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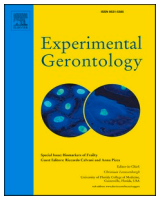

Review

Research progress on aging mechanism and drugs and the role of stem cells in anti-aging process

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ABSTRACT

There have been many discussions on longevity from ancient times to the present day. In the Laozi, it is said, "Heaven and earth are long and enduring because they do not arise from themselves, so they can live forever." In Zhuangzi - Zai You, it is also said, "Keep your mental peace, and your body will be healthy. Don't strain your body and don't consume your spirit to live a long life." It is clear that people attach importance to anti-aging and the desire for longevity.

Throughout human history, we have treated aging as an inevitable process, but with the development of medical science, we have become more aware of the various molecular changes in the human body. In an aging society, more people are suffering from age-related diseases such as osteoporosis, Alzheimer's disease, and cardiovascular disease, which has led to a search for anti-aging. However, by 'living longer' we mean not only living but also living longer in good health. The mechanisms of aging are still unclear and there is a great deal of interest and curiosity in how to combat aging effectively.

Some potential criteria exist for the determination of anti-aging drugs: the first criterion is the ability to exert life-extending effects in model organisms, preferably in mammals; the second criterion is the ability to prevent or delay several age-related diseases in mammals; and the third criterion is the ability to inhibit the transition of cells from a quiescent to a senescent state. Based on these criteria, the current anti-aging drugs often involved are rapamycin, metformin, curcumin and other polyphenols, polysaccharides, resveratrol, etc.

The most studied and relatively well-understood pathways and factors of aging are currently known to include seven enzymes, six biological factors, and one chemical, which mainly involve more than ten pathways such as Nrf2/SKN-1; NFκB; AMPK; P13K/AKT; IGF; and NAD.

1. Definition of aging

1.1. Definition of Chinese medicine

After a person has passed through the prime of life, he or she is bound to undergo a regular process of functional deterioration, rooted in the decline of the five organs. In terms of the laws of human life, the age of 40 is "decline". Ancient texts define 50 as 'old age', and when combined with modern definitions, it is generally defined as 'old age' between the ages of 60 and 65, a range that is considered to be defined with the times.

Senility first appeared in "It was the month of the old man when he was old, and he received a few sticks and a diet of cereal and porridge." The word "decline" refers to the decline in the functioning of the body, "old" refers to old age, and "senility" refers to old age and weakened energy.

1.2. Modern medical definitions

Aging goes hand in hand with development; it is an inevitable stage of human life.

Development refers to the development of the phenomenon of life, the change of an organism from the beginning of its life to maturity, and the process of self-construction and self-organization of the biological organism, including the continuous differentiation and refinement of the functions of the organ systems, continuous psychological and intellectual development and continuous acquisition and improvement of skills.

Aging refers to the progressive reduction of the body's physical and psychological adaptability to the environment and its gradual tendency

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to die. It can be divided into physiological aging and pathological aging. The former refers to the physiological degenerative process that occurs after maturity, while the latter is an age-related change due to various external factors (including various diseases).

Biologically speaking, aging is a spontaneous and inevitable process that occurs over time in living organisms. It is a complex natural phenomenon that manifests itself in the form of degenerative structural lesions and functional decline, with diminished adaptability and resistance. Physiologically, aging is seen as the developmental history of the individual, starting from the fertilized egg and continuing into old age. Pathologically, aging is the result of stress and strain, injury and infection, the decline in immune response, nutritional disorders, metabolic disorders, and the accumulation of neglect and substance abuse.

2. Mechanisms of aging

2.1. Theory of Chinese medicine

In Chinese medicine, there are different theories of aging, including the theory of weakness of the five viscera, the theory of weakness of the kidneys, the theory of weakness of the spleen and stomach, the theory of imbalance of yin and yang, the theory of liver depression and the theory of phlegm and blood stasis (Haiying et al., 2020). Aging begins with a deficiency of essence in the kidneys and progresses in the order of aging of the kidneys, liver, heart, spleen, and lungs, followed by a deficiency of essence in the five organs, a decline in the functions of the five organs, a deficiency in the production of qi and blood by the five organs, and then the appearance of aging, and finally the exhaustion of essence in the kidneys (Zhang, 2015).

2.2. Modern medical theory

Aging has been attributed to molecular cross-linking, free radical-induced damage, changes in immune function, telomere shortening, and the presence of senescence genes in DNA. The six commonly used theories of aging include the free radical theory, the genetic theory, the apoptosis theory, the immune theory, the telomere theory, and the mitochondrial theory. There are twelve common features of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (Lopez-Otin et al., 2023). In contrast, $p16^{INK4a}$, dysfunctional telomeres, and increased expression of senescence markers such as senescence-associated secretory phenotypes (SASP), a regulator of senescence, all accelerate senescence (He and Sharpless, 2017).

