



Molecular Mechanisms Behind Organ-Related Aging and Regulatory Effects of Natural Therapeutics

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Abstract

Aging as a complex process is marked by physiological and functional deterioration, making the individual vulnerable to age-related diseases. Different organs experience unique aging processes that lead to conditions such as cardiovascular, cancer, metabolic, and musculoskeletal disorders. Understanding of these processes is essential to formulate effective interventions. To this end, plant-derived bio-actives are effective antiaging agents due to their specific mechanism of action. Phytochemicals in these plants possess antioxidant, anti-inflammatory, and senolytic activities that qualify them as good candidates for antiaging interventions. These molecules are also reported to act on important aging pathways such as immunomodulation, control of inflammation, reduction of oxidative stress, and senescence. The current review emphasizes the organ-specific mechanisms of aging and the role of certain plant constituents that have shown promising antiaging activity. By overviewing the natural interventions against aging mechanisms, this review provides a foundation for future research focused on using natural antiaging interventions involving phytochemicals.

Keywords Resveratrol · Aging · Genetics · Phytochemicals · Fisetin

Introduction

Aging is a continuous deterioration of the physiological state of the body and an increase in the susceptibility to age-related disorders. This biological process affects every organ and tissue within the body and is controlled by various genetic as well as environmental factors [1]. With the advancement in medical technology and the upgrading of living conditions, there is an increase in the average life expectancy. However, this has also increased the proportion of elderly people globally. According to WHO (World Health Organization), currently, there are 1.4 billion people who are aged above 60 years and this number is predicted to reach 2.1 billion by 2050 [2].

While the increased life expectancy is a notable achievement, it is also accompanied by a rise in age-related diseases such as cardiovascular diseases, arthritis,

cancer, and neurodegenerative disorders [3]. This aging population can be a source of significant economic burden, particularly for low-income countries, as more than 60% of the population will reside in low and middle-income regions by 2050 [2].

Certain key hallmarks are considered characteristics of aging [4]. These hallmarks of aging are further grouped into three categories namely Primary, antagonistic, and integrative hallmarks. Primary hallmarks are genomic instability, telomere shortening, epigenetic alterations, and loss of proteostasis. These primary hallmarks are known to disrupt normal cellular functions. Antagonistic hallmarks appear in response to the impairment caused by these primary hallmarks and include dysfunction of nutrient sensing, mitochondrial dysfunction, and cellular senescence. This leads to integrative hallmarks i.e., stem cell depletion and altered intercellular communication that have a direct impact on

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tissue homeostasis and function. These hallmarks collectively contribute to a decline in function with aging [3, 5].

Aging and its Related Disorders

The multifactorial process of aging affects individuals on multiple levels including cell, tissue, organ, and system levels. This results in the development of various age-related disorders including cardiovascular diseases, diabetes mellitus, arthritis, cancer, and neurodegenerative diseases like Alzheimer's disease and Parkinson's disease [6]. It was reported that 31.4% of the diseases are age-related [7]. The effects of aging hallmarks like chronic inflammation, oxidative stress, mitochondrial dysfunction, and cellular senescence are not isolated but rather highly interconnected and collectively accelerate the aging process [8, 9]. Among these age-related disorders, heart diseases are the leading cause of death causing 40% of all deaths followed by cancer and neurodegenerative diseases like Alzheimer's disease [10]. Aging causes pathological changes in the cardiovascular tissues causing hypertrophy, altered left ventricular diastolic function, and deteriorated endothelial function. Cellular aging causes a decline in adrenergic signal transduction and affects calcium regulation which contributes to reduced muscle strength of left ventricular [11]. Aging poses a risk of cancer because senescent cells accumulate with time and the upregulated expression of SASP leads to an inflammatory state that is conducive to cancer [12]. Age also affects the immune system thus compromising its ability to fight and increasing the risk of autoimmune diseases. The age-dependent changes in memory subsets, its decreased sensitivity to T-cell receptor stimulation, and the transformed cytokine secretion profile aggravate the situation [13]. Musculoskeletal disorders are common in elderly people. Among them, sarcopenia and osteoarthritis are common degenerative conditions causing sarcopenia and a decline in function. An increased number of ROS in the skeletal muscles leads to cell apoptosis while loss of muscle size causes loss of motor units and eventually impairment of muscle function [14].

