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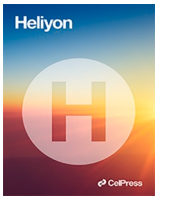

Review article

The molecular mechanism of aging and the role in neurodegenerative diseases

Juanli Zhao [a,b], Zhenjie Han [a], Li Ding [b], Ping Wang [d], Xiutang He [c,**], Li Lin [a,*]

[a] Laboratory of Medical Molecular and Cellular Biology, College of Basic Medical Sciences, Hubei University of Chinese Medicine, Wuhan, 430065, China
[b] Department of Pharmacology, College of Pharmacy, Hubei University of Chinese Medicine, Wuhan, 430065, China
[c] Center for Monitoring and Evaluation of Teaching Quality, Jingchu University of Technology, Jingmen, 448000, China
[d] Hubei Research Institute of Geriatrics, Collaborative Innovation Center of Hubei Province, Hubei University of Chinese Medicine, Wuhan, 430065, China

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ABSTRACT

Aging is a complex and inevitable biological process affected by a combination of external environmental and genetic factors. Humans are currently living longer than ever before, accompanied with aging-related alterations such as diminished autophagy, decreased immunological function, mitochondrial malfunction, stem cell failure, accumulation of somatic and mitochondrial DNA mutations, loss of telomere, and altered nutrient metabolism. Aging leads to a decline in body functions and age-related diseases, for example, Alzheimer's disease, which adversely affects human health and longevity. The quality of life of the elderly is greatly diminished by the increase in their life expectancy rather than healthy life expectancy. With the rise in the age of the global population, aging and related diseases have become the focus of attention worldwide. In this review, we discuss several major mechanisms of aging, including DNA damage and repair, free radical oxidation, telomeres and telomerase, mitochondrial damage, inflammation, and their role in neurodegenerative diseases to provide a reference for the prevention of aging and its related diseases.

1. Introduction

The World Health Organization (WHO) reports that the global population of people aged 60 years and older will increase to 2.1 billion by 2050, and 80% of old people will be living in low- and middle-income countries [1]. This is undoubtedly a challenge for the whole world. While the improved quality of life has led to increased human life expectancy, age-related diseases have come along with it. Aging involves the process of decline in physical function. It is characterized by a gradual decline in the capacity of an organism to adapt to its environment and a reduction in the regenerative capacity of systemic tissues and organs throughout the body. These changes are the primary risk factors for several human diseases, including cancer, diabetes, cardiovascular disease, and neurodegenerative diseases [2] (Fig. 1). The accumulation of senescent cells within the nervous system is thought to be an important factor in

* Corresponding author. Laboratory of Medical Molecular and Cellular Biology, College of Basic Medical Sciences, Hubei University of Chinese Medicine, No.16 of Huangjia Lake Western Road, HongShan District, 430065, Wuhan, China
** Corresponding author. Center for monitoring and evaluation of teaching quality, Jingchu university of Technology, No.33 of Xiangshan Avenue, Jingmen, 448000, Hubei Province, China
E-mail addresses: 199507008@jcut.edu.cn (X. He), linli@hbtcm.edu.cn (L. Lin).

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the development of neurodegenerative diseases. In particular, the incidence of Alzheimer's disease (AD) is thought to be positively associated with increasing age. Similarly, the incidence of Parkinson's disease (PD) increases with age [3], posing a threat to people's health. Understanding the mechanisms underlying the characteristics of aging facilitates the identification of interventions. Here, we review the molecular mechanisms associated with aging and elucidate the role of aging in neurodegenerative diseases to utilize aging effectively and safely as a potential therapeutic target and provide solutions for improving human health and longevity.

2. Molecular mechanisms of aging and the role in neurodegenerative diseases

Aging is a complex process classified as replicative senescence (e.g., telomere damage) and stress-induced senescence (e.g., oxidative stress). It manifests as DNA damage, cell cycle arrest, altered secretion-related factors, metabolic abnormalities, and morphological changes. Aging involves complex molecular mechanisms, which is the reason for continuous research in this area. In 2013, Carlos and colleagues [2] suggested nine aging characteristics, including genomic instability, loss of proteostasis, telomere attrition, dysregulated nutrient-sensing, mitochondrial failure, cellular senescence, depletion of stem cells, and altered intercellular communication. These hallmarks are interrelated and their interactions ultimately lead to aging-associated functional decline. Several molecular mechanisms are associated with aging, and this article focuses on these aspects, such as the DNA damage theory, which suggests that cellular senescence is an accumulation of DNA damage, the genetic senescence theory, which suggests that cellular senescence is regulated by senescence-related genes, the telomere theory, according to which, the shortening of chromosomal telomeres is the cause of aging and the length of chromosomal telomeres determines the life span of the cell, and finally, the free radical theory, which suggests that aging is the accumulation of cellular damage due to free radicals produced by the body's metabolism, etc.

2.1. DNA damage and repair

DNA is the primary unit of heredity necessary to maintain the stability of the genetic material of a species and enable the species to reproduce and develop. DNA damage, caused by many exogenous and endogenous factors, occurs in all organisms and is central to many biological processes. The three main sources of DNA damage include environmental factors, respiration, and reactive oxygen species (ROS) produced by lipid peroxidation. The DNA damage response prevents the cell cycle from proceeding until the damage is repaired. Cellular defense against DNA damage is driven by DNA repair mechanisms, each with unique characteristics; these mechanisms can eliminate most of the damage in the genome [4]. A few examples of the many DNA repair pathways include base excision repair (BER), non-homologous end joining (NHEJ), nucleotide excision repair (NER), homologous recombination (HR), mismatch repair (MMR) and other DNA repair processes. DNA repair is necessary to maintain the genetic stability of cells. Dysregulation or disruption of DNA repair pathways can increase genomic instability, promoting aging and related diseases. Persistent DNA damage that cannot be repaired, interferes with replication. Different repair processes were initially thought to be independent.However, recent studies have shown that many of the DNA damage response-processes have overlapping networks and that they often share specific underlying components. The different repair mechanisms overlap and the DNA damage response is also related to other important DNA transaction mechanisms, such as transcription and replication [5]. The mitochondrial genome encodes 13 proteins [6]. The cell's genome is exported to the cytoplasm, where it is broken down as DNA damage rises. If the degradation is not complete, an immunological reaction is elicited. Microglia perceive the presence of DNA in the cytoplasm as a dangerous signal, which when activated, releases a large number of different pro-inflammatory factors that lead to synaptic dysfunction, neuronal death, inhibition of neuronal formation, and disruption of the blood-brain barrier; this in turn leads to the development of neurodegenerative diseases [7]. In the AD postmortem patient brain, elevated DNA double-stranded or single-stranded breaks and reduced expression of repair factors are exhibited [8,9].