The pathways and factors that are currently known to be well studied regarding the mechanisms of aging include six enzymes and seven biological factors, which mainly involve more than ten pathways such as Nrf2/SKN-1; NFκB; AMPK; P13K/AKT; IGF; NAD; and mTOR.

2.2.1. AMPK

AMPK (Adenosine 5′-monophosphate (AMP)-activated protein kinase), or AMP-activated protein kinase, is a key part of bioenergetic regulation and is expressed in a variety of metabolically relevant organs. Genetics and pharmacology suggest that AMPK is required for the body to maintain glucose balance. AMPK responds to changes in intracellular adenine nucleotide (AMP) levels, and an increase in AMP/ADP/NAD+ activates AMPK, which in turn increases the rate of the catabolic (ATP production) pathway while decreasing the rate of the anabolic (ATP utilization) pathway, which can increase ATP (Carling, 2017).

AMPK can limit ROS(reactive oxygen species) production by increasing mitochondrial UCP2 expression, i.e. AMPK-dependent UCP2 upregulation is a compensatory mechanism that counteracts intracellular oxidative stress (Xie et al., 2008). UCP2 (Uncoupling protein2) is a mitochondrial inner membrane protein belonging to the uncoupling protein family, which eliminates the concentration of transmembrane protons on both sides of the inner mitochondrial membrane, thereby slowing down the oxidative phosphorylation process, preventing the normal production of ATP and preventing the accumulation of oxidative stress (Pierelli et al., 2017). UCP2 upregulation exerts a protective effect by reducing oxidative stress, inflammation, and cell damage (Forte et al., 2021). The main source of oxidative stress in cells is mitochondrial reactive oxygen species (mitoROS), and UCP2 is one of the main antioxidant proteins that control the maintenance of ROS levels in mitochondria (Tian et al., 2018).

Some of the pathways of the anti-aging effects of AMPK are shown in Fig. 1.

Activation of AMPK induces the expression of thioredoxin (Trx), a small, widespread protein whose main role is to act as a hydrogen-supplying enzyme in reactions, and Trx is an important antioxidant that reduces oxidized proteins through thiol-disulfide exchange reactions, controls protein function and maintains the reduced state of cysteine residues in proteins (Nagarajan et al., 2017; Flores et al., 2012). Trx is an important antioxidant that reduces oxidized proteins through thiol-disulfide exchange reactions, controls protein function, and maintains the reduced state of cysteine residues in proteins.

The antioxidant effect of AMPK can be mediated through activation of the Nrf2/SKN-1 signaling pathway and induction of antioxidant haem oxygenase-1(HMOX1/HO-1)gene expression via the Nrf2 signaling pathway.

2.2.2. Sirtuins

Sirtuins, known as ‘longevity proteins’, are a collective term for the Sirtuin family of proteins (silencing information regulatory proteins), which are essentially NAD-dependent deacetylases. The main role of Sirtuins is the deacetylation of lysine residues, which involves a two-step process:

1. Sirtuins cleatves NAD+ to NAM.
2. Transfer of the acetyl group from the substrate to the ADP-ribose fraction of NAD+ to form 2'-*O*-acetyl-ADP-ribose and deacetylated protein.

In mammals, seven members of the Sirtuins family have been identified: SIRT1 to SIRT7. The positions of the seven members in the cell are shown in Fig. 2. SIRT1, SIRT6, and SIRT7 are mainly located in the nucleus, SIRT2 is mainly found in the cytoplasm, and SIRT3, SIRT4, and SIRT5 are known as mitochondrial Sirtuins and are located in the mitochondrial matrix. (i) SIRT1 is involved in the regulation of cell cycle progression and self-renewal gene networks and is a conserved regulator of lifespan (Imperatore et al., 2017). (ii) SIRT2 neither induces nor

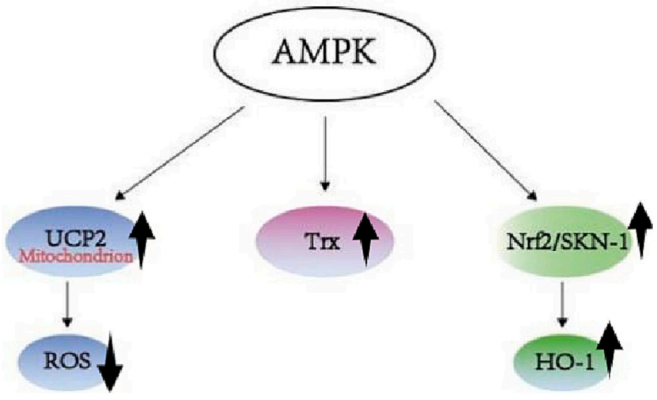

Fig. 1. Mechanism of AMPK anti-aging action.AMPK limits ROS production by increasing mitochondrial UCP2 expression; activation of AMPK induces Trx expression; and AMPK activates the Nrf2/SKN-1 signaling pathway and induces antioxidant heme oxygenase-1 gene expression via the Nrf2 signaling pathway.