The mechanistic target of rapamycin (mTOR) plays a central role in regulation of cellular metabolism and function through two different complexes: mTORC1 and mTORC2. Together these complexes influence the cellular growth but when the growth slows down, it regulates aging and other nutrient-sensing processes [15]. mTORC1, in particular is nutrient-sensing kinase and during nutrient-rich conditions its activations inhibits autophagy, whereas nutrient-deprived conditions induce autophagy via down-regulation of mTOR pathway [16]. Availability of certain nutrients especially amino acids regulates the mTORC1 recruitment by signaling the Regulator-Rag complex

through v-ATPase signaling. mTORC1 can also be activated by certain growth factors such as insulin and insulin-like growth factor-1 (IGF-1) via PI3K/AKT pathway. On the other hand, mTORC2 activates in response to insulin/insulin-like growth factor-1 (IGF-1) signaling pathway and activates many kinases downstream including the activation of Akt/PKB, a key regulator for cell survival. Impairment in its activation disrupts the metabolic and immune functions resulting in glucose intolerance and diabetes. Overall, the over activation of mTOR suppresses autophagy while inhibition of it can result in promoting autophagy [17]. *Sirtuins* are Nicotinamide Adenine Dinucleotide (NAD⁺) dependent class III histone deacetylases enzymes and play vital role in metabolism and aging [18]. When there is low nutrient availability, the NAD⁺ levels increase that cause the deacetylation of proteins like ATG5, ATG7, and LC3. A high level of NAD⁺ was also found to improve the biological processes of the body by DNA repair modulation, managing metabolic stress symptoms and by improving the mitochondrial function [19]. These proteins play a crucial role in autophagy. Moreover, SIRT1 when deacetylated can control genes involved in cellular stress response and autophagy by modulating certain transcription factors like p53 and FOXO3a [20].

Both these pathways including mTOR and *sirtuins* converge at regulating autophagy and aging. SIRT1 inhibits the mTOR signaling by interacting through upstream regulator TSC2. However, there is a feedback loop where the mTOR signaling can also modulate SIRT1 activity because

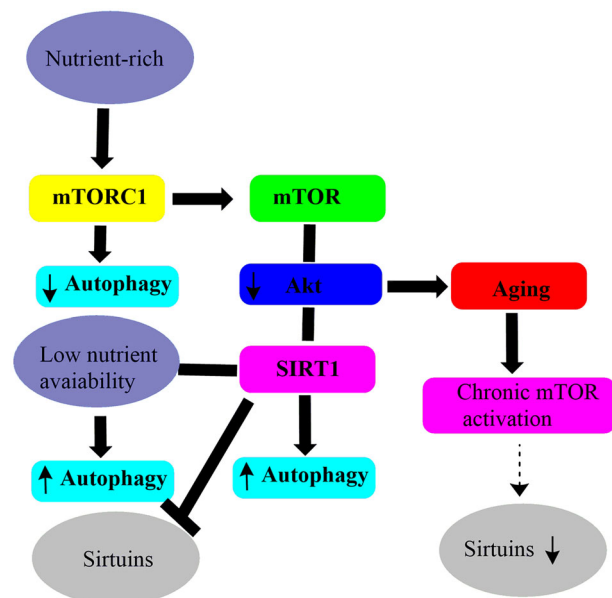


Fig. 1 Nutrient-rich conditions, mTORC1 activation leads to increased mTOR signaling and inhibition of autophagy. While under low nutrient conditions, SIRT1 is upregulated that suppresses mTOR signaling and increased autophagy. Moreover, SIRT1 negatively regulates mTOR activity and facilitates autophagy