The causes of DNA damage can be broadly classified as endogenous and exogenous (Fig. 2). The causes of exogenous DNA damage can be broadly of three types: physical, chemical, and biological factors. Common physical factors mainly include ultraviolet (UV) radiation and ionizing radiation. The UV radiation is of three types, UV-A, UV-B, and UV-C. Compared to UV-A and UV-B radiation, UV-C has the highest capacity to absorb DNA and generate the most photo products. Consequently, covalent interactions between two

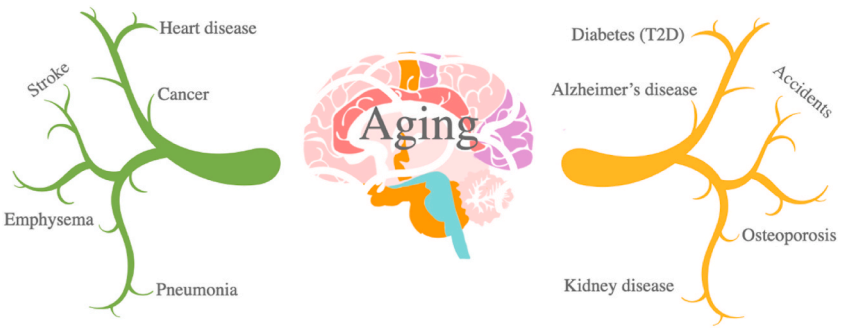

Fig. 1. Diseases associated with aging. The incidence of diabetes, heart disease, cancer, Alzheimer's disease, and other diseases increases significantly with age.

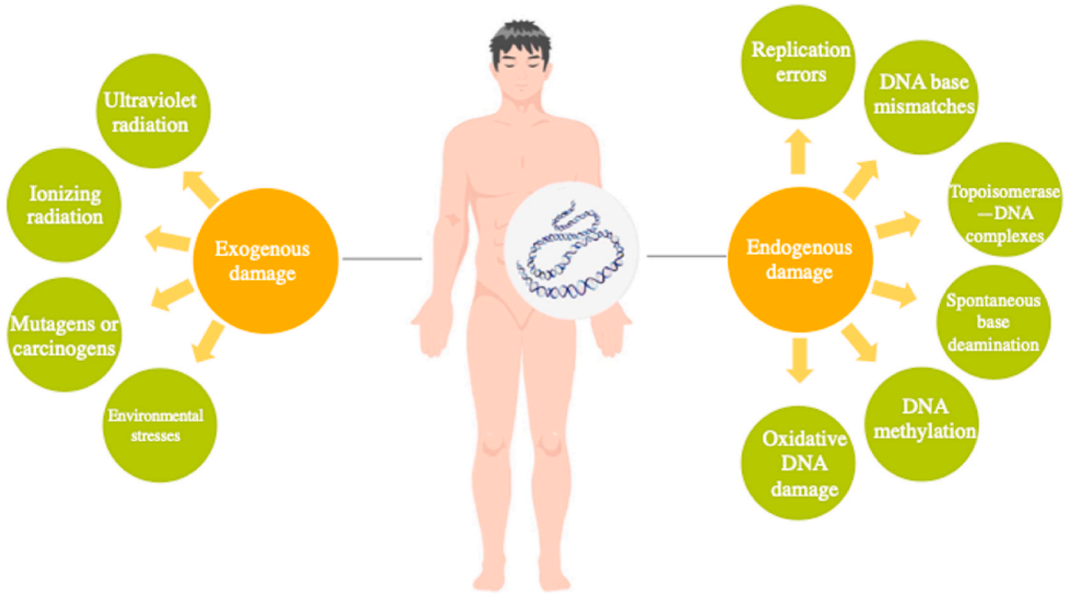

Fig. 2. The factors causing DNA damage. DNA damage can be caused by several factors, which can be classified as exogenous or endogenous.

neighboring pyrimidines are one of the mechanisms through which UV-C might harm DNA [10]. UV-B can also lead to the formation of pyrimidine dimers, though less effectively. UV-A causes DNA damage by activating photosensitizers and causing photo-oxidation processes that result in DNA adduct formation [11]. Ionizing radiation can directly or indirectly cause DNA damage when radiation breaks down the surrounding water to produce highly reactive hydroxyl radicals, which increases the formation of DNA reactive radicals and causes DNA damage [12]. Chemical agents and environmental stress are also important factors in causing DNA damage [13,14]. A few examples of endogenous DNA damage are topoisomerase-DNA complexes, spontaneous base deamination, replication mistakes, DNA base mismatches, oxidative DNA damage, and DNA methylation. The topoisomerase enzyme is an important source of endogenous DNA damage; it creates DNA damage by removing the tension of the helix on DNA during replication and transcription [15]. Base deamidation is a major cause of spontaneous mutations in human cells, and leads to DNA base lesions. ROS are by-products of the electron transport chain during the cellular respiration of aerobic organisms. Excess ROS can damage a variety of oxidized bases [16,17]. Excess ROS is associated with aging-related diseases like AD and heart failure [18,19]. DNA methylation is also a major source of DNA damage, and will be discussed later in the article.

DNA double-strand break (DSB) is serious DNA damage, and cells undergo DBS damage on a daily basis; therefore, cells need efficient and diverse DNA DSB repair to cope with different DSBs to maintain genome stability and prevent diseases [20]. DSBs in the neuronal genome led to neuronal functional impairment. Studies have shown that DSBs begin to accumulate in the hippocampus of patients in the early stages of AD, with a gradual decrease in DNA repair function. Immunohistochemical analyses have shown the co-localization of DSBs and phosphorylated Tau in the cortex of patients with AD. Therefore, DSBs are implicated in AD-related neurodegeneration and neurodegeneration [21]. Excessive damage to the DNA may lead to the accumulation of phosphorylated Tau proteins in cells, which can lead to the formation of neurogenic fibril tangles, further exacerbating chromatin instability and leading to neuronal degeneration. Besides DNA damage, defects in DNA repair may be an important cause of AD; pathologic deposition of Aβ may inhibit the expression of breast cancer type 1 susceptibility protein (BRCA1) in neurons, leading to reduced DSB repair and AD-related cognitive deficits [22].

