as

Table 2

Molecular mechanisms of anti-ageing/age-related diseases via regulation of SIRTs by TCM

Active ingredients	Source	Experimental model	Efficacy	Mechanism	References
Polysacchharides	*Cornus officinalis* Sieb. et Zucc.	Eye lens of D-galactose-induced ageing rats	Inhibits or delays apoptosis of epithelial cells in eye lens and slows the progression of age-related cataract	May regulate the expression of downstream genes p53 and FOXO1 probably through regulation of SIRT1	(Li *et al.*, 2014)
Extracts	*Ginkgo biloba* Linn.	Natural ageing rats	Decreases the number of 8-OHDG-positive cells, delays relative telomere shortening, increases expression of SIRT1, declines expression of p21 without an obvious change of p53 in number	May be associated with the expression of SIRT1 and p21 protein	(Hao *et al.*, 2013)
Icariin	*Epimedium brevicornu* Maxim.	Aged mice	Improves the expression of SIRT6 and reduces that of NF-κB protein, as well as the inflammatory response of old mice	Closely related to NF-κB signalling pathway and SIRT6 histone deacetylase	(Chen *et al.*, 2012)
Butein	*Butea monosperma* Lam. Kuntze	Yeast *Saccharomyces . cerevisiae (S. cerevisiae)*	Increases lifespan by 31% at a concentration of 10 μM	Activates SIRT1	(Howitz *et al.*, 2003)
Resveratrol	*Polygonum cuspidatum*	Natural senescence of HUVECs	Reverses the senescence of HUVECs	Possibly increases the expression of SIRT1 thus decreasing the apoptosis levels of HUVECs	(Jiang *et al.*, 2016)
		Wild-type adult worms	Increases lifespan	Dependent upon SIRT2.1 but not DAF-16/FOXO activity	(Viswanathan *et al.*, 2005)
		Flies	Increases longevity by −20% at 200 μM	Dependent on SIRT2	(Bauer *et al.*, 2004; Wood *et al.*, 2004b)
		Budding yeast *S. cerevisiae*	Increases cell survival and extends lifespan by −70% at a concentration of 10 μM	Stimulates SIRT2 activity, increases DNA stability	(Howitz *et al.*, 2003)
		Caenorhabditis elegans	Extends lifespan	Through SIRT1-dependent autophagy	(Morselli *et al.*, 2010)
		Drosophila and *C. elegans*	Extends lifespan	Through up-regulation of SIRT2 and AMPK	(Bass *et al.*, 2007)
		Anoxic cardiocytes	Protects the cardiomyocytes from hypoxia-induced apoptosis and promotes cell cycle arrest	Increases the level of SIRT1, which plays a role by the regulation of Foxo1 and its downstream genes such as Bin and p27	(Wang *et al.*, 2009b)

(Continues)

Table 2 (Continued)

Active ingredients	Source	Experimental model	Efficacy	Mechanism	References
Silymarin	*Silybum marianum* Linn. Gaertn.	Isoproterenol-induced injury in cultured rat neonatal cardiac myocytes	Protects isoproterenol-treated rat cardiac myocytes from death, decreases production MDA, release of LDH and pro-apoptotic cytochrome c from mitochondria, increases superoxide dismutase activity and mitochondrial membrane potential	Through resuming mitochondrial function and regulating the expression of SIRT1 and Bcl-2 family members	(Zhou *et al.*, 2006)
Quercetin	*Herba hyperici*	Male ICR mice 8 weeks of age	Increases mRNA expression of PPARγ coactivator-1α (PGC-1α) and SIRT1, mtDNA and cytochrome c concentration, maximal endurance capacity and voluntary wheel-running activity	Increases mitochondrial biogenesis through up-regulation of PGC-1α, SIRT1 and mtDNA	(Davis *et al.*, 2009)
Tetrahydrocurcumin	*Curcuma aromatica* Salisb.	Drosophila flies	Increases healthspan but not maximum lifespan, suppresses oxidative stress	Regulates sirtuins and FOXO-responsive pathways	(Argyropoulou *et al.*, 2013)

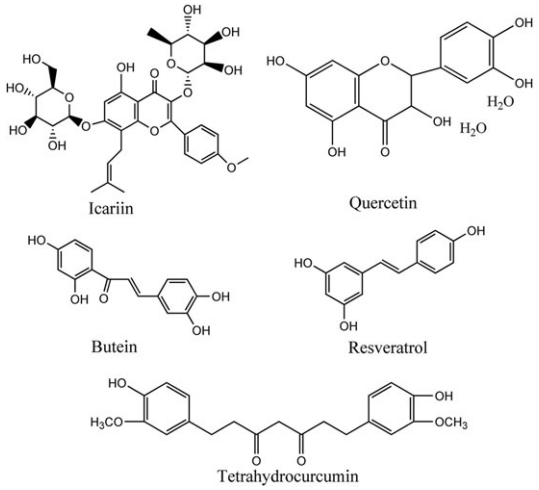

Figure 2
Structural formula of active ingredients with anti-ageing/age-related diseases effects from traditional Chinese medicine by regulating sirtuins.

reducing the positive rate of TdT-mediated dUTP nick end labelling cells in myocardial tissue and increased levels of p-AMPK protein, in a dose-dependent manner, indicating that its anti-ageing function may be related to AMPK activation (Yang *et al*. 2012). Reportedly, curcumin (Figure 3) activates signalling pathways downstream of the anti-ageing modulators AMPK and the transcription factor Nrf2 and suppresses inflammatory processes mediated by NF-kB signalling (Salminen *et al*. 2012; Surh *et al*. 2008). Because of these promising findings, curcumin was tested in humans as a possible treatment for Alzheimer's disease (Baum *et al*. 2008; Ringman *et al*. 2005).

Regulation of INS/IGF-1

INS/IGF-1 can affect the lifespan of a variety of organisms including yeast, worms, flies, mammals and humans, characterized by the weakening of insulin signalling, the enhancement of insulin sensitivity and the reduction of the plasma levels of insulin-like growth factor-1 (Bonafe *et al*.. 2003; Longo and Finch 2003; Cheng *et al*. 2004; Richardson *et al*. 2004). Roth *et al*. have reported that people with low insulin levels usually have a longer survival (Roth *et al*. 2002).