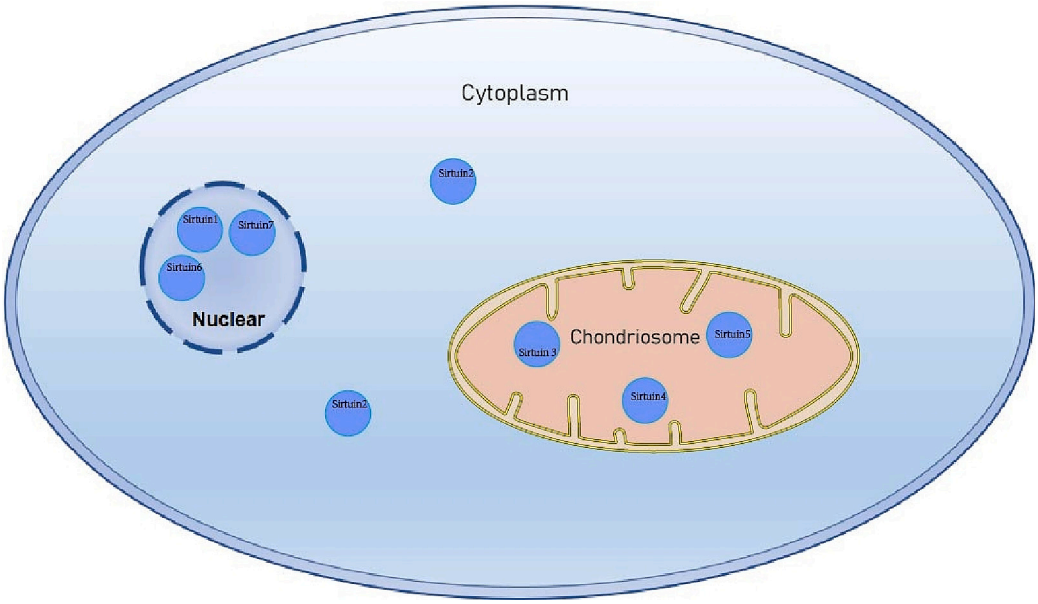

Fig. 2. Distribution of Sirtuins in the cell.SIRT1, SIRT6, and SIRT7 are mainly located in the nucleus, SIRT2 is mainly found in the cytoplasm, and SIRT3, SIRT4, and SIRT5 are located in the mitochondrial matrix.

prevents senescence, but is a protein that is abundantly expressed during senescence, so it can be used as a cellular senescence marker (Anwar et al., 2016). (iii) SIRT3 supports the maintenance of mitochondrial homeostasis by regulating the acetylation levels of its substrates (Zhang et al., 2020a), whereas mitochondrial homeostasis controls plasticity in stem cell and tissue maintenance during senescence (Brown et al., 2013). Since 2003, when SIRT3 was first reported to be positively associated with longevity, many subsequent studies have confirmed this result (Zhang et al., 2020a). SIRT4 is also a lysine deacylase that maintains enzyme quality in the leucine metabolic pathway and ensures complex formation, and is a key player in the regulation of insulin secretion and maintenance of glucose homeostasis during aging (Anderson et al., 2017).SIRT5 is a global regulator of lysine succinylation in mitochondria, regulating fatty acid oxidation and ketone body production (Rardin et al., 2013). SIRT6 is also a nuclear silencing regulatory protein with three main distinct enzymatic activities, including hydrolysis of long-chain fatty acid acyl groups, deacetylation and ADP ribosylation, involved in DNA repair, gene expression, telomere maintenance, nucleosome and chromatin remodelling, cell cycle, and maintenance of metabolic homeostasis (Chang et al., 2020). SIRT6 is thought to be at the crossroads of aging, regeneration, and epigenetics (Tabibzadeh, 2021). SIRT7 is the only sirtuin that is highly enriched in the nucleolus compartment and is directly or indirectly involved in regulating the aging process, such as maintaining homeostasis, preventing stem cell depletion, and participating in intercellular communication. SIRT7 is currently the least studied human sirtuin (Lagunas-Rangel, 2022).