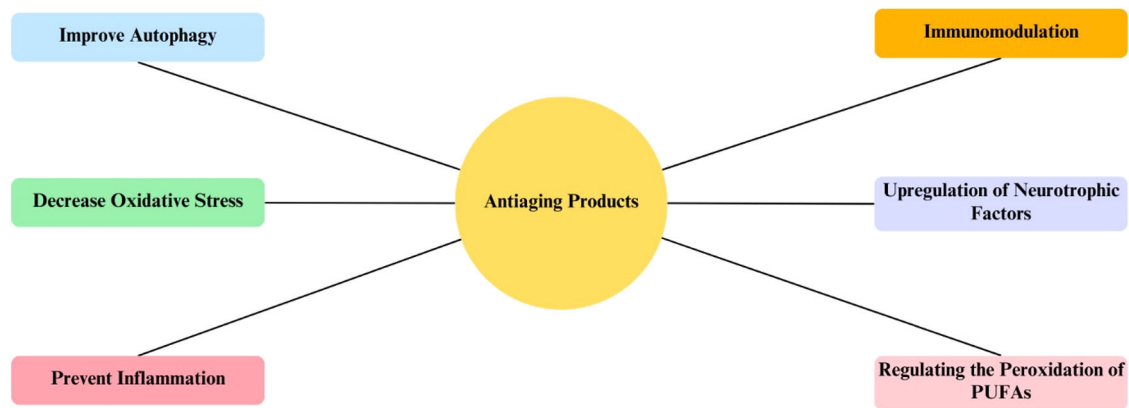


Fig. 2 Targets of antiaging products

its inhibition upregulates SIRT1 expression and deacetylase activity as depicted in Fig. 1 [19]. When there is chronic prolonged activation of mTOR and compromised activity of sirtuins, it results in the gradual accumulation of damaged cellular content causing age-associated conditions [21]. For instance, Natural alkaloids such as berberine and lycorine modulate signaling pathways like PI3K/Akt/mTOR (PAMT) resulting in downregulation of mTOR pathway, playing a role in age-associated diseases [22].

Natural Anti-Aging Products as Treatment Against Different Body Organs

Aging processes are intricate and render anti-aging a very difficult field. The multifaceted process of aging affects multiple physiological functions, making antiaging interventions complicated and challenging. The objective of the field is to extend the life span as well as to live a healthy life for a long time. Several approaches are under exploration to target the biological hallmarks of aging. These include pharmaceutical interventions and drug therapies like the use of senolytic drugs that are capable of eliminating the senescent cells from the body. Dasatinib and Quercetin are some of the drugs that have been effective in clearing the cells that have ceased to divide and are responsible for aging [23]. Mitochondria-directed antioxidants such as SkQ1 and MitoQ have been tested in efforts to lower oxidative damage induced by mitochondria dysfunction [24]. Other types of antiaging interventions that aim to address other aging hallmarks involve metabolic manipulation, cellular reprogramming, telomere re-activation, stem cell therapy, and autophagy stimulation. Lifestyle interventions in the form of caloric restriction, stress relief, and physical exercise are also found to contribute to healthy aging and longevity [25]. While advancements have been made with drug and lifestyle treatments, most of these antiaging methods have certain challenges and risks. Senolytic drugs eliminate the senescent

cells but their use in the long run is a concern because they can alter the equilibrium of cellular repair and immunity. Mitochondrial-targeted antioxidants can interfere with intrinsic reactive oxygen species (ROS) signaling as well. Further, metabolic modulation and cellular reprogramming, such as seen in telomere reactivation and stem cell therapy, carry the possibility of tumorigenesis along with other unforeseen consequences [24, 26].

Although there is considerable potential in these interventions but they are accompanied with notable risks such as impaired immune regulation and tumorigenic potential. These limitations urge the researchers to explore safer and more sustainable approaches-such as plant-based antiaging agents. Being antioxidant and anti-inflammatory, bioactive compounds of certain plants offer a holistic alternative to synthetic interventions with minimum harmful side effects while promoting healthy aging [27].

Natural products are found to prevent aging and enhance quality of life [28]. Most of these compounds work by improving autophagy, decreasing oxidative stress, preventing inflammation, and regulating amino acid metabolism [28, 29]. Other possible mechanisms include improved immune function, upregulation of neurotrophic factors, and regulating the oxidative degradation of polyunsaturated fatty acids (PUFAs) [30]. The targets of antiaging products are depicted in Fig. 2.

Explained below are the physiological changes and their mechanisms that are accompanied by aging in a few of the organ systems and natural products that have been used to target them.

Brain

The major morphological feature of brain aging is alteration in brain shape and anatomy as it undergoes atrophy resulting in cognitive deficit, and reduced motor function [31–33]. However, this organ-level change starts at the cell