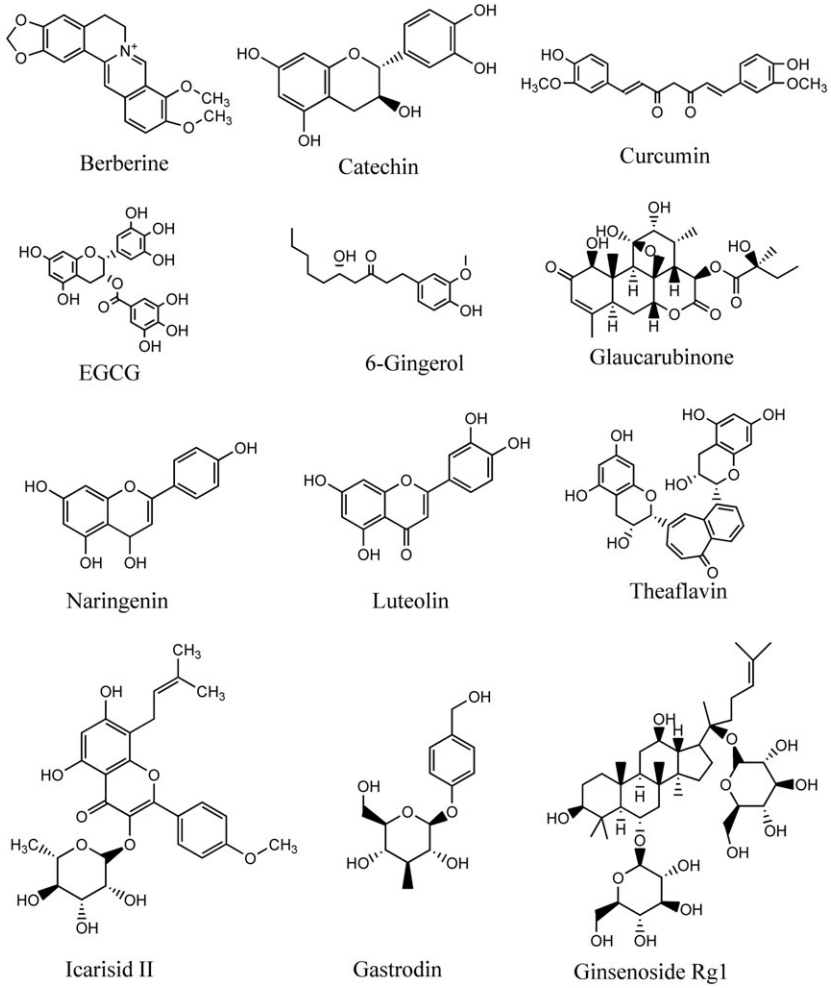

Figure 3
Structural formula of active ingredients with anti-ageing/age-related diseases effects from traditional Chinese medicine by regulating nutrient and energy sensing pathways.

The INS/IGF-1 signalling pathway can be used as a new target for developing drugs to prevent and treat age-related diseases, thus delaying ageing and prolonging life. As a result, much attention has been paid to the correlation between INS/IGF1-signalling pathway and senescence (Cheng *et al*. 2004). Cai *et al*. found that icariside II could increase thermo- and oxidative stress tolerance, decrease the rate of locomotion decline in late adulthood and extend lifespan by 20% in worms, and it was postulated that the lifespan extension caused by icariside II was dependent on the INS/IGF-1 and DAF-2/FOXO (and likely HSF1) signalling pathways (Cai *et al*. 2011). There is much work on TCM regulating nutrient and energy sensing pathways to delay ageing and prevent age-related diseases and some specific examples are shown in Table 3.

From the data shown above, we draw the conclusion that nutrient sensing signalling pathway could control lifespan in many species, and this possibility has received much support from a large number of experiments. What is more, INS/IGF, TOR and AMPK signalling pathways can systematically coordinate to modulate each other, thereby controlling cellular/organism homeostasis and function in response to adverse environmental conditions.

Free radicals scavenging

Generated from the mitochondria electron transport chain, ROS are closely related to ageing (Lee and Wei 2001). Although ROS are much needed (at low concentration) for the body to perform normal physiological functions, including transferring energy to maintain the vitality, killing cells, eliminating inflammation and decomposing poisons; abnormally high levels of ROS will lead to ageing and even death, as they can trigger free radical chain reactions because of its unpaired electrons and high reactive activities (Chen 2004; Jia *et al*. 2007).

TCM exerts free radical scavenging mainly through three ways. Firstly, TCM can achieve the purpose by enhancing function of the antioxidant system in the body through increasing the activity and content of various antioxidant enzymes such as SOD and GSH peroxidase (GSH-Px). The stress-induced synthesis of some of these enzymes is mainly triggered by Nrf2, which plays a central role in the protection of cells against oxidative and xenobiotic damage (Kensler and Wakabayashi 2010; Sykiotis and Bohmann 2010). Briefly, Nrf2 could activate transcription in response to oxidative stress mainly by translocating into the nucleus and recruiting the small muscle aponeurotic fibrosarcoma (sMaf) protein when stimulated (Espinosa *et al*. 2014). Then, the Nrf2-sMaf heterodimer binds to the antioxidant response element, which is a cis-acting DNA regulatory element that activates the promoter region of many genes encoding phase II detoxification enzymes and antioxidants, thereby contributing to the maintenance of cellular redox homeostasis (Lee *et al*. 2015). Reportedly, honokiol (Figure 4) could achieve desirable anti-ageing effects by decreasing the content of methane dicarboxylic aldehyde (MDA) and increasing the activity of antioxidant enzymes, such as SOD and GSH-Px in serums and tissues of mice injected with D-galactose for six consecutive weeks to simulate natural-aged mice (Hao *et al*. 2009). Secondly, TCM can scavenge free radicals directly. For example, *C. songaricum* extracts (20 mg·mL^{-1}) enhanced cognitive behaviour, increased resistance to stress and extended female mean lifespan of flies, indicating that *C. songaricum* flavonoids acted as free radical scavengers (Yu *et al*. 2010; Liu *et al*. 2012). Thirdly, TCM can inhibit lipid peroxidation. Lipid peroxidation is a common way of damaging tissues by oxygen free radicals through following ways: oxygen free radicals + cell membrane lipid → lipid peroxidation reaction → lipid peroxidation → MDA + cell components → lipofuscin (Xu *et al*. 2006). In support, oxymatrine extracted from *Sophora flavescens* could improve the learning and memory ability of ageing mice induced by intraperitoneal injection of D (+)-galactose, and the anti-ageing effect was possibly related to its resistance to oxygen free radicals, as well as lipid peroxidation. Furthermore, a recent study demonstrated that oxymatrine could be *in vivo* converted to matrine that might be a novel drug used for curing type 2 diabetes and hepatic steatosis (Wang *et al*. 2005; Zeng *et al*. 2015). The majority of published studies are listed in Table 4.

To sum up, a number of experiments have proved that ageing is closely related to free radicals, the theory of which has been widely accepted and becoming an active area. As stated above, TCM can exert anti-ageing activities by free radicals scavenging, anti-lipid peroxidation and up-regulation of the antioxidative defence system.

Anti-damage of DNA

DNA damage, the primary programme of ageing in the body, can be roughly divided into four types: base damage, glycosyl damage, bond rupture and DNA chain cross linking. Many studies have shown that DNA damage and self-repair ability are closely related to ageing. Damage of DNA is the main reason leading to mutations, cancer, ageing and death, because it can directly affect DNA replication, transcription and protein synthesis, thereby affecting cells' growth, development, genetics, metabolism, reproduction and other vital biological activities (Jiang 2005).

TCM and its active ingredients could protect the integrity of DNA duplex and prevent gene mutation by resisting DNA damage (Jiang 2005). An experiment was carried out to study whether *Radix puerariae* (*R. puerariae*) and puerarin (Figure 5) have effects on delaying naturally senile mice of 18 months old and discovered that the rate of missing mtRNA in the elderly control group, the middle *R. puerariae* dose group and the middle puerarin dose group in all are 0.13, 0.11 and 0.11, respectively, indicating that puerarin could retard mitochondrial DNA damage (Wu *et al*. 2011). Furthermore, a metabolomics approach has been already used in a pharmacological study of *Salvia miltiorrhiza (S. miltiorrhiza)*. For example, Jiang *et al*. identified 26 primary and secondary metabolites in *S. miltiorrhiza* from different regions and demonstrated that malonate and succinate possibly were the key markers for discriminating the geographical origin (Jiang *et al*. 2014). The application of metabolomics in *S. miltiorrhiza* provided novel insights into its essence. It was found that salvia acid B (Sal B) extracted from *S. miltiorrhiza*, exerted anti-ageing effects on D-galactose-induced senile mice models presumably by promoting anti-oxidation and affecting