2.2. The free radicals oxidative stress theory

Aging is mostly influenced by the accumulation of oxidative damage to mitochondria and mitochondrial DNA (mtDNA); decreased mitochondrial function is an important factor in aging [23]. Excess ROS cause oxidative stress, which further promotes oxidative damage to lipids, proteins, nucleic acids, and polyunsaturated fatty acids in cells. Increased oxidative stress in the brain promotes Aβ deposition, a biomarker of AD. Aβ induces oxidative stress toxicity due to free radicals in neurons and activates microglia, which further induces oxidative stress, which in turn regulates apoptosis, causing a progressive increase in apoptosis and neuronal death, forming a vicious circle and aggravating neuronal damage. One of the triggers of oxidative damage is excess free radicals [24], produced in large amounts when the body is under stress and cause oxidative damage to cells and tissues. Free radicals damage cells by destabilizing cell membranes, activating apoptotic signal transduction pathways, inducing apoptosis, and causing degeneration of cellular proteins, sugars, and lipids. The capacity to resist stress in response to stress is a major defense mechanism; during aging, the adaptive capacity of the cell decreases, and stress resistance is lost, thus accelerating aging. The relationship between stress and longevity is defined as a "toxic excitation effect." The endoplasmic reticulum (ER) contains three stress sensor branches, protein

kinase-like ER kinase, inositol-requiring enzyme-1 (IRE1), and activating transcription factor 6 pathways, which recognize stress-related disturbances in ER function and differentiate the intensity of Endoplasmic reticulum stress (ERS) [25]. Mammals have two forms of IRE1, including IRE1α and IRE1β; in contrast to IRE1α, IRE1β is not universally expressed but only in intestinal and lung epithelial cells. IRE1α and IRE1β proteins in humans are encoded, respectively, by the *ERN1* and *ERN2* genes. Protein kinase-like ER kinase is an ER transmembrane kinase that mediates the transcriptional and translational control of the unfolded protein response (UPR) program. Activating transcription factor 6 is packaged into vesicles for transport to the Golgi upon detection of unfolded protein accumulation. Each of these three pathways plays key roles in ER homeostasis and metabolism. ERS is a stress-protective response in eukaryotic cells, that helps the cells reduce the accumulation of unfolded proteins in the ER. Unfolded proteins could activate the UPR, which can enhance the ability of the ER to process unfolded or misfolded proteins, reduce ERS, and maintain the homeostasis of the internal environment of the of the ER. However, persistent ERS induces apoptosis. UPR is one of the most classical stress pathways, which controls ER homeostasis through an intracellular signal transduction mechanism and reduces the effects of ERS through its activation [26].

Redox imbalance leads to oxidative stress, which is associated with pathologies related to neurodegenerative diseases. For example, when oxidant production exceeds the scavenging capacity of the antioxidant defense system in the AD brain, ROS and reactive nitrogen species react with proteins and lipids, disrupting their function and leading to gradual neuronal cell damage and even brain death. The absence of ROS, reactive nitrogen species, and oxidative stress in the human cerebrovascular endothelium leads to increased expression of amyloid precursor protein (APP), which results in an increase in the level of Aβ peptides [27]. These findings suggest that oxidative stress promotes Aβ formation.

2.3. The telomere theory

The DNA repeating sequences (TTAGGG) and particular protein complexes come together to produce the highly conserved hairpin-like structure known as telomeres, the sequences of consecutive repeated nucleotides found at the ends of linear chromosomes [28]. They maintain chromosome stability by protecting chromosomal ends [29]. Telomere length peaks at birth and declines with age, and telomeres in cells become shorter with each cell division due to a lack of telomerase. The adult leukocyte telomeres are estimated to be shortening at a rate of 24.7 bp per year [30]. Therefore, telomere length can be used as a timer of cell age [31]. Gomes NM et al. [32] found an inverse correlation of telomere length with mammalian lifespan and that telomerase expression co-progressed with body size. Telomeres are closely related to aging and are biological markers of cellular senescence, and a trigger of aging. The telomere theory proposes that the aging of human cells and body functions is regulated by the telomere/telomerase system. Each time a cell divides or replicates, telomeres of its chromosomes lose some nucleotides due to a dysfunctional DNA polymerase enzyme that does not fully replicate its chromosomes, stalling the cell division and leading to cellular senescence and death [33]. Many telomere-related proteins are found in telomeres, and some of these proteins, such as DNA protein kinase, p53, and polyadenosine diphosphate ribose polymerase, are also implicated in DNA damage response mechanisms (PARP) [34,35]. Senescent cells, including proteases, growth factors, and inflammatory cytokines, emit a variety of extracellular substances that affect nearby non-senescent cells. At this point, the immune system is activated and may be compromised in the removal of senescent cells by the immune system, causing the accumulation of senescent cells, thus exacerbating tissue dysfunction and tissue aging. Besides reducing the amount of mitotically active cells in the tissue, the buildup of senescent cells triggers the release of proteases, growth factors, and inflammatory cytokines, all affecting cell development and repair [36]. The ribonucleoprotein complex known as telomerase comprises terminal reverse transcriptase, telomerase reverse transcriptase, telomerase RNA template, and telomerase-related proteins [37]. Telomerase can synthesize telomeric terminal repeats using its own carried RNA as a template, compensating for the reduction in telomere length during cell division [38]. The telomere length shortening to the limit after the limited division of somatic cells, results in apoptosis and senescence. Telomerase-mediated regulation of telomere length affects cellular senescence. According to this theory, the aging of human cells and body functions is regulated by the telomere/telomerase system. Each time a cell divides or replicates, its chromosomal telomeres lose some nucleotides due to a dysfunctional DNA polymerase that cannot to fully replicate its chromosomes, causing cell division to stop and leading to cellular senescence and death.

In recent years, some neurodegenerative diseases have been shown to be associated with the amplification of trinucleotide repeats. Diseases such as Huntington's disease (HD), AD, and Friedreich ataxia (FA) are associated with the amplification of GGC, CAG, or CAA repeats [39]. Leukocyte telomere length is associated with morbidity and mortality due to neurodegenerative diseases, like dementia [40]. An experiment at the Department of Psychiatry (Innsbruck or Klagenfurt, Austria), demonstrated shorter average monocyte telomere length in patients with AD than in healthy subjects, and there was a significant negative correlation between telomere length and age [41].