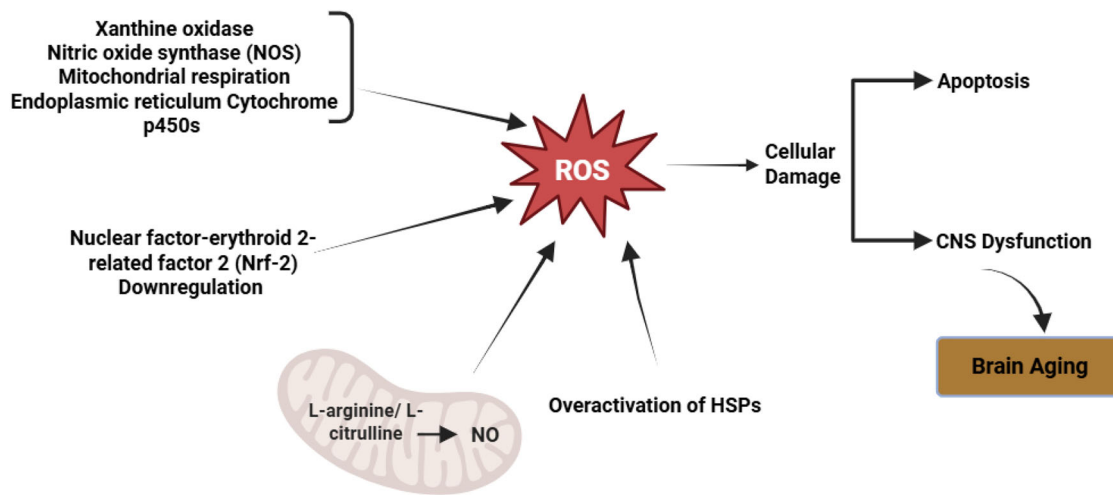


Fig. 3 Oxidative stress underlying brain aging

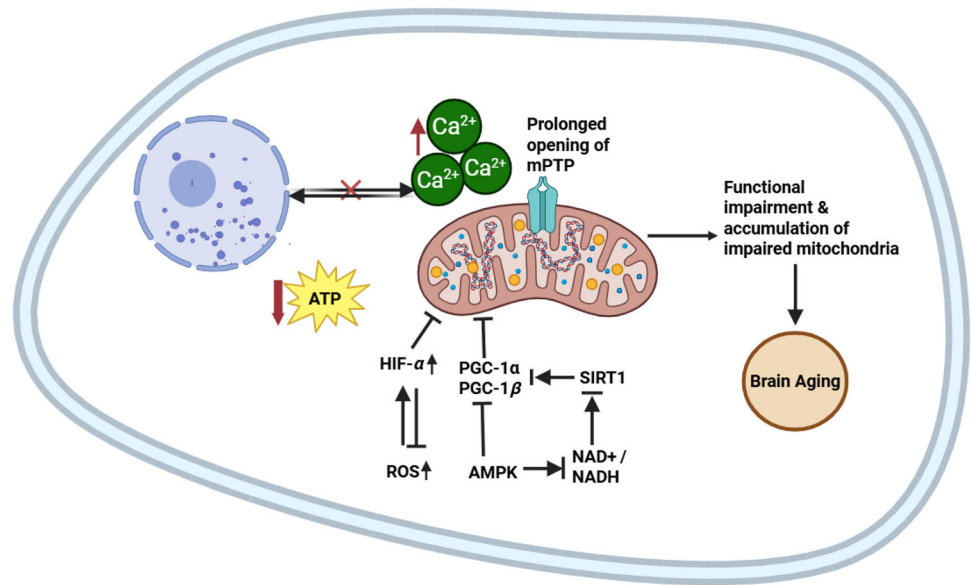
level with the slowing of the metabolic process and ischemia [34–36]. These changes manifest at the tissue level as demyelination [37, 38], and tissue softening due to the degeneration of Gray matter and white matter [39–41].

The hallmarks of aging in brain cells that are identical to other cells include accrual of oxidative damaged molecules, compromised regulation of neuronal Ca^{2+} homeostasis, dysregulated bioenergetics, stem cell exhaustion, poor waste disposal mechanism, and inflammation [42, 43]. The metabolic pathways involved in brain aging are as follow. In mammals, ROS production is carried out by xanthine oxidase, nitric oxide synthase (NOS), mitochondrial respiration, endoplasmic reticulum, and cytochrome p450s. Free radicals like nitric oxide ($\text{NO}\cdot$), superoxide anion ($\text{O}_2^{\cdot-}$), and hydroxyl radical ($\text{HO}\cdot$) are subcategories of ROS with unpaired electrons. Several enzymatic and non-enzymatic systems, collectively called antioxidants, maintain the homeostasis of ROS in the cell [44–46]. The transcription factor, nuclear factor-erythroid 2-related factor 2 (Nrf-2) controls the transcription of antioxidant enzymes including glutathione reductase (GR), catalase (CAT), glutathione (GSH), and superoxide dismutase (SOD) that neutralize the ROS production. Moreover, elevated intracellular levels of Ca^{2+} , L-arginine, and L-citrulline generate NO [45]. With aging, ROS generation increases while antioxidant activity decreases resulting in a redox imbalance. Evidence shows that this oxidative stress in the brain is responsible for protein and lipids modification that results in brain dysfunction while NO-dependent oxidative stress causes apoptosis in motor neurons (Fig. 3). Heat-shock proteins (HSP) are the body's intrinsic defense mechanism against oxidative stress and protect against neuronal damage and protein denaturation. These HSPs are activated in response to certain environmental stressors and drugs but their overstimulation is detrimental [47–49].