Table 3

Mechanisms of anti-ageing/age-related diseases via regulation of nutrient and energy sensing pathways by TCM

Active ingredients	Source	Experimental model	Efficacy	Mechanism	References
Total saponins	*Panax notoginseng* Burk. F.H.Chen	Serum, glucose and oxygen deprivation (SGOD)-induced apoptosis of H9c2 cells, ligation of the left anterior descending coronary artery-induced apoptosis of cardiomyocytes in SD rats	Inhibits H9c2 apoptosis induced by SGOD, prevents reduction of mitochondrial membrane potential, reduces positive rate of TdT-mediated dUTP nick end labelling cells in myocardial tissue and increases levels of p-AMPK protein in a dose-dependent manner	May be of great connact with activation of AMPK	(Zhang and Liu, 2011)
Berberine	*Coptis chinensis* Franch.	6-month-old female db/db mice	Lowers body weight, fat pad weight and blood sugar levels, improves index of insulin sensitivity, activity of skeletal muscle mitochondrial COX and content of ATP, increases phosphorylation levels of AMPK, and enhances the transcriptional activity of PGC-1α	Activates AMPK /PGC-1α signalling pathway and improves mitochondrial energy metabolism	(Wang *et al.*, 2014b)
		Dietary obese rats	Improves metabolism	Activates AMPK by inhibiting the biosynthesis of ATP in mitochondria	(Yin *et al.*, 2008)
Astragalus polysaccharide	*Astragalus membranaeus* Fisch. Bge.	Fat plus low-dose streptozotocin (STZ)-induced type 2 diabetic rats	Lowers content of blood glucose, serum triglycerides and glycosylated haemoglobin, enhances insulin sensitivity, increases phosphorylation levels of AMPK and acetyl-CoA carboxylase (ACC)	May be associated with up-regulation of AMPK activity	(Zhang *et al.*, 2008b)
		Fat plus STZ-induced diabetic cardiomyopathy rats	Improves insulin resistance and that could be characterized by lowering blood sugar and elevating ISI index	May be related to up-regulation of AMPK activity, uncoupling protein 2 expression and energy metabolism type 2 diabetes mellitus rats	(Wang *et al.*, 2009b)
Gastrodin	*Gastrodia elata* Bl.	Oleic acid-induced HL-7702 cells	Inhibits oleic acid-induced fat accumulation of HL-7702 cells and lowers triglyceride content	Dependent on the activation of AMPK pathway in the cells	(Geng *et al.*, 2015)
Ginsenoside Rb1	*Panax ginseng* C. A. Meyer	Natural ageing mice	Decreases the activity of MAO, the expression of PAI 1 protein and the phosphorylation of mTOR protein	May be implemented by mTOR/p70s6k pathway partially or fully	(Peng *et al.*, 2014)
6-Gingerol	*Zingiber officinale* Roscoe	Angiotensin II (Ang II)-induced rat aortic VSMCs senescence	Markedly decreases Ang II-induced VSMCs celluar senescence, cell cycle arresting in G0/G1 phase, the protein	May attenuate VSMCs senescence through inhibition of mTOR/P70-S6 K pathway	(Zhou *et al.*, 2014)

(Continues)

Table 3 (Continued)

Active ingredients	Source	Experimental model	Efficacy	Mechanism	References
			level of mTOR and phosphorylated p70-S6 K		
Icariside II	*Epimedium brevicornu* Maxim.	*C. elegans*	Increases thermo and oxidative stress tolerance, decreases the rate of locomotion decline in late adulthood, extends lifespan by 20%	Dependent on the INS/IGF-1 and DAF-2/FOXO and likely HSF1 signalling pathways	(Cai *et al.*, 2011)
Glaucarubinone	*Simarouba glauca* DC	*C. elegans*	Significantly extend −80% lifespan at 100 nM ; reduced the body fat content	May act through the nutrient sensing pathway	(Zarse *et al.*, 2011)
Catechin	*Camellia sinensis* O. Ktze.	Hepa 1–6, L6, and 3 T3-L1 cells and BALB/c mice	Up-regulates the downstream target ACC	By the activation of LKB1/AMPK	(Murase *et al.*, 2009)
Curcumin	*Curcuma longa* Linn.	Diabetic rats induced by high-fat diet plus streptozotocin	Improves muscular insulin resistance by increasing oxidation of fatty acid and glucose	Mediated through LKB1-AMPK pathway	(Na *et al.*, 2011)
		Alzheimer's disease trangenic mice model	Suppresses indices of inflammation and oxidative damage in the brain and decreases the overall amyloid content and plaque burden	Activates signalling pathways downstream of the anti-ageing modulators AMPK and NRF2, suppress inflammatory processes mediated by NF-kB signalling	(Lim *et al.*, 2001; Salminen *et al.*, 2012; Salvioli *et al.*, 2007; Sikora *et al.*, 2010; Surh *et al.*, 2008)
Luteolin	*Reseda odorata* Linn.	A cell model of steatosis induced by palmitate	Reduces lipid accumulation	ActivateS AMPK, ACC-1, CPT-1, down-regulates sterol regulatory element binding protein 1c and fatty acid synthase	(Liu *et al.*, 2011b)
Naringenin	*Citrus maxima* Burm. Merr.	Skeletal muscle cells	Increases glucose uptake	Through activation of AMPK	(Zygmunt *et al.*, 2010)
Quercetin	*Herba hyperici*	High-cholesterol-induced neurotoxicity in old mice	Reduces high-cholesterol-induced A β deposits and improvesbehavioural performance	Activates AMPK, increases HMGCR and ACC ,decreases eIF2α phosphorylation	(Lu *et al.*, 2010)
Theaflavin	*Camellia sinensis* O. Ktze.	HepG2 cells exposed to a long-chain mixture of FAs and male Wistar rats 5 weeks old fed with high-fat diet	Reduces lipid accumulation, suppresses fatty acid synthesis, stimulates fatty acid oxidation, inhibites acetyl-coenzyme A carboxylase activities	By stimulating AMPK through the LKB1 and reactive oxygen species pathways	(Lin *et al.*, 2007)
Epigallocatechin gallate	*Gamellia sinensis* O.Ktze	Rat pancreatic beta cells	Reduces glucotoxicity-induced pancreatic beta cell death	Increases insulin sensitivity through activating AMPK signalling to inhibit the activities of lipogenic enzymes and ameliorating mitochondrial function	(Cai and Lin, 2009)
		Rat L6 cells treated with dexamethasone	Improves insulin-stimulated glucose uptake,improves insulin resistance	Increases GLUT4 translocation to plasma membrane, activates AMPK and PI3K/Akt	(Zhang *et al.*, 2010)

(Continues)

Table 3 (Continued)