2.2.3. NAMPT

Nicotinamide phosphor-ribosylltransferase (NAMPT) is a key enzyme in the control of nicotinamide adenine dinucleotide (NAD), catalyzing the conversion of nicotinamide (NAM) and phosphoribosyl pyrophosphate to β-nicotinamide mononucleotide (NMN) in the salvage pathway of NAD synthesis in mammals. NAD is involved in cellular redox reactions as an essential coenzyme and is a substrate for NAD-dependent enzymes (e.g. sirtuins). The NAD synthesis salvage pathway is shown in Fig. 3. NAMPT influences the activity of NAD-dependent enzymes through NAD biosynthetic activity, thereby regulating cellular metabolism (Garten et al., 2015). NAMPT affects the activity of NAD-dependent enzymes through NAD biosynthetic activity,

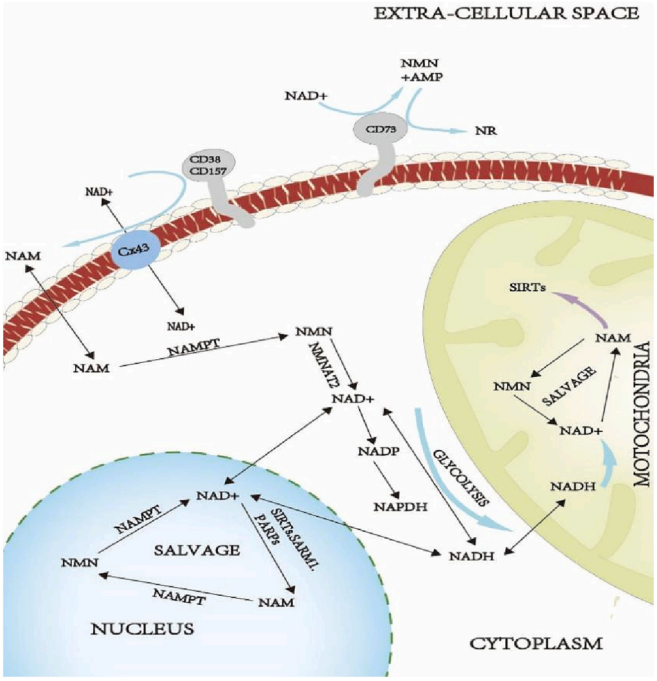

Fig. 3. Distribution and processes of NAD salvage pathway in cells. In mammals, the NAD salvage pathway is considered to be the most important NAD+ synthesis pathway for maintaining normal intracellular NAD+ levels. The majority of the NAD salvage pathway in cells is distributed in the nucleus and mitochondria. In the salvage pathway, NMN acts as the initiating molecule, which is derived from food intake and as a byproduct of NAD + -depleting enzymes such as NAD + -dependent protein deacetylase (Sirtuin), PARP, CD38, etc. First, NAM is catalyzed by NAMPT to produce NMN, and then NMN is catalyzed by NMNAT to produce NAD+.

thereby regulating cellular metabolism. In various metabolic disorders and during aging, NAMPT is lost and NAD levels are reduced. Brain NTP levels and mRNA expression levels of NADH reductase, cytochrome C oxidase, and citrate synthase are the main indicators of mitochondrial dysfunction (Luo et al., 2021). Overexpression of NAMPT can improve

senescence-related manifestations in late mesenchymal stem cells by regulating intracellular NAD levels, NAD/NADH ratio, and Sirt1 activity, while NAMPT can inhibit MSC senescence through the NAD-Sirt1 signaling pathway (Pi et al., 2019).

In humans, NMN (β-nicotinamide mononucleotide) is the most direct precursor of NAD, and NMN is also widely used in anti-aging studies. Supplementation with NMN can remodel the gut microbiota and extend the telomere length of PBMC in aging mice (Niu et al., 2021). NMN supplementation improves blood flow and increases endurance in aged mice by promoting a SIRT1-dependent increase in capillary density (Das et al., 2018). NMN also exerts neuroprotective effects through SIRT1/HO-1 signaling (Chen et al., 2020). NMN also exerts neuroprotective effects through SIRT1/HO-1 signaling.

2.2.4. P13K/Akt

PI3K (phosphatidylinositol-3-kinase) has both Ser/Thr kinase and phosphatidylinositol kinase activities, and Akt is a Ser/Thr protein kinase. The PI3K/Akt pathway can be considered a major regulator of cancer, in addition to being involved in important physiological processes such as brain metabolism, synapse formation, cell growth and survival, as well as regulating the cellular response to oxidative stress (Gabbouj et al., 2019).Lifespan appears to be associated with reduced activity of this pathway (Tabibzadeh, 2021).The PI3K/Akt pathway is currently regulated by natural drugs that regulate cell proliferation, migration, survival and apoptosis, such as Radix Astragali (RA) and Radix Astragali preparata (RAP) to alleviate the symptoms of aging (Gong et al., 2021). This pathway can also be regulated by ginsenosides to inhibit chondrocyte senescence and apoptosis (Zhang et al., 2020b).