2.4. Energy metabolism and aging

Abnormal energy metabolism is an important factor in aging. Alterations in cellular energy metabolism are mainly reflected in reduced mitochondrial function and altered energy metabolism pathways such as the insulin/Insulin-like growth factor 1 (IGF-1) signaling pathway. The decrease in mitochondrial function is indicated by decreased membrane potential, increased proton leakage, decreased fusion and division rates, and increased mass and the variety of tricarboxylic acid cycle metabolites [42].

2.4.1. Regulation of the insulin/IGF-1 signaling pathway in aging

The insulin/IGF-1 signaling pathway was found to control mammalian lifespan [43]. Evidently, aging is accelerated by increased

insulin/IGF-1 pathway activity and longevity is extended by abnormalities in this route. The control of protein synthesis and energy metabolism, and the proliferation and differentiation of insulin/IGF-1 sensitive cells, are just a few of the crucial roles that the insulin/IGF-1 pathway plays in the body. Although the number of mitochondria are increased in senescent cells, the ability to produce ATP is impaired. During senescence, two genes, including the forkhead box O (*FoxO*) and mechanistic target of rapamycin (*mTOR*) signaling are involved in aging that are controlled by insulin/IGF-1 signaling [44]. Through many signaling pathways, the insulin/IGF-1 pathway can control immune system function, and data suggest that insulin/IGF-1 signaling can promote a range of anti-inflammatory/immunosuppressive responses [45], whereas persistent low-grade inflammation is linked to aging [46]. The transcription factor signal transducer and activator of the transcription 3 (STAT3) protein is a that encourages immune-suppressive cells [47]. STAT3 signaling inhibits inflammatory responses and accelerates cellular senescence through the STAT3/p53/SOCS pathway [48].

2.4.2. Regulation of the mTOR signaling pathway in aging

A crucial element of cellular metabolism, mTOR, an atypical serine/threonine protein kinase, is involved in many important molecular signaling pathways and is a central node in the regulatory network of cell growth. Combining data on nutrients and energy may coordinate the production or breakdown of cellular components. In mammals, it serves as the catalytic component of two distinct complexes, known as mTOR complex 1 (mTORC1) and mTORC2; their sensitivities to auxin and rapamycin vary. The conductance functions for mTORC1 and mTORC2 in cells are different (Fig. 3). To control the anabolic balance and intracellular catabolism, mTORC1 amalgamates information about nutrition availability and environmental factors, while mTORC2 controls cytoskeletal behavior and activates several pro-survival pathways. Compared to mTORC1, mTORC2 is an acute rapamycin inhibitor and is effective only against chronic rapamycin [49]. The focal point of cellular response to external stimuli, mTORC, regulates growth and metabolism and maintains body homeostasis; besides, its activation is dependent on growth factors, energy status, and nutrients. Activated mTORC1 signals downstream by phosphorylating two key substrate proteins, ribosomal S6 kinase 1 and eukaryotic initiator 4E binding protein 1 [50]. Additionally, mTORC1 promotes de novo synthesis of lipids via the sterol response element binding protein transcription factors, that control the expression of metabolic genes involved in the synthesis of fatty acids and cholesterol [51], required by the cell to form and expand new membrane. mTORC1 could also promote messenger RNA translation and protein synthesis by phosphorylating eukaryotic initiator 4E binding protein 1 and ribosomal S6 kinase 1. Aging is a process involving a series of abnormal protein accumulation and the most common molecular features are related to mis-synthesis or translation. Inhibition of mTORC1 overactivation and reduction of abnormal protein synthesis can delay aging to some extent (Fig. 4) [52].

2.4.3. Regulation of the AMPK signaling pathway in aging

AMP-activated protein kinase is a regulator of energy metabolism, stress tolerance, and cellular proteostasis. Health and longevity are regulated by AMPK signaling [53]. ATP depletion and ROS accumulation activate AMPK, a heterotrimer complex made of two regulatory subunits and a catalytic component. AMPK stimulates the synthesis of ATP by raising the activity or expression of proteins involved in catabolism. It also conserves ATP by blocking the biosynthetic route [54]. AMPK is located upstream of several signaling

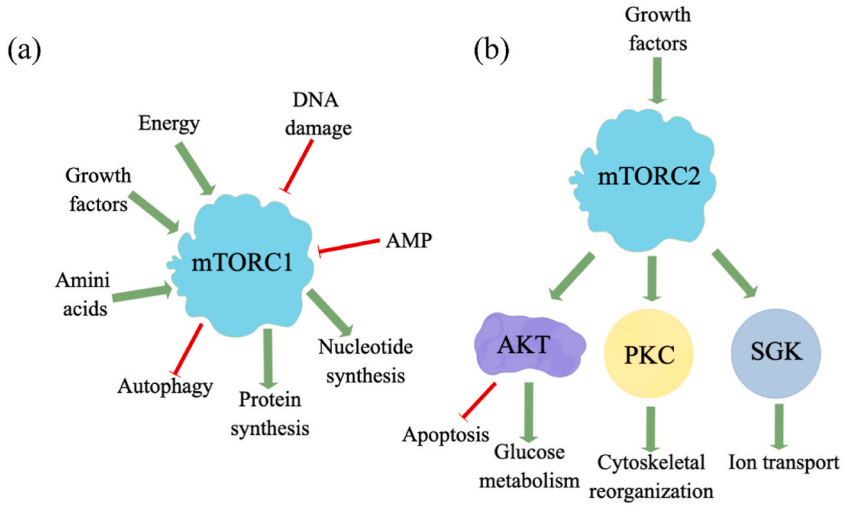

Fig. 3. The role of mammalian/mechanistic target of rapamycin 1 (mTORC1) and mTORC2. Adequate energy and growth factors activate mTOR signaling. (a) mTORC1 activation inhibits autophagy and other protein degradation pathways and activates protein and nucleotide synthesis. It also activates protein and nucleotide synthesis. On the contrary, DNA damage and some other stresses can inactivate mTORC1. AMP can also inhibit mTORC1 by activating AMP-activated protein kinase (AMPK). (b) mTORC2 can be activated by growth factors and insulin, and mTORC2 can activate AKT, which can inhibit apoptosis by regulating forkhead box O (FOXO), and AKT is also important for regulating glucose metabolism. mTORC2 can regulate protein kinase C (PKC), an important in cytoskeletal reorganization. mTORC2 can also regulate serum and glucocorticoid-induced kinase (SKG), which is important for ion transport.