Active ingredients	Source	Experimental model	Efficacy	Mechanism	References
		Overnight-fasted Wistar rats	Prevents free fatty acids-induced peripheral insulin resistance, decreases plasma markers of oxidative stress, increases antioxidant enzymes and reverses IH-induced	Through decreasing oxidative stress and PKCθ membrane translocation, activating the AMPK pathway and improving insulin signalling pathway *in vivo*	(Li *et al.*, 2011a)
		Ageing endothelial cells	Reduces endothelial cellular senescence and dysfunction	By inhibiting mTOR/S6 K signalling and ROS production	(Rajapakse *et al.*, 2011)
		Drosophila and *C. elegans*	Extends lifespan	Through up-regulation of Sir2 and AMPK	(Bass *et al.*, 2007)
		Neuronal cells AD	Lowers Aβ accumulation	By activation of AMPK and induction of autophagy via inhibiting mTOR	(Vingtdeux *et al.*, 2010)
		HepG2 cells incubated with Arachidonic acid and iron	Inhibits apoptosis, ROS production and glutathione depletion, attenuates superoxide generation in mitochondria,... inhibits mitochondrial dysfunction	Through AMPK-mediated inhibitory phosphorylation of GSK3β downstream of poly(ADP-ribose)polymerase-LKB1 pathway	(Shin *et al.*, 2009)
		Middle-aged mice fed with a high-calorie diet	Shifts the physiology of treated mice towards that of mice on a standard diet, significantly increases their survival	Restores normal insulin sensitivity, reduces IGF-1 levels, increases AMPK activity, improves mitochondria number and function	(Baur *et al.*, 2006; Lagouge *et al.*, 2006)

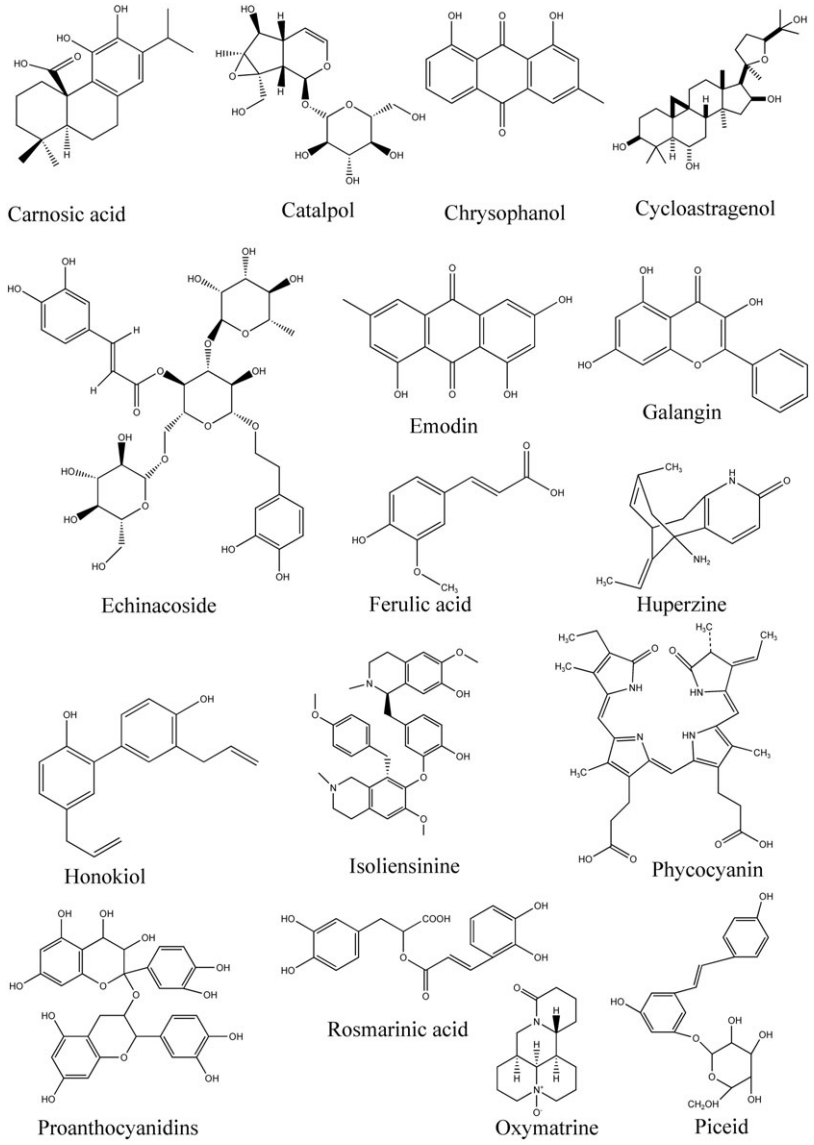

Figure 4
Structural formula of active ingredients with anti-ageing/age-related diseases effects from traditional Chinese medicine by free radical scavenging.

mitochondrial DNA levels, based on the findings that there was a better performance in Morris water maze test and stand-jumping test, an increase of cerebral SOD activity, a reduction of MDA content and mitochondrial DNA level in Sal B treatment group (Gao *et al*. 2009). Additionally, Chen *et al*. showed that tea polyphenols have anti-ageing effects and could significantly increase DNA methylating enzyme activity (Chen *et al*. 2001). Many other studies involved in the mechanism of anti-damage of DNA by TCM active ingredients are shown in Table 5.

Effects of TCM on DNA-repair are being constantly revealed with the in-depth understanding on the procedure of DNA damage and repair (Jiang 2004). However, the targets of drugs are rarely involved in current studies. Therefore, more researches are needed to explore the mechanisms of DNA repair by TCMs.

Chinese compound prescription and its extracts

Chinese compound prescription (CCP) is usually composed of several kinds of single herbs, each of which contains multiple effective constituents (Peng *et al*. 2015). In fact, the safety and effectiveness of CCP have been confirmed by the clinical practice for thousands of years. In the past decades, more and more attention in TCM has been focused on the effects of active ingredients from formulae (Yin *et al*. 2015). Of note, synergism, when the effects of the combination are greater than that of the individual drug, is a core principle of TCM and has played an essential role in improving its clinical efficacy (Zhang *et al*., 2014b).

Although the mechanisms of CCP are unclear owing to its complex composition, a large number of

Table 4

Mechanisms of anti-ageing/age-related diseases via free radicals scavenging by TCM

Active ingredients	Source	Experimental model	Efficacy	Mechanism	Reference
Curcumin	*Curcuma longa* Linn.	Drosophila flies	Suppresses oxidative stress and lipid peroxidation, reduces accumulation of malondialdehyde (MDA), improves locomotor performance	Modulates a number of stress-responsive genes, including the antioxidant enzyme superoxide dismutase	(Lee *et al.*, 2010; Shen *et al.*, 2013)
Echinacoside	*Cistanche tubulosa* Schenk Wight	D-galactose-induced aged mice	Repairs the damage induced by ROS, improves the memory ability, delays ageing process	Enhances the activities of GSH-Px and SOD, reduces the content of MDA and the activity of MAO	(Muteliefu *et al.*, 2004)
Isoliensinine	*Nelumbo nucifera* Gaertn	D-galactose-induced ageing mice	Markedly counteracts loss of body weight and liver index, significantly increases the antioxidative effect	Increases activities of SOD and GSH-Px in surum and liver tissue, reduces content of MDA	(Liu *et al.*, 2011a)
Huperzine a	*Huperzia serrata* Thunb. ex Murray Trev.	D-galactose-induced senile mice	Improves disorder of learning and memory and neuron protection	Significantly reduces the content of NO, the activity of NOS and the level of Ga2+ in brain cell plasma, increases the activities of GSH-Px and SDH	(Lv *et al.*, 2007)
Quercetin	*Herba hyperici*	*C. elegans*	Significantly improves the mean and maximum lifespan by 36 and 20% respectively with little effect on its reproductive capacity	Might improve the stress resistance	(Han *et al.*, 2011)
		Human RPE cells treated with oxidative stress mediated by H_2O_2	Diminishes the decrease of mitochondrial function, reduces the activation of caspase-3 from 1.9 to 1.4 fold, decreases the levels of caveolin-1 mRNA and caveolin-1 protein, attenuates the increase in β-galactosidase–positive cells	Reduces mitochondrial dysfunction and cellular senescence	(Kook *et al.*, 2008)
Polysaccharide	*Arimillaria mellea* Vahl ex Fr. Quel.	*C. elegans*	Significantly extends the lifespan without damage to the reproductive capacity, increases the expression of HSP-16.2 and SOD-3	Maybe by increasing the capacity of stress resistance	(Chen *et al.*, 2013)
Rosmarinic acid	*Rosmarinus officinalis* Linn.	D-galactose-induced ageing mice	Increases the activity of SOD and GSH-Px in serum and brain, decreases the levels of MDA and triglyceride, extends hypoxia-resistance time at normal pressure	Increases the activity of antioxidase, removes free radicals, reduces the production of lipid peroxidation	(Wang *et al.*, 2009b)
Piceid	*Polygonum cuspidatum*	*C. elegans* model	Significantly increases the lifespan by 13%	Significantly enhances the swallowing rate, motility, intestinal lipofuscinosis and the reproductive capacity and remarkably decreases the lipofuscin	(Chen, 2012)