2.2.5. mTOR

The mammalian target of rapamycin (mTOR) is a protein kinase with two complexes, mTORC1 and mTORC2. mTORC1 is usually the direct target of the clinically important drug rapamycin. mTOR induces cellular autophagy and promotes cellular degradation and recycling; mTOR is also involved in the transport and expression of nutrient transporter proteins; optimal activity of mTOR is necessary to maintain Optimal mTOR activity is necessary to maintain metabolic homeostasis, prevent disease and prolong life span (Szwed et al., 2021). In the central nervous system, mTOR inhibition by mTOR inhibitors such as rapamycin, caloric restriction, and ketogenic diets has been shown to prevent neurodegeneration and protect vascular, metabolic and mitochondrial function in the aging brain (Lee et al., 2018).

mTOR is closely related to the PI3K/Akt signaling pathway and is a key regulator of insulin β-cell and immune cell metabolism and function (Tuo and Xiang, 2018).

2.2.6. PKA

PKA, also known as cyclic adenosine phosphate-dependent protein kinase (cAPK), is dependent on the amount of cyclic adenosine phosphate in the cell and can transfer phosphate groups from ATP to serine or threonine residues of specific proteins for phosphorylation, thereby regulating the activity of target proteins. In addition to this, it is also important in energy homeostasis and memory formation as it is known to phosphorylate over 250 substrates (Postler, 2021). PKA is composed of two regulatory subunits and two catalytic subunits, with four subtypes of regulatory subunits (RIα, RIβ, RIIα, RIIβ) and three types of catalytic subunits (Cα, Cβ, Cγ) (Enns et al., 2010).

As an upstream inhibitor of AMPK, the reduced activity of PKA activates AMPK, as well as stress response proteins, maintains cellular homeostasis, increases the body's antioxidant action and slows the aging process (Salminen et al., 2016). As the accumulation of visceral fat is a high-risk factor for the development of age-related diseases, PKA is a potential inhibitory target for aging intervention as a gene signal that plays a key role in the regulation of metabolism and lipid storage (Enns and Ladiges, 2010).

2.2.7. FOXO

FOXO, also known as Forkhead Box O, is a family of transcription factors, which are the most primitive and fundamental anti-stress signaling molecules involved in metabolic regulation, cell survival and proliferation differentiation, tumor suppression, DNA damage repair and resilience (Tia et al., 2018). They are activated by phosphorylation, ubiquitination, methylation and glycosylation to form four types: FOXO1, FOXO3, FOXO4, and FOXO6, which modify and exert their transcriptional activity (Obsil and Obsilova, 2011). In humans, FOXO3, FOXO1, and FOXO4 and their downstream effectors are thought to be critical in the fight against aging and aging-related diseases (Morris, 2005). Free radical-induced damage is thought to be one of the causes of aging, and FOXO1 activates the expression of superoxide dismutase (SOD1), catalase (Cat) and glutathione peroxidase (Gpx1) in pancreatic β-cells (Zhang et al., 2016) and inhibits the expression of thioredoxin (Trxs)-interacting proteins to achieve protection against oxidative stress in β-cells (Kibbe et al., 2013). A hallmark of aging is an imbalance in proteostasis, which is maintained by FOXO through the removal of damaged and aggregated proteins from cells by the autophagy and ubiquitin proteasome systems (Webb and Brunet, 2014). Among other things, FOXO3 also regulates stem cell homeostasis, reduces inflammation and is seen as a potential target for intervention to promote healthy aging and extend lifespan (Morris et al., 2015).

2.2.8. IGF

Insulin-like growth factor (IGF) is characterized by a high degree of complexity, with multiple ligands, receptors and regulatory proteins, including three main ligands, IGF—I, IGF-II and insulin, with pleiotropic effects, mediating activation of PI3K-AKT through the association of surface receptor tyrosine kinases (RTKs), type 1 IGF receptor (IGF-11R) and insulin receptor (INSR) and MAPK, among other pathways (Osher and Macaulay, 2019). It is also involved in mammalian growth and metabolism, regulating cell growth, proliferation and migration differentiation (Annunziata et al., 2011).

2.3. Geroprotector

The term “Geroprotector” literally means “prevention of aging” and essentially means “stopping the aging process and thus prolonging life”. The main selection criteria for a potential Geroprotector are as follows: 1. The ability to extend life; 2. The ability to slow down changes in cells, molecules and other physiological biomarkers of the aging process, or improve them to a youthful state; 3. Low toxicity; 4. The target and mechanism of action of geroprotective agents should be conservative; 5. Geroprotector should improve the health-related quality of life of the treated person in terms of physical, psychological and social functioning; 6. They should have a significant protective effect on different modes of organisms; 7. May delay the progression of one or more age-related diseases; 8. May increase the resistance of organisms to adverse factors (Moskalev et al., 2017).