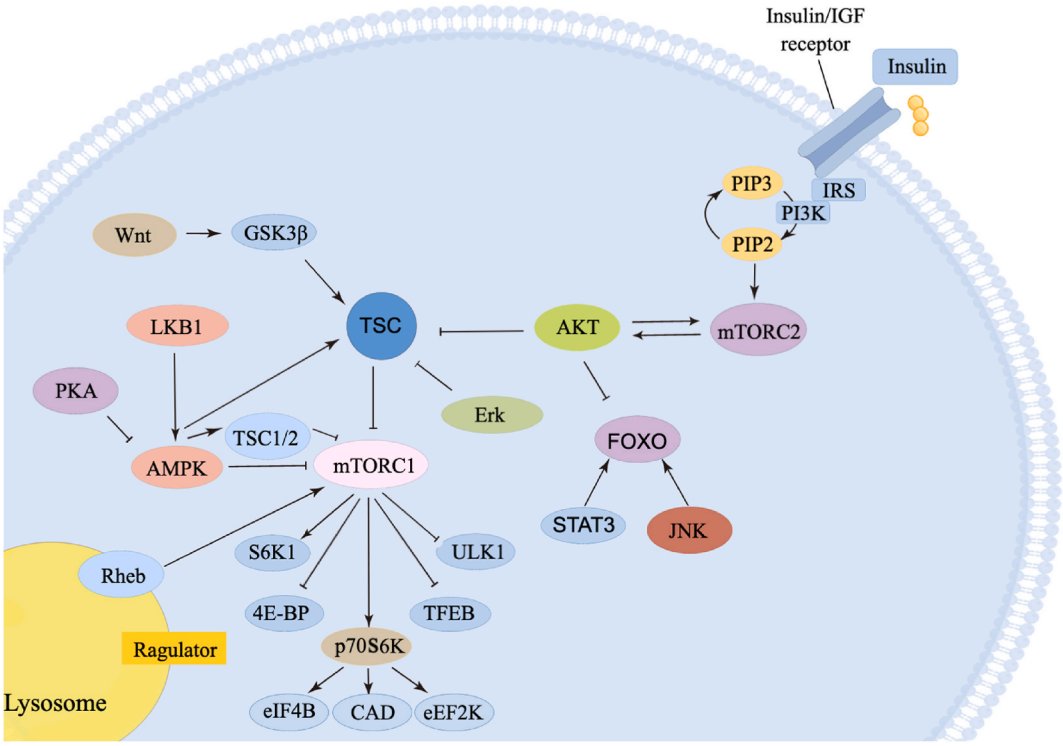

Fig. 4. Regulation of the insulin/insulin growth factor, AMP-activated protein kinase (AMPK), and mammalian target of rapamycin (mTOR) in aging. When insulin and ATP are sufficient, Rheb on the lysosome activates mTORC1 to control cellular synthesis and metabolism. An important function of mTORC1 is to phosphorylate and activate p70 ribosomal protein S6 kinase (p7S6K), an important hub in the mTOR signaling pathway, which promotes intracellular pyrimidine pair synthesis and is important for mTORC1 synthesis. mTORC1 can also inhibit Unc-51-like kinase 1 (ULK1), transcription factor EB (TFEB), and 4E-binding protein (4E-BP). AMPK activated by liver kinase B1 (LKB1) inhibits mTORC1 through a series of processes. AMPK, Wnt, and other inputs are concentrated on the tuberous sclerosis complex (TSC), which inhibits mTORC1 activation.

pathways that regulate the aging process. To reduce the depletion of nicotinamide adenine dinucleotide phosphate brought upon by glucose deprivation, AMPK modulates redox status by reducing fatty acid synthesis and enhancing fatty acid oxidation [55]. It can control immune responses by synergizing with immune signaling pathways, that affect immune metabolism and immune cell function. For example, AMPK signaling can enhance energy metabolism and ER and oxidative stress associated with metabolic disorders and the aging process. It reduces the activity of NF–B system, which in turn curbs the pro-inflammatory response; however, the capacity of AMPK to activate declines with age and metabolic stress, which would speed up the aging process [56].

In eukaryotes, mitochondria are the site of oxidative metabolism and energy release. Mitochondrial dysfunction is crucial in the pathogenesis of neurodegenerative diseases like AD [57]. The high energy metabolic demands of the brain and relatively inactive antioxidant mechanisms make it sensitive to the accumulation of oxidative damage in proteins, lipids, and nucleic acids. Mitochondria are involved in many apoptotic pathways, and in most such pathways, mitochondria play the role of initiation and amplification. In mitochondrial dysfunction, the permeability of the outer mitochondrial membrane increases, and apoptosis-associated proteins present between the outer and inner mitochondrial membranes diffuse into the cytoplasm and cause apoptosis, e.g., cytochrome C, a major player in endogenous apoptotic pathways. Neuroapoptosis due to mitochondrial dysfunction contributes to the loss of neurons and cognitive dysfunction in AD.

2.5. *The genetic aging theory*

The complicated process of biological aging is influenced by both environmental and hereditary variables. Although living environment and lifestyle have always influenced human longevity, research has found that genetics plays a significant role in aging and longevity [58,59]. According to a genome-wide analysis, around 57 genetic loci are linked to lifespan. Cellular performance and stress resistance are affected by epigenomic alterations with age [60]. Danish and Swedish twin studies [61] found that the genetic influence on mortality increases with age. In a genome-wide association analysis of 1320 English centenarians, Anastasia Gurinovich et al. [62] found a correlation between longevity variations and proteome signatures.

Since the discovery of α-synuclein (α-Syn) in the 1990s, many PD-related genes have been reported, and seven rare highly exonic single gene alterations, *LRRK2*, *SNCA*, *VPS35*, *PINK1*, *PRKN*, *GBA*, and *DJ-1*, and have all been shown to be associated with typical familial PD [63,64]. Molecular genetic studies of AD have shown that in the mode of inheritance, early-onset, EOAD is inherited as an

autosomal dominant trait, presenting familial Early-on-set, EOAD is autosomal dominant and familial, and the causative genes include the App gene on chromosome 21, PSEN1 on chromosome 14, and PSEN2 on chromosome 1; late-onset, LOAD has a relatively complex inheritance base, with a heritability of about 60 %–80 %, and is predominantly sporadic. There is significant genetic heterogeneity and racial differences [65].