(Continues)

Table 4 (Continued)

Active ingredients	Source	Experimental model	Efficacy	Mechanism	Reference
Green tea catechins	*Gamellia sinensis* O.Ktze	SAMP10 mice	Reduces carbonyl protein levels in the brain	Through decreasing carbonyl proteins and increasing GPx activity	(Kishido *et al.*, 2007)
Mogroside	*Siraitia grosvenorii* Swingle C. Jeffrey ex Lu et Z. Y. Zhang	D-galactose-induced ageing mice and *Drosophila melanogaster*	Against ageing and prolongs the average life expectancy and maximum lifespan	Improves SOD activity and decreases MDA content	(Xiao *et al.*, 2014)
Gypenosides	*Gynostemma pentaphyllum* Thunb. Makino	Human aged skin fibroblasts	Weakens oxidative stress, increases the ability of proliferation and therefore delays cells ageing	Increases the activity of SOD, CAT and GSH-Px	(Cong *et al.*, 2014)
Oxymatrine	*Sophora flavescens* Alt.	D-galactose-induced ageing mice	Improves the learning and memory ability	Defends against oxygen free radicals and reduces the lipid peroxidation	(Zi *et al.*, 2012)
Total alkaloid	*Corydalis yanhusuo* W. T. Wang	D-galactose-induced ageing mice	Restores the ability of learning and memory and plays a role in anti-ageing	Increases SOD, CAT and ChAT activity in the brain and reduces AChE activity	(Bai *et al.*, 2008)
Resveratrol	*Veratrum nigrum* Linn.	D-galactose-induced ageing mice	Maintains the normal morphological structure of nerve cells, decreases oxidative stress responses and has protective effects on brain tissues	Significantly increases the number of nerve cells, the organ coefficients and activities of GSH-Px, SOD and CAT, significantly decreases activity of MAO and content of MDA	(Cui *et al.*, 2013)
		D-galactose-induced myocardial cell senescence	Reduces the degree of D- galactose-induced myocardial cell senescence	Reduces β- galactosidase and MDA levels, increases SOD activity and LC3II/LC3I level	(Guo *et al.*, 2012)
Honokiol	*Magnolia officinalis* Rehd. et Wils.	D-galactose-induced ageing mice	Delays changes of quasi-ageing	Enhances SOD, CAT and GSH-Px activity, decreases MDA content	(Hao *et al.*, 2009)
Chrysophanol	*Rheum officinale* Baill.	Scopolamine-induced acquisition disturbance, sodium nitrite-induced consolidation impairment, 30% ethanol-induced retrieval deficit of memory and aluminium-induced acute ageing in mice	Improves the impairments of memory acquisition and promotes the tolerance of rats	Increases plasma SOD activity	(Li *et al.*, 2005)
Flavonoid	*Oxytropis glabra* Lam. DC.	D-galactose-induced ageing mice	Significantly prolongs the survival time under hypoxic condition and the swimming time at normal temperature and has obvious effects on anti-senility	Significantly declines the content of MDA and LPO and increases the activity of SOD, GSH-Px and CAT in serum and tissue	(Wang *et al.*, 2013)
Galangin	*Zingiber officinale* Roscoe	D-galactose-induced senescent mice	Improves the cognitive function of aged mice	Attenuates the decreased activities of SOD, GPx and CAT, reduces MDA levels	(Fu *et al.*, 2012)

(Continues)

Table 4 (Continued)

Active ingredients	Source	Experimental model	Efficacy	Mechanism	Reference
Puerarin	*Radix puerariae*	D-galactose-induced ageing rats	Plays a part in anti-ageing	Increases SOD and GSH-Px activity in serum, decreases MDA and LPF levels	(Peng, 2009)
Sodium ferulate	*Angelica* sinensis Oliv. Diels/*Ligusticum chuanxiong* Hort.	D-galactose-induced ageing mice	Significantly promotes the activity of SOD in brain and serum, GSH-Px in blood, remarkably inhibits the increase of MDA in serum and liver, MAO of brain, restrains the decrease of weight and the index of thymus and spleen	Increases the activity of antioxidase, removes the accumulation of metabolites in the body and increases the weight immune organ	(Zhu *et al.*, 2004)
Carnosic acid	*Rosmarinus officinalis* Linn.	Human embryonic lung diploid fibroblasts 2BS cell line	Delays senescence of 2BS cells	Increases the cellular viability and the percentage of S distribution, dramatically reduces the SA-β-Gal positive rate, the percentage of G1/G0, the intracellular MDA level and p53 and p21 protein expression	(Tao *et al.*, 2014)
Lotus seedpod procyanidins	*Nelumbo nucifera* Gaertn.	D-galactose-induced ageing mice	Has significant antioxidant effect	Significantly increases the activities of SOD and GSH-Px in brain, remarkably decreases the content of MDA	(Chen *et al.*, 2009)
Catalpol	*Rehmannia glutinosa* Gaert. Libosch. ex Fisch. et Mey.	D-galactose-induced sub-acute senescent mice	Reverses the D-galactose-induced behavioural impairments	Increases the activities of SOD and GSH-PX, decreases the MDA level	(Zhang and Liu, 2011)
Cycloastragenol	*Astragalus propinquus* Schischk.	D-galactose-induced ageing mice	Has a remarkable effect of anti-decrepitude	May improve the activities of T-SOD and T-AOC, reduces the contents of MDA and HYP	(Cao *et al.*, 2012)
Phycocyanin	*Porphyra yezoensis* veda	D-Galactose-induced mice models of subacute ageing	Has excellent anti-ageing activity	Significantly increases SOD activity, thymus index and spleen index, as well as decreases MDA content	(Zhao and Tang, 2012)
Garlicin	*Allium sativum* Linn.	D-galactose-induced AD mice	Improves ability of spatial learning and memory	Reduces MDA content, increases SOD activity	(Hu *et al.*, 2010)
Emodin	*Rheum officinale* Baill.	Hyperlipidaemia quail	Has significant lipid-lowering effect and anti-ageing effects	Lowers LPO content in serum and LF content in brain, increases SOD content and thymus weight as well as spleen weight	(Han *et al.*, 2009)
Salvianolic acid B	*Salvia miltiorrhiza* Bunge.	Glucocorticoid-induced ageing skin of rats	Significantly increases epidermal thickness and content of elastic fibres, alleviates ageing-like changes	Inhibits lysophosphatidylcholine-induced increase of matrix metalloproteinase-2 activity, scavenges free radicals, improves immune status and has anti-lipid peroxidation	(Zhang *et al.*, 2008a)