Based on the above criteria, a variety of drugs and compounds have been included as geroprotective agents, which are classified as chemical drugs and Chinese medicines and their extracts.

2.3.1. Metformin

As the most widely used oral hypoglycemic agent for the treatment of type II diabetes worldwide, metformin has been shown that it not only shows good effects on glycemic control, but also can delay aging and reduce the incidence of aging-related diseases (Soukas et al., 2019). It is generally accepted that the main hypoglycaemic effect of metformin is mediated by the inhibition of hepatic gluconeogenesis in a redox-dependent manner, and that inhibition of complex I is central to several mechanisms in the inhibition of hepatic gluconeogenesis (LaMoia and Shulman, 2021). Following the inhibition of complex I, the level of AMPK activation by AMP increases (Miller et al., 2013). Cellular uptake of metformin via OCT1, involved in metabolic, oxidative and

inflammatory processes, activates AMPK (Hawley et al., 2002), maintains SIRT1 activity when NAD levels are decreased (Cuyàs et al., 2018), down-regulates the insulin/IGF-1 signaling pathway (Sarfstein et al., 2013), Rag GTPase-dependent inhibition of mTORC1 (Kalender et al., 2010), etc. thereby improving nutrient signaling, enhancing intercellular communication, improving protein homeostasis, maintaining genomic stability, enhancing cell regeneration, attenuating cellular senescence, and regulating mitochondrial function through PGC-1α, thereby attenuating the features of senescence (Soukas et al., 2019).

2.3.2. Rapamycin

After its discovery, rapamycin was initially used as an antifungal and immunosuppressive agent, and as it continued to be studied, its role in cancer continued to expand. By inhibiting the evolutionarily conserved protein kinase mTOR, rapamycin promotes cell growth, proliferation and survival, and has anti-tumor activity (Julien and Roux, 2010). In 2009, Harrison et al. published in Nature that rapamycin could extend lifespan by inhibiting mTOR signaling, delaying cancer death and/or delaying the mechanisms of aging (Harrison et al., 2009). This is the first demonstration that mammals can extend their lifespan through pharmacology. In addition to having a significant effect on lifespan extension, rapamycin also has an impact on the delay or treatment of aging-related diseases (Ganesh and Subathra Devi, 2023). In the nervous system, rapamycin reduced the aggregation and accumulation of Aβ and tau, restored cerebral blood flow, improved vascular function, reduced microglia activation and improved cognitive behavior and memory in AD mice (Richardson et al., 2015). And Lin et al. showed that rapamycin could safeguard the integrity of the blood-brain barrier and protect cerebrovascular function in apolipoprotein Eε4 gene carriers (Lin et al., 2017). In addition, it was also shown that rapamycin-treated neurons exhibited high levels of cell viability and low levels of apoptosis in damaged neurons (Wang et al., 2014). In the cardiovascular system, rapamycin has been shown to slow or reverse cardiac age-related hypertrophy and improve aging ventricular function, significantly reduce specific inflammatory cytokines in cardiac blood, especially in cardiac tissue, and thus prevent local and systemic tissue damage in the heart (Flynn et al., 2013).

2.3.3. Aspirin

Aspirin (acetylsalicylic acid) is an old synthetic anti-inflammatory drug, but as research continues, other effects of aspirin have been discovered. As aspirin can block the production of PGE2 (prostaglandin E synthase) by irreversibly acetylating COX (cyclooxygenase), inhibiting COX activity (Dovizio et al., 2012) as well as inhibiting NF-κB activation (Chen and Stark, 2019), thereby limiting the progression of cancer. Aspirin also limits cancer progression by activating the AMPK pathway (Hammerlindl et al., 2018) and inhibiting the PI3K/AKT pathway (Uddin et al., 2010) which slows down the proliferation of cancer cells. Aspirin also has an anti-thrombotic effect by reducing platelet aggregation through both cyclooxygenase inhibition and thromboxane synthesis (Ornelas et al., 2017). Aspirin is also used in the treatment of cancer cells. In addition, aspirin is also used to prevent pre-eclampsia and psychoneurobiological disorders (Hybiak et al., 2020). Aspirin is also used to prevent pre-eclampsia and psychoneurobiological disorders. However, with research in the field of anti-aging. The protective effects of aspirin include the activation of AMPK/Akt/eNOS (Ou et al., 2012). Activation of AMPK improves endothelial function by counteracting oxidative stress in endothelial cells (Wang et al., 2010), increases the expression of the antioxidant MnSOD and promotes mitochondrial biogenesis (Kukidome et al., 2006).