2.6. Immunity and aging

One of the key factors of aging involves the change in some functions and structures of the immune system, one of which is the decline in immunity. Immune senescence causes inflammaging, a response often considered harmful and the root cause of most diseases in middle-aged and elderly people [66]. The concept of inflammaging was first introduced more than two decades ago by Franceschi et al. [67], who proposed aging as a chronic, sterile, and low-grade inflammatory condition. Due to the chronic low level of inflammation, the immune cells are constantly on alert, leading to decreased immune function or immune paralysis [68]. The immune system is a complex network of cells and proteins and is classified into innate and adaptive immunity; the synergy among them is a prerequisite for the proper action of the immune system. One of the factors of inflammatory aging is chronic stimulation of the immune system by viruses such as cytomegalovirus (CMV).

In recent years, immune dysfunction has been proposed to be one of the pathogenic mechanisms of AD, and a large number of genomics studies have shown that immune function-related gene loci are closely related to AD risk gene loci and are potential mechanisms for AD pathogenesis, these genes include triggering receptor expressed on myeloid cells 2 (*TREM2*), cluster differentiation 33 (*CD33*) [69], and genes coding for four transmembrane structural domains A subfamily (membrane spanning four domains), and the other four transmembrane structural domains. These genes include triggering receptors expressed on myeloid cells 2 (*TREM2*), Cluster differentiation 33 (*CD33*), and membrane spanning four domains subfamily A (*MS4A*). Under physiological conditions, microglia are activated by phagocytosis and Aβ clearance to exert neuroprotective effects in response to noxious stimuli. Once excessive Aβ exceeds the microglial processing capacity, microglia are over-activated, releasing a large amount of pro-inflammatory cytokines, and inducing and exacerbating chronic inflammatory responses, thus accelerating neuronal damage.

2.7. Senescence-associated secretory phenotype (SASP) and aging

Although cell cycle arrest is the hallmark of senescence, senescent cells also exhibit a wide range of additional associated phenotypic alterations [70]. Senescent cells undergo metabolic reprogramming, chromatin remodeling, and morphological alterations before secreting a complex concoction of mostly inflammatory chemicals known as the SASP [71]. It consists of several families of soluble (1L-6, 1L-7, 1L-13, etc.) and insoluble (e.g., collagens, fibronectin) substances that can influence neighboring cells by activating various cell surface receptors and associated signal transduction pathways, subsequently leading to the development of a various diseases. SASP mediates many biological effects of senescent cells and can enhance and propagate senescence through the autocrine/paracrine pathways [72]. One of primary roles of SASP is to communicate with various immune cells, including natural killer (NK) cells, macrophages, and T cells, to facilitate the removal of senescent cells [73]. However, unlike them, the expression of many secreted factors in SASP does not alter as cells senescence and evolve dynamically over time. This is even though several factors increase their secretion during senescence. SASP is also a dynamic developmental process as it is produced under different aging triggers, cell types, and environments [74]. Data suggest that once established, SASP is irreversible in most senescent cells. This also suggests that SASP is a more persistent feature of aging than a state of growth arrest [71]. SASP is also involved in wound healing and promotes tissue repair [75]. The effects of SASP on the body are complex, and persistent SASP causes chronic inflammation. The primary signaling pathways regulating SASP development include ERK1/2-Ribosomal S6 kinase 1, nuclear factor-κB, and mTOR pathways [76–78]. Many aging-inducing factors can activate SASP by regulating these signaling pathways, such as, DNA damage [79].

Decreased secretion of IGF-1 and neurotrophic growth factor in senescent astrocytes lead to decreased neuronal production or increased neuronal loss. Senescent astrocytes secrete SASP factor and IL-6, that activate microglia and limit the uptake of Aβ by microglia. SASP factor can disrupt endothelial cell tight junctions, induce leukocyte migration, and lead to the disruption of the blood-brain barrier. Disruption of the blood-brain barrier is accompanied with many neurological disorders, including epilepsy and multiple sclerosis (MS), as well as neurodegenerative diseases affecting the elderly, such as AD and PD [80].

2.8. Autophagy and aging

Growth, development, aging, disease states, and other activities are directly associated with autophagy, a gene-controlled, lysosome-dependent intracellular breakdown system that is a highly regulated and evolutionarily conserved catabolic process. Autophagy moves organelles and macromolecules like proteins to the lysosomes, where they are degraded. Based on the mode of transport, three categories of autophagy can be distinguished: chaperone-mediated autophagy, macroautophagy, and microautophagy. The procedure known as microautophagy enables cytoplasmic contents to enter the lysosome through an invagination or distortion of the lysosomal membrane. Chaperone-mediated autophagy can specifically phagocytose a large amount of cytoplasm and has high specificity. Key autophagy-related (ATG) proteins comprise the core autophagic machinery that controls macroautophagy [81]. Under normal growth conditions, macroautophagy protects cells by specifically degrading redundant or damaged organelles but also helps cells respond to extracellular and intracellular stresses. The three main kinases that regulate macroautophagy include Protein kinase A (PKA), AMPK, and mTORC1. PKA has also been demonstrated to activate mTORC1 indirectly by inactivating AMPK [82]. Altered or dysfunctional autophagy can lead to the accumulation of abnormal proteins or damage to organelles and ultimately to aging or aging-related diseases

[83,84].

The autophagy-lysosome pathway, which removes damaged mitochondria from AD neurons, is inhibited, leading to the accumulation of a large number of dysfunctional mitochondria. Oxidative damage and lack of cellular energy lead to an increase in mitochondrial autophagy, leading to an abnormal accumulation of Aβ and Tau proteins, resulting in synaptic loss and cognitive dysfunction, and autophagy is a key factor in the regulation of AD. Abnormal accumulation of Aβ in autophagic vesicles disrupts the maturation of autophagic vesicles and excessive accumulation of autophagic vesicles in dystrophic synapses, resulting in neurodegeneration and a decline in the number of neurons and glial cells. Mitochondrial autophagy also plays an important role in the regulation of PD. The formation of mitochondrial autophagosomes is inhibited by the formation of Lewy bodies in neuronal cells, characterized by abnormal deposition of α-syn. Low or high levels of mitochondrial autophagy can induce PD by promoting neuronal death [85]. Deposition of mutant huntingtin (mHTT) mutations in the cytoplasm causes neurotoxicity, resulting in neuronal degeneration and impaired neuronal function. Increased expression of mHTT activates the classical autophagy pathway PI3K/AKT/mTOR, which inhibits autophagy and aggravates the symptoms of HD.