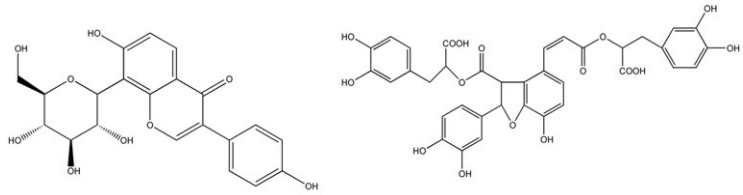

Figure 5
Structural formula of puerarin and salvianolic acid B with anti-ageing/age-related diseases effects from traditional Chinese medicine by anti-damage of DNA.

experimental studies have shown that several anti-ageing mechanisms mentioned above are also applicable to CCP. Specifically, a traditional Chinese herbal formula, Zuoguiwan pill, composed of seven herbal constituents, was found to exert anti-ageing effects by improving blood anti-oxidative ability and decreasing DNA damage of lymphocytes (Xia *et al*. 2012). Similarly, it could significantly decrease the levels of 8-hydroxy-2′-deoxyguanosine in the cerebral genome of 24-month-old rats, suggesting that the underlying mechanism relies on the protection and repair on DNA in cerebral genome (Zhao *et al*. 2002). Furthermore, there was a dose-dependent increase in the expression of FOX, SIRT1 and c-Myc in ovary cells of sub-acutely ageing rats induced by D-galactose after treatment with a decoction of *Fallopia multiflora* (*F. multiflora*), suggesting that this decoction could block ovary apoptosis probably by regulating the expression of FOX, SIRT1 and c-Myc (Zhang *et al*., 2013a). Additionally, Zhang *et al*. applied ultra high performance liquid chromatography coupled with the quadrupole time-of-flight MS metabolomics to evaluate the therapeutic effect of Liuwei Dihuang (LWDH) pills, Jinkui Shenqi (JKSQ) pills and their combinations (administration of JKSQ pills in the morning and LWDH pills at night) on kidney deficiency in Sprague–Dawley rats induced by dexamethasone and D-galactose (Zhang *et al*., 2014b). The results showed that the group treated with JKSQ pills in the morning and LWDH pills at night displayed the strongest rehabilitation for metabolic disorder, and it concluded that lipid metabolism and energy metabolism might be closely related to kidney deficiency and ageing as most of potential biomarkers identified of the kidney deficiency and ageing are related to fatty acids. Similarly, extracts of TCM are the other active ingredients possessing anti-ageing functions under investigation. In support, aqueous extracts of *Portulaca oleracea* possibly exert anti-ageing effects on senile mice by inhibiting expression of p53 gene and activating telomerase, so as to protect against telomere shortening in brain (Huang *et al*. 2007). Moreover, Guo *et al*. found that alcoholic extracts of *C. officinalis* can fight against senility by inhibiting the non-enzymic glycosylation of proteins *in vivo* and reducing DNA damage of peripheral blood lymphocyte (Guo *et al*. 2005).

A systematic review of the clinical and non-clinical efficacy of anti-ageing herbs was published based on six human and 61 animal studies, most of which showed significantly improved brain function, sexual disorder and skin wrinkling (Hasani-Ranjbar *et al*. 2012). For example, Lee *et al*. investigated the clinical efficacy of *P. ginseng* in the cognitive performance of Alzheimer's disease patients and found that the mini-mental state examination scores and Alzheimer's disease assessment scale scores both were significantly decreased after treatment with *P. ginseng* (Lee *et al*. 2008). Additionally, several other clinical trials were also performed with CPP or TCM extracts and demonstrated beneficial effects (Zhang *et al*. 1992; Zhang 1993; Wang 1994; Tian *et al*. 1997; Xu and Zhi 1998; Sugiyama 2006; Amagase and Nance 2008; Yonei *et al*. 2008; Gim *et al*. 2009). More related researches are listed in Table 6 as below.

In summary, there is much evidence, as mentioned above, for the anti-ageing effect of combinatorial intervention in TCM to achieve synergistic interactions that could produce sufficient effects at low doses. However, the regulation of compatibility, principles of composition and effective substance basis of CPP or TCM extracts are poorly understood, thus hampering the development and modernization of TCM (Sheridan *et al*. 2012). Therefore, chemical fingerprinting coupled with systems biology should be applied to TCM to scientifically and accurately explore the pharmacokinetics of multi-ingredients in TCM (Zhang *et al*., 2014b).

Limitations and prospects

Above all, active ingredients from TCM without serious adverse reactions seem to provide an intriguing way forward to exert anti-ageing effects. Unfortunately, it must be highlighted that there are still many limitations and problems unresolved at the current stage. Firstly, the efficacy and/or safety of many TCM products largely rely on poor-quality researches that are probably limited by the inadequate or inconsistent methods being used and risk of bias of the included studies, thereby failing to draw firm conclusions of efficacy. Therefore, high quality research in the field of TCM is emphatically needed to firmly establish the efficacy and/or safety of many TCM products. Simultaneously, there are potentially serious adverse events (Chan 2015), although relatively infrequent, as well as the interactions (Izzo 2012; Milic *et al*. 2014) between herbal medicines and prescribed medicines, that have been described, implying that more meticulous attention should be paid to herbal research. In fact, it is advisable to make sure that the herbal remedies are

Table 5

Mechanisms of anti-ageing/age-related diseases via anti-damage of DNA by TCM

Active ingredients	Source	Experimental model	Efficacy	Mechanism	Reference
Tea polyphenols	*Camellia sinensis* O. Ktze.	12–13-month-old mice	Significantly increases the DNA methylating enzyme vitality in the liver	Increases the DNA methylating enzyme vitality by altering conformation of DNA methylase and making it easier to transfer methyl to normal methylation sites	(Chen *et al.*, 2001)
Resveratrol	*Reynoutria japonica* Houtt.	Natural ageing mice	Reduces the rate of mtRNA deletion and the percent of deletion on chief mtRNA	Avoids the mtDNA damage	(Zhang *et al.*, 2011a)
Puerarin	*Radix puerariae*	Skin of natural ageing mice	Slows down the natural ageing of skin	Reduces deletion mutation of mtDNA, improves the vitality of GSH-Px	(Li *et al.*, 2011a; Wu *et al.*, 2011)
Salvia acid B	*Salvia miltiorrhiza* Bunge	D-galactose-induced ageing mice	Exhibits better performance in Morris water maze test and stand-jumping test, significantly reduces mitochondrial mtDNA and MDA levels, improves cerebral SOD activity	Promotes anti-oxidation, reduces mitochondrial DNA level	(Gao *et al.*, 2009)
Polysaccharide	*Zostera marina* L.	Reactive oxygen species-induced lymphocyte DNA damage	Helps to maintain normal structure and function of cells	Scavenges free radical and reduces oxidative stress-induced DNA damage	(Zhan *et al.*, 1999)
	Spirulina	UV-induced DNA damage of human embryo lung diploid fibroblastic	Prevents the level of DNA damage induced by UV irradiation and promotes DNA repair capacity	Increases the activity of DNA endonuclease and DNA ligase in dose-dependently	(Deng *et al.*, 2001)

Table 6

Mechanisms of anti-ageing/age-related diseases by Chinese medicine compounds and extracts