2.3.4. Polyphenols (resveratrol, curcumin)

Polyphenols are the largest group of phytochemicals and act as a strong antioxidant, complementing and enhancing the function of antioxidant vitamins and enzymes in the body. Depending on the chemical structure of the glycosidic elements, polyphenols can be classified as phenolic acids, flavonoids, isoflavones, flavonoids, flavanols, anthocyanins and phenolic amides, etc. The presence of these polyphenols is highly diverse, being present in fruits, vegetables, cereals and various other types of foods, all with different degrees of antioxidant activity due to their different chemical structures (Tsao, 2010). They have different degrees of antioxidant activity due to their different chemical structures. Several other flavonoid polyphenols are important for human health, such as resveratrol and curcumin.

Curcumin is a yellowish polyphenolic compound extracted from the rhizome of turmeric, which has been shown to have a wide range of biological activities including antioxidant, immunomodulatory, anti-inflammatory, anti-tumor, antibacterial, neuro-, cardiac, renal and hepatoprotective effects (Amalraj et al., 2017). Due to the presence of curcumin's enol isomers (CurE), each curcumin molecule can reduce at least two free radicals and has excellent antioxidant activity at pH 7.4 (Barzegar, 2012). Curcumin also exerts its antioxidant effects by inhibiting the inflammatory signaling-mediated upregulation of Keap1, thereby activating Nrf2, which has an anti-oxidative stress effect, and by inhibiting the activation of NF-κB (Ren et al., 2019; Concetta et al., 2019).

Resveratrol is a polyphenol found naturally in grapes, peanuts, berries and many other foods that has many health-promoting effects, including beneficial effects on cardiovascular, inflammatory, neurodegenerative, metabolic and age-related diseases (Weiskirchen and Weiskirchen, 2016). It is also known for its antioxidant activity. In terms of antioxidant activity, resveratrol improves oxidative defense systems by down-regulating ERK activation and modulating the activity of ROS and antioxidant enzymes (Singh and Vinayak, 2017). It protects against ROS by inhibiting the iNOS-p38MAPK signaling pathway to scavenge free radicals (Fu et al., 2018). Resveratrol activates AMPK to improve mitochondrial function in vitro and in vivo (Price et al., 2012),and maintains the stability of FoxO1 and redox by phosphorylating FoxO (Yun et al., 2014),and regulates antioxidant gene expression through the Keap1-Nrf2 pathway and upregulates Sirt1 (Meng et al., 2018). For aging-related diseases, such as neurodegenerative diseases, resveratrol enhances the secretion of neurotransmitters and increases the production of new neurons, thus providing a protective effect (Sarubbo et al., 2015). In cardiovascular diseases, resveratrol improves oxidative stress by enhancing the production of NO (Rajapakse et al., 2011), improving oxidative stress and restoring Sirt1 activity (Sin et al., 2015).Overall, resveratrol exerts its anti-aging effects by inhibiting oxidative stress, suppressing inflammation, modulating mitochondrial function and regulating apoptosis (Zhou et al., 2021).

2.3.5. Polysaccharides

A wide range of natural polysaccharides, including plant, animal and microbial polysaccharides, are biomolecules with immunomodulatory, anti-tumor, anti-inflammatory and anti-aging effects (Weiskirchen and Weiskirchen, 2016).Angelica sinensis polysaccharide (ASP) not only regulates the Sirt/FoxO1 pathway (Peng et al., 2022) and down-regulation of p53 protein expression to increase telomere length and telomerase activity in HSCs (Zhang et al., 2013). It can also slow down the aging of endothelial cells by inhibiting oxidative stress and enhancing the phosphorylation of Akt/hTERT (Lai and Liu, 2015). LBPs (*Lycium barbarum* polysaccharide) can reduce ROS production and apoptosis, upregulate Bax protein, increase SOD and GSH enzyme activity levels, and attenuate the senescence of human lens epithelial cells (Qi et al., 2014). Astragalus polysaccharide (APS) also exhibits antioxidant activity, scavenging free radicals, improving oxidative stress, inhibiting lipid peroxidation and chelating Fe^{2+} in vitro (Pu et al., 2015). It also modulates telomerase activity (Jia et al., 2012). It can also modulate telomerase activity, and increase superoxide dismutase (Huang et al., 2013), and increase glutathione and antioxidant capacity. Overall, the anti-aging mechanism of polysaccharides is mainly through the regulation of telomeres and telomerase, scavenging free radicals, enhancing immunity, and improving oxidative stress (Xu et al., 2022).