2.9. The DNA methylation theory and aging

DNA methylation, an epigenetic mechanism in the mammalian genome, characterizes the presence of methyl groups in CpG dinucleotides; most CpG is usually in a methylated state. These dinucleotides are related to levels of gene expression and are typically located close to gene promoters. DNA methylation produces multiple layers of expression regulation, which influences insulator elements, chromatin conformation, and transcription factor binding sites [86]. DNA methylation follows the patterns of the human life cycle. DNA methylation has been found to change with age and occurs throughout the genome, being more pronounced at repetitive elements [87,88]. This phenomenon can promote aging and related diseases. Levels of DNA methylation in the blood of a newborn were shown to be lower than those in the majority of other age groups [89]; in the first year of life, the mean DNA methylation levels in the blood increased. The pace of this alteration varies even though overall DNA methylation in the genome rises with age and gradually declines later in life. In the early years, a higher rate of change is observed than later years and the location of these chromosomal alterations changes [90]. The epigenetic drift and the epigenetic clock are two phenomena that relate DNA methylation with aging. The epigenetic drift includes age-related genomic changes, whereas the epigenetic clock shows the association between DNA methylation and age [91,92]. Both these phenomena explain changes in DNA methylation with aging; the epigenetic clock has the potential to be a biomarker of aging because it can indicate functional epigenetic alterations often linked with aging in people. In addition to its role in aiding in X chromosome inactivation and allelic imprinting, DNA methylation also regulates gene expression by affecting the binding of transcription factors bind to histones. Altered DNA methylation may lead to certain aging-related diseases, such as degenerative diseases [93].

Methylation of DNA is the catalytic formation of 5-methylcytosine (5 mC) from cytosine in the genome under the catalytic action of DNA methyltransferase, using S-adenosylmethionine as a methyl donor. Research reveals that 5 mC can be oxidized to 5-hydroxymethylcytosine (5hmC) under ten-eleven translocation, and 5hmC is also a stable epigenetic marker. Hüls et al. [94] conducted a study on the association between brain DNA methylation and cognitive trajectory changes in 636 patients and found an aberrant DNA methylation of CLDN5, an important protein encoding the blood-brain barrier. This dysfunction of the blood-brain barrier caused by aberrant modification of CLDN5 may have an important role in the early cognitive decline of AD patients. The main pathological changes include the presence of large amounts of SNCA in the neuronal cytoplasm and the death of dopaminergic neurons in the substantia nigra densa. The level of DNA methylation is significantly increased in the cerebral cortex of patients with PD [95]. HD is a neurological disease of autosomal dominant inheritance, with *HTT* being the causative gene. The aberrant amplification of triple-codon CAG in the first exon of the gene leads to the pathogenesis of HD. DNA methylation is altered in HD mice striatal tissue, especially in genes related to neurodevelopment.

3. Aging and neurodegeneration

Aging is a process wherein the function of an organism decreases with the passage of time. It is accompanied by the accumulation of cognitive decline and physical damage, as well as an increased risk of developing neurodegenerative diseases. This significantly impacts the quality of life and increases the risk of death, and exerts a burden on families and society. Aging is an important risk factor for neurodegenerative diseases, accompanied by atrophy of the central nervous system, protein aggregation, and enhanced numbers of senescent cells in the brain [96]. Neurodegenerative diseases, like PD, AD, HD, MS, and amyotrophic lateral sclerosis, usually occur in the elderly population [97]. In one study, the hippocampus of a mouse model of early aging considerably expressed more amyloid precursor protein and overproduced amyloid beta (Aβ); both memory and learning abilities were decreased [98,99]. The total gray matter volume, cortical gray matter volume, and subcortical gray matter volume of the brain decrease with age. The cortical gray matter in the temporal, parietal, and frontal lobes also becomes thinner; brain atrophy also occurs [100]. AD typically characterizes neurodegeneration, most of which is sporadic and has an older age of onset than the genetic one. Its hallmarks include reduced synaptic connection and gradual, cumulative neuronal death are [101]. AD and aging are closely associated and aging may contribute to the development of AD by affecting immune system function and energy metabolic processes [102]. Inflammatory processes are associated with cellular metabolism. As people age, microglial function decreases; in fact, in the aging brain, microglia function is impaired, which leads to the activation of chronic neuroinflammation [69]. Senescent cells are transformed into pro-inflammatory mediators by SASP, and inflammation is a potential risk factor for AD [103]. Elizabeth P. Crowe et al. [104], showed that oxidative stress-induced senescence causes several transcriptomic changes in human astrocytes, including the enhanced expression of genes

related to inflammation, extracellular remodeling, and apoptosis resistance and the down-regulation of cell cycle-related genes and those related to nervous system development and differentiation. Microglia and astrocytes are present in large numbers in the brain and play an important role in conferring immunity in the brain. Senescent microglia increase the number of pro-inflammatory cells and senescent astrocytes are abundant in the frontal cortex of AD patients and upregulate genes related to pro-inflammatory cytokines. These are one of the causes of AD Aging leads to a decrease in mitochondrial energy function, and the uptake of glucose by neurons is reduced. This change leads to changes in the transduction of several signaling pathways that regulate energy metabolism; for instance, alterations in insulin signaling can lead to insulin resistance. The hallmark of PD is the loss of neurons in the dense region of the substantia nigra. According to reports, several SASP-related variables are upregulated in PD, along with the increase in serum IL-6 levels [105]. MS is a chronic, immune-mediated condition affecting the brain and spinal cord and is characterized by inflammatory demyelination, astrocyte proliferation, and neuronal and axonal loss [106]. The inducers of aging include ROS-mediated cellular DNA damage and mitochondrial dysfunction produced by oxidative stress. Neurodegeneration in progressive MS is caused by aging-related loss of function. To summarize, aging contributes in some way to neurodegenerative diseases.