Active ingredient	Source	Experimental model	Efficacy mechanism	Mechanism references	References
Vigconic 28	*Panax ginseng*/*Cervus nippon*/*Cordyceps sinensis*/*Salvia miltiorrhiza*/*Allium tuberosum*/*Cnidium monnieri*/*Euodia rutaecarpa*	C57BL/6 J mice	Retards ageing in mice	Likely by affecting mitochondria functionality	(Ko *et al.*, 2010)
Liu Wei Dan Kun decoction	*Rehmannia glutinosa* Gaertn./*Rhizoma dioscoreae*/*Cornus officinalis* Sieb. et Zucc./*Poria cocos* Schw. Wolf./*Alisma plantago-aquatica* Linn./*Paeonia suffruticosa* Andr./*Salvia miltiorrhiza* Bunge/*Leonurus artemisia* Lour. S. Y. Hu	Aged mice	Increases retention rate of double-stranded DNA and restores partial damaged DNA	Reduces the damage of DNA in aged mice, increases resistance to radiation and improves the ability to repair DNA damage	(Yang *et al.*, 1995)
Formula of tonifying kidney and spleen, nourishing blood and promoting blood flow	*Lycium chinense* Miller/*Fallopia multiflora* Thunb. Harald./*Epimedium brevicornu* Maxim./*Fructus ligustri* Lucidi/*Angelica sinensis* Oliv. Diels *Cuscuta chinensis* Lam. /*Astragalus membranaeus* Fisch. Bge./*Polygonatum sibiricum* Delar. ex Redoute	Senile Balb/c mice of 12–14-month-old	Decreases depletion of kidney mtDNA in senile Balb/c mouse significantly	Inhibits deletion mutation of mtDNA, reduces oxidative damage of mtDNA, protects mtDNA	(Wang *et al.*, 2006)
Liuweidihuang Decoction	*Rehmannia glutinosa* Gaertn./*Cornus officinalis* Sieb. et Zucc./*Rhizoma dioscoreae*/*Paeonia suffruticosa* Andr./*Alisma plantago*-aquatica Linn./*Poria cocos* Schw. Wolf.	Drosophila and D-galactose-induced ageing mice	Prolongs the surviving-time, improves the anti-oxidation ability, increases telomerase activity	Antioxidant and increases telomerase activity	(Wu and Dong, 2003)
Pill of kidney-qi-tonifying	*Radix rehmanniae* Exsiccata./*Rhizoma dioscoreae*/*Cornus officinalis* Sieb. et Zucc./*Alisma plantago-aquatica* Linn./*Poria cocos* Schw. Wolf./*Paeonia suffruticosa* Andr./*Cinnamomum cassia* Presl/*Aconitum carmichaeli* Debx.	Cy-clophosphamide-induced damage of DNA in mice	Antagonizes DNA damage caused by cyclophosphamide	Enhances the body's ability to prevent DNA damage	(Zhou *et al.*, 1998)
Decoction of four mild drugs	*Panax ginseng* C. A. Meyer/*Atractylodes macrocephala* Koidz./*Poria cocos* Schw. Wolf./*Glycyrrhizae*	D-galactose-induced ageing mice	Decreases the MDA content of heart, liver and brain, increases the telomerase activity in heart	Antagonizes free radical injury, improves telomerase activity	(Yang *et al.*, 2005)

(Continues)

Table 6 (Continued)

Active ingredient	Source	Experimental model	Efficacy mechanism	Mechanism references	References
			and brain tissues but with no effect on that in liver tissue		
		D-galactose-induced ageing mice	Significantly improves the ability of learning and memory, increases the activities of GSH-Px and SDH respectively in brain tissues, decreases the concentration of Ca^{2+} ions, prevents the damage of mtDNA in hippocampus	Enhances the antioxidative ability, regulates the homeostasis of Ga2+, inhibits the damage of mtDNA caused by oxidative stress for ageing brain	(Li *et al.*, 2009)
Formula with effects of anti-ageing and extending lifespan	*Eucommia ulmoides* Oliver/*Lycium chinense* Miller	Aged rats of 85 weeks old	Improves the biochemical changes	Decreases the DNA single chain break and increases their unscheduled DNA synthesis	(Guo *et al.*, 1997)
Zuoguiwan pill	*Rhizoma dioscoreae*/*Lycium chinense* Miller/*Cornus officinalis Sieb.* et Zucc./*Cyathula officinalis* Kuan/*Cuscuta chinensis* Lam. *Gelatinum cornu* Cervi/ *Colla carapacis* et Plastri Testudinis	D-galactose-induced ageing rats	Slows down the ageing progress	Through improving the blood anti-oxidative ability and decreasing the DNA damage of lymphocytes	(Xia *et al.*, 2012)
		Natural ageing 24-month-old rats	Has effect of neural protection and repairment on brain	By down-regulating levels of genomic DNA 8-OH-dG	(Zhao *et al.*, 2002)
Five seeds combo	*Lycium chinense* Miller/*Cuscuta chinensis* Lam./*Schisandra chinensis* Turcz. Baill./*Plantago asiatica* Linn./*Rubus idaeus* Linn.	Thirty-eight aged men with symptoms of senility and aged rats of 22 months old	Has protective effect on oxidative damage of mtDNA	Raises the activities of mitochondrial respiratory chain complexes I and IV, reduces the mitochondrial DNA deletions	(Wang *et al.*, 2001)
Liquid of tonifying kidney and synergia	*Rehmannia glutinosa* Gaertn./ *Lycium chinense* Miller/*Scutellaria baicalensis* Georgi/*Angelica sinensis* Oliv. Diels	60Co γ irradiation-induced damage on mice	Effectively prevents the apoptosis of lymphocyte, protects lymphocyte from injury	Reduces the cleavage rate of DNA	(Feng *et al.*, 2005)
Capsule of tonifying qi and resolving turbidity	*Astragalus membranaeus* Fisch. Bge./*Fructus ligustri* Lucidi/ *Atractylodes lancea* Thunb. DC./ *Bombyx mori* L./*Salvia miltiorrhiza* Bunge/*Euonymus alatus* Thunb. Sieb.	The spontaneous type 2 diabetes KKAy mice fed with high fat diet	Improves insulin resistance	Probably related to raising expression levels of GLUT-4 and AMPK protein in skeletal muscle and the activity of MLYCD in fat	(Guo *et al.*, 2013)
Decoction of *Fallopia multiflora*	*Fallopia multiflora* Thunb. Harald./ *Cistanche deserticola* Ma/Aerva sanguinolenta Linn. Blume/ *Epimedium brevicornu* Maxim./ *Salvia miltiorrhiza* Bunge/*Poria cocos* Schw. Wolf.	D-galactose-induced ageing rats	Reduces the incidence of ovary apoptosis	Maybe regulated by the expression of FOX, SIRT1 and c-Myc and blocking apoptosis	(Zhang *et al.*, 2013a)

(Continues)

Table 6 (Continued)