2.4. The impact of stem cells on aging

Stem cells are a class of cells with an unlimited or immortal capacity for self-renewal, capable of producing at least one type of highly differentiated daughter cell; stem cells are a class of cells from the embryo, fetus or adult body that have the capacity for unlimited self-renewal and proliferation and differentiation under certain conditions, capable of producing daughter cells that are identical in expression and genotype to their own, and also capable of producing specialized cells that make up the tissues and organs of the body. Stem cells are the most primitive cells at the top of the cell lineage and are capable of differentiating to produce a specific tissue type in vivo. Multi-differentiation potential and self-renewal are the basic characteristics of stem cells. In adult organs, stem cells can repair tissues by continuously dividing, or be in an ecological niche of quiescence in a homeostatic state (Lin et al., 2021). They also can divide symmetrically to increase their number during development or divide asymmetrically to renew themselves and produce more progenitor cells of different differentiation types.

Stem cells are also currently being widely studied and used in the field of anti-aging. Throughout our lives, damage and repair are constantly taking place in our bodies and homeostatic balance is maintained, where tissue homeostasis is constantly monitored, and damaged or dead cells are repaired and replaced (Piper and Partridge, 2018). Stem cells play a vital role in this process, producing specialized cells in organs and tissues in response to injury and thus maintaining functional morphological stability (Kaur et al., 2018). In general, stem cells contribute to tissue repair following tissue injury through a variety of mechanisms, including immune regulation of the local microenvironment, differentiation into functional cells, secretion of various biological factors through paracrine secretion, immune regulation and intercellular mitochondrial transfer, with different adult stem cells having different functional properties (Lin et al., 2021). Different adult stem cells have different functional properties. The depleted stem cells still can self-renew and proliferate, but with an increased risk of mutational defects and a reduced proliferative capacity of stem cells (He and Sharpless, 2017). Therefore, with the advancement of stem cell technology, it can be applied to anti-aging, to improve the regenerative and repair capacity of the elderly, to delay aging and to prevent age-related diseases, etc. (Yu, 2018) The use of stem cells in anti-aging can be used to improve the regenerative and repair capacity of the elderly, delay aging and prevent age-related diseases.

Studies have shown that adipose-derived mesenchymal stem cells can accelerate mitochondrial autophagy, eliminate intracellular ROS and ultimately slow down the aging process (Lv et al., 2021). In the area of anti-aging of the skin, MSCs have been shown to improve skin condition by improving antioxidant activity, promoting cell proliferation and improving skin morphology (Jo et al., 2021). Studies have shown that the role of stem cells in tissue regeneration and repair is based on their ability to proliferate and differentiate, but also on their secretory function, which allows them to secrete growth factors and cytokines to regulate the tissue microenvironment (Yu, 2018). It has also been suggested that exosomes play an important role in the paracrine role of MSCs (Liang et al., 2014). Due to their unique miRNA, lnRNA and enzyme content MSC-exosomes possess a significant anti-aging effect, reducing senescent cells in tissues by inducing regeneration in senescent cells and reducing SASP (Ha et al., 2020).

3. Conclusion

Aging is an extremely complex process, with increasing age or excessive external stress and stimulation, resulting in increased damage and disorders in the body, although we can maintain homeostasis and compensate for damage by adjusting the expression of various factors in our body through proliferation and differentiation through various mechanisms we have ourselves such as scavenging free radicals and resisting oxidative stress, thus maintaining our normal function and morphology, but due to the proliferation and other However, as the number of gene replications increases, the loss of information during replication and the occurrence of mutations lead to the weakening of the repair capacity of cells, resulting in accelerated aging. However, as research continues, we have discovered a variety of methods that can delay or ideally stop aging, such as the use of synthetic anti-aging drugs, targeted anti-aging drugs, pharmacological treatments such as herbal drugs, and biological treatments such as stem cell therapy, of which these methods have all slowed the aging process to varying degrees, giving us great hope. However, it is still unclear whether there are specific molecular markers that can be used to measure or determine the aging process, and whether the stem cells used in stem cell therapy for the aging act by proliferation and differentiation to replace the originally damaged aging cells, or whether the action of stem cell exosomes stimulates the activation of stem cells that were originally present in the damaged area in a "dormant" state. "This may also be a question that we should explore in the future.

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CRediT authorship contribution statement

Yuxuan Zhang reviewed the literature and wrote the manuscript. Qingjuan Li, Yuhu Niu, Kaixin Wei conducted the literature summaries and analyses. Xiuwei Wang gave detailed guidance on article writing. Bo Niu, Li Zhang conducted the article direction establishment and thought guidance.

Declaration of competing interest

The authors report there are no competing interests to declare.

Data availability

No data was used for the research described in the article.

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