4. TCM—A potential anti-aging treatment

For thousands of years, Chinese medicine has been dedicated to the study of anti-aging, with a purpose to achieve a long and healthy life. Many herbs have shown anti-aging effects and are effective in extending life expectancy and improving a healthy lifespan. TCM scavenges free radicals through three main ways. First, TCM can improve the performance of antioxidant system of the body by raising the levels and activity of superoxide dismutase, glutathione (GSH) peroxidase (GSH-Px), and other antioxidant enzymes. Second, herbal medicine can directly scavenge free radicals. The third approach is that herbal medicine can inhibit lipid peroxidation. Wang et al. [107] discovered that D (+)-galactose-induced learning and memory abilities of aging mice may be improved by oxymatrine derived from *Sophora flavescens*, which may be related to its antioxidant radical and lipid peroxidation effects. The natural medicine herbal epimedii is used to treat a variety of age-related illnesses, including cardiovascular conditions and neurological disorders. Icariin, the main component of epimedii, protects venous endothelial cells from oxidative damage, DNA damage, and -amyloid-mediated neurotoxicity [108]. Icariin and its derivatives may play beneficial roles as signaling regulators in various age-dependent diseases [109]. Shikai Yan et al. investigated the anti-aging effect of total flavones of epimedium (TFE) on rats by liquid chromatography-mass spectrometry metabolomics, and found the anti-aging property of TFE is through lipid metabolism and antioxidant effect [110]. Wai-Jiao Cai et al. examined the anti-aging properties of icariin by culturing type *Caenorhabditis elegans* N2 worms in a liquid medium using three different concentrations of icariin (low, medium, and high levels). Icariin extended *C. elegans* lifespan [111]. Ginsenoside Rg1 significantly shortens telomeres to delay hematopoietic stem cell senescence [112]. Signal

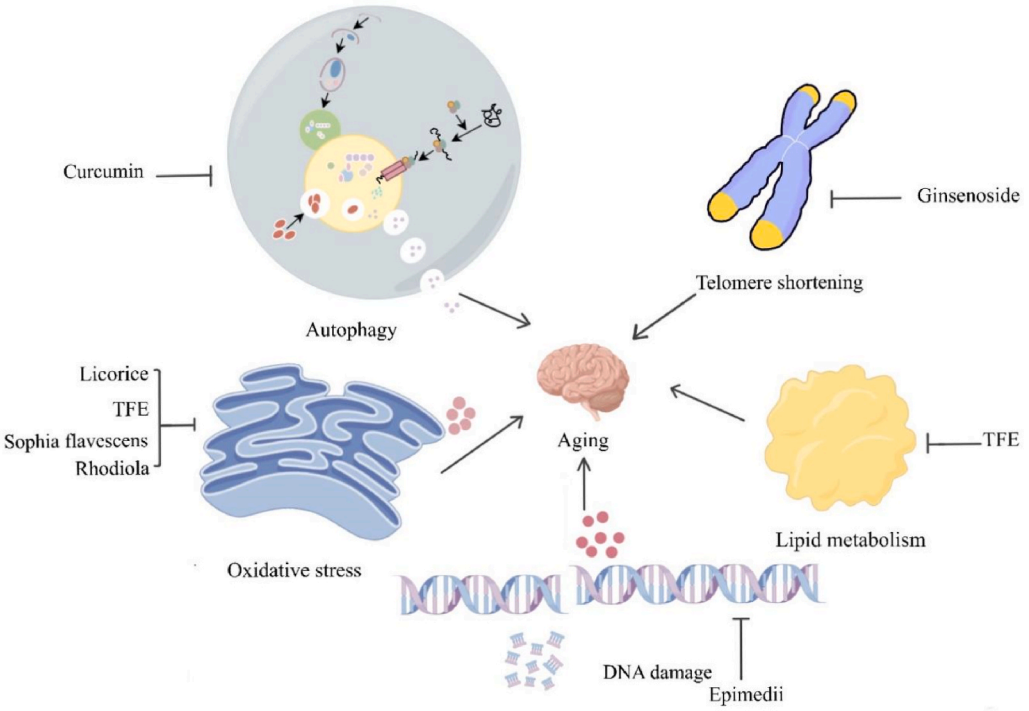

Fig. 5. Anti-aging pathways of TCM. Curcumin anti-aging is associated with autophagy, Epimedii anti-aging is associated with DNA repair, Licorice, Sophia fiavescens, Rhodiola anti-aging is associated with Anti oxidation. Ginsenoside anti-aging is associated with Prevents telomere shortening. TFE is anti-aging through lipid metabolism and antioxidant effect.

transduction pathways related to nutrient and energy metabolism control biological aging. Chinese herbs can be used to combat aging and prevent diseases related to aging by modulating AMPK activity. In fact, Yang et al. [113] found that the anti-aging function of *Damnacanthus officinarum* extract may be related to AMPK activation. Further, Rhodiola may extend life span and improve healthy lifespan by reducing oxidative stress [114]. Licorice is one of the most famous herbal remedies, which may also include antioxidants. Inés Reigada et al. showed that licorice prolongs the life span of *C. elegans* and reduces oxidative stress. Curcumin anti-aging is associated with autophagy and oxidative stress [115,116], which has a high safety profile. The anti-aging mechanisms of several common TCM are shown in the following figure (Fig. 5).

5. Conclusions

Aging is an outcome of the interaction of several factors. Over the past two decades, research on aging-related mechanisms has made great progress. Many aging-related hypotheses have been proposed; several aging signal transduction pathways and the related associations have been elucidated. However, the key mechanisms of aging need to be further investigated. Past studies have been based on mice, nematodes, and fruit flies, and clinical studies need to be further refined. Recent studies have shown that more diseases are closely related to aging; therefore, aging and aging-related diseases still deserve further research. The role of aging in neurodegenerative diseases makes it a potentially reliable target for treating neurodegenerative diseases and opens new treatment pathways for neurodegenerative diseases. With the increase in human life expectancy, the health of the elderly has become a global concern. In our future research, we will conduct more in-depth studies to investigate aging and related diseases and identify potential anti-aging drugs.

Data availability statement

Data sharing is not applicable to this article as no datasets were created or analyzed in the current study.

Ethics Approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Juanli Zhao: Writing – original draft. **Zhenjie Han:** Formal analysis. **Li Ding:** Formal analysis, Investigation. **Ping Wang:** Project administration, Supervision. **Xiutang He:** Supervision, Writing – review & editing. **Li Lin:** Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

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