Active ingredient	Source	Experimental model	Efficacy mechanism	Mechanism references	References
Tablets of anti-ageing; tablets of extending lifespan by Radix Polygoni Multiflori	*Radix ginseng* Rubra/*Rehmannia glutinosa* Gaert. Libosch. ex Fisch. et Mey./*Asparagus cochinchinensis* Lour. Merr./*Ophiopogon japonicus* Linn. f. Ker-Gawl./*Cortex Lycii*/*Poria cocos* Schw. Wolf./*Fallopia multiflora* Thunb. Harald.	D-galactose-induced ageing rats	Improves the ageing symptom and the reduction of body weight, significantly increases the skin water content, sucrose consumption and bone narrow DNA content	May be related to enhance the capability of rapairing DNA damage	(Xiao *et al.*, 2010)
Electuary of Li yongkang	*Codonopsis pilosula* Franch. Nannf./*Dipsacus japonicus* Miq./*Cornus officinalis* Sieb. et Zucc.	Ozone-induced ageing mice	Enhances the ability of climbing rope, swimming, frost resistance, the total serum IgG concentration, blister of the sole, the thymus index and telomerase activity in thymus	Enhances telomerase activity, probably for the reason that the organs are rich in lymphocytes	(Yang *et al.*, 2000)
Epimedii and Fructus Lycii	*Epimedium brevicornu* Maxim./*Lycium chinense* Miller	22-monthold rats	Protects aged rats from oxidative damage to mitochondria	Reduces the ratio of deleted/normal mtDNA, the activity of mitochondrial respiratory chain enzyme complexes and the rate of ATP synthesis	(Wang *et al.*, 2002)
Erzhi pill	*Ligustri* Lucidi Ait./*Eclipta prostratal*	*C. elegans*	Increases the acute heat stress ability of *C. elegans* without affecting its fecundity	By regulating gene expression of IIS signalling pathway, neuroendocrine and biological clock	(Wang, 2010)
Extracts from TCM	*Portulaca oleracea* Linn.	D-galactose-induced ageing mice	Significantly increases the activity and length of telomerase in senile mouse brain, decreases the expression of p53 gene	Possibly through inhibiting the p53 gene expression and activating the telomerase	(Huang *et al.*, 2007)
	Rosa damascena	*Drosophila* flies	increased longevity by 27%, with no reduction in fecundity	Attributed to the antioxidant action	(Jafari *et al.*, 2008)
	Hericium erinaceus Bull. Ex Fr.	D-galactose-induced ageing mice	Has significant antioxidative effect in apolexis brain tissues	Increases expression of SOD and GSH-Px, decreases MDA content	(Liu *et al.*, 2011b)
	Cornus officinalis Sieb. et Zucc.	D-galactose-induced ageing rats	Plays certain role in delaying ageing	Inhibits the *in vivo* protein non-enzymatic glycosylation, decreases the DNA damage of peripheral blood lymphocyte	(Guo *et al.*, 2005)
	Cynomorium songaricum Rupr.	Flies	Enhances cognitive behaviour and resistance to stress, extends female mean lifespan	The *C. songaricum* flavonoids act as free radical scavengers	(Liu *et al.*, 2012; Yu *et al.*, 2010)

(Continues)

Table 6 (Continued)

Active ingredient	Source	Experimental model	Efficacy mechanism	Mechanism references	References
	Vacciniumuliginosum Linn.	Drosophila flies	Significantly extends mean lifespan, enhances the locomotor performance	Via the up-regulation of antioxidant enzymes (e.g. superoxide dismutase and catalase)	(Peng *et al.*, 2012)
	Rhodiola rosea	Fruit fly and Drosophila melanogaster	Increases longevity without negative effects on reproduction or 2metabolic rate	strongly suggesting that *Rhodiola* is not a mere dietary restriction mimetic	(Jafari *et al.*, 2007)
	Ginkgo biloba	nematode	Extends nematode lifespan by 10%	By enhancing resistance to thermal and oxidative stress	(Collins *et al.*, 2006)
	Damnacanthus officinarum	*C. elegans*	Shows *in vivo* neuroprotective and lifespan extending activity by 10–30%	Mechanism unknown	(Yang *et al.*, 2012)
	Ligusticum Chuanxiong Hort.	*C. elegans*	Increases the average life span of nematodes by 29.9% and the maximum life span by 9.4%	By antioxidant stress, regulating IIS signalling passway, inhibiting fat accumulation, improving mitochondrial activity and other genes related to energy metabolism	(Wang, 2010)
	Panax ginseng C. A. Meyer/ *Panax notoginseng* Burkill F. H. Chen ex C. H. Chow/*Ligusticum chuanxiong* Hort.	Angiotensin II-induced ageing of HUVECs	Delays the ageing of HUVECs induced by angiotensin II	Possibly by down-regulating the expression of NADPH oxidase subunit p47phox through AT1R and further reducing superoxide anion production	(Yang *et al.*, 2009)
	Coptis chinensis Franch.	High fat diet-induced metabolic syndrome rats	Enhances the insulin sensitive index M-value and protein level of p-AMPK-α, reduces wet weight of innards fat	Decreases the level of TC, TG in serum and improves insulin sensitivity by activation of AMPK in muscle tissues of metabolic syndrome rats	(Qiao *et al.*, 2010)
Decoction	*Polygonatum sibiricum* Delar. ex Redoute	D-galactose-induced ageing mice	Significantly increases the telomerase activity in gonad and brain without significant change of MDA levels	Significantly activates the telomerase activity	(Li *et al.*, 2002)

chemically characterized, standardized if possible and of known quality when prescribing for population in specific conditions, such as during pregnancy and by breastfeeding women, in the paediatric and adolescent population, as well as in the geriatric population (Izzo *et al*. 2016). Furthermore, many factors, such as the herb–drug interactions, the methods used for processing, combining and decocting, as well as the clinical context and testing methods used, could affect the toxicity of TCM (Liu *et al*. 2014). Thus, predicting safety of TCM at an early stage is a great challenge for drug development and requires considerable effort (Wang *et al*. 2015).

As is known to us all, TCMs not only possess multiple bioactive components and various pharmacological activities but also might generate other bioactive or inactive metabolites when delivered *in vivo*. It is really difficult to figure out whether the anti-ageing effect is attributed to a (n) single and exact mechanism or owing to the synergistic therapeutic efficacies. Probably, TCM cannot be expected to have the target as clearly defined as that of a single compound, leading to the paradox that the theory of the whole view of TCM is reflected in all its aspects, whereas new studies of TCM are becoming more and more detailed and molecular . On the other hand, multi-component treatments might hit multiple targets and exert synergistic therapeutic efficacies, at least in some formulae, thereby controlling complex diseases (Fu *et al*. 2007; Grivicich *et al*. 2008; Panchabhai et al. 2008; Sharma *et al*. 2008). Meanwhile, the bioactive metabolites generated when delivered *in vivo* should also be considered for their multi-targeting roles on complex diseases. Specifically, there were some published data in several clinical models of Alzheimer's disease confirming this (Qin *et al*. 2009; Ksiezak-Reding *et al*. 2012; Wang *et al*., 2014b; Zhao *et al*. 2015; Ho *et al*. 2016). Moreover, the clinical implications of TCMs in ageing-related diseases are still unclear for the reason that current studies on TCM with anti-ageing effects mainly stayed in the very earliest stage, and clinical trials are infrequent or performed without sufficient rigour and recorded detail. Undoubtedly, more high quality clinical trials are much needed to confirm the promising activities of the ingredients from TCM, and the findings must be interpreted vigilantly and cautiously. Additionally, few studies at the current stage focus on the relationship between the anti-ageing activities of TCM components and their chemical structures, which is potentially of great importance to the exploration of TCMs with anti-ageing effects.

Modern technology such as the *in situ* hybridization, immunohistochemistry and gene chip should be fully utilized to explore the ' regulatory effects of TCMs, which are characterized by multi-tissues and multi-indexes. Specifically, metabolomics, which has already been employed to identify and analyse the active ingredients of TCM, is inherently appropriate to provide novel insights into the essence and molecular basis of TCM (Shi *et al*. 2011; Cao *et al*. 2015). In conclusion, tackling ageing and age-related diseases is a much needed task that, evidently, requires great commitment in both basic and clinical studies, aiming to identify and validate new drug targets and in new drug development.

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Conflict of interest

The authors declare no conflicts of interest.

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