Mitochondrial oxidative phosphorylation serves as the major source of ATP in axonal transport. For a smooth process of oxidative phosphorylation, there is a functional interaction between mitochondrial DNA (mtDNA) and nuclear DNA. The lack of this functional communication can result in low production of ATP. Low levels of ATP disturb axonal transport and cause axonal degeneration. Mitochondrial regulation is moderated by Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) and PGC-1 β that react to the variations in levels of AMP/ATP and NAD^+/NADH ratio [50, 51]. Increased oxidative stress levels are controlled by Hypoxia-inducible factor 1 alpha (HIF-1 α) which reverses mitochondrial damage and decreases ROS levels [52]. Mitochondrial damage results in prolonged mitochondrial membrane permeability transition pores (mPTP) opening and Ca^{2+} ions homeostasis imbalance which are important for apoptosis [53]. This leads to functional impairment of mitochondria and subsequent accumulation of impaired mitochondria which ultimately contributes to brain aging as depicted in Fig. 4.

Researchers have been working on natural products that could be used as neuroprotectants against brain aging. Polyphenols inhibit enzymes like cyclooxygenases and lipoxygenase 15 that are involved in inflammation responsible for certain neurological disorders [54]. Reference [55] reported the anti-aging potential of a natural dietary polyphenol, curcumin, and described that curcumin protects the brain by modulating the glial neuroprotection, targeting different proteins, and functioning as an antioxidant, and anti-inflammatory agent. Reference [56] was demonstrated that curcumin reduced brain inflammation in diabetic mice by lowering the level of malondialdehyde (MDA) level and increasing activity of increasing the activity of SOD. Moreover, it downregulated the Bax and poly (ADP-ribose) polymerase expression that suppressed the apoptosis in the cerebral cortex, contributing to

Fig. 4 Mitochondrial dysfunction contributing to brain aging



the amelioration of cognitive impairment [57]. Curcumin treatment suppressed the LPS-induced inflammatory response by inducing anti-inflammatory mediators and by down-regulation of the JAK/STAT pathway [58, 59].

Another way to prevent degenerative effects in the brain was described by [60] which included regulating gut microbiota using tea polyphenols. The study reported that tea polyphenols may be used as potential neuroprotective agents. Epigallocatechin gallate (EGCG) is the predominant catechin found in tea. It was found that it can pass the blood-brain barrier and affect neural differentiation. It suppressed the triggering of extracellular signal-regulated kinase cascade (ERK) along with causing a shift in enzyme activity that resulted in increased activity of α -secretase and inhibition of β - and γ -secretase [61]. Other components present in green tea include theanine and arginine which have proved to have anti-stress effects. Since stress accelerates brain aging, green tea could be used as a potential suppressor of brain aging [62, 63].

Polyamines (spermine & spermidine) were administered to senescence-accelerated mice that lowered the extent of Malondialdehyde (MDA) formation— a result of peroxidation of polyunsaturated fatty acid. Moreover, it upregulated the expression of neurotrophic factors, improved autophagy, and prevented apoptosis [64]. Research by [65] revealed the anti-aging effect of *Chrysanthemum indicum* Linne (*C. indicum*) with a possible underlying mechanism of decreased oxidative stress and apoptosis.

Liver

The liver plays a major role in homeostasis via the control of energy metabolism. Any dysregulation would contribute

to aging and ailments associated with age like insulin resistance and diabetes mellitus [66, 67]. This organ contains four cell types including hepatocytes, hepatic stellate cells (HSCs), Küpffer cells (KCs), and liver sinusoidal endothelial cells (LSECs). The cellular level changes are subsequently integrated at the organ level. Hepatocytes, playing the central role, control the synthesis of plasma proteins (fibrinogen & albumin), bile salts, and cholesterol. They are also involved in the regulation of carbohydrate metabolism & drug metabolism. These biological processes are regulated through mechanisms such as gene transcription, mitochondrial respiration, and protein synthesis [68–70].

As aging progresses, the cellular demand for ATP exceeds supply due to a decline in mitochondrial numbers, which consequently slows down the basal metabolic rate [71, 72]. Hepatocytes decrease in number while there is an increased number of polyploid hepatocytes. The aged hepatocytes produce an increased number of cytokines which results in higher oxidative stress and ROS production. This results in the accumulation of lipid peroxidation products, activation/inactivation of various signaling pathways, and DNA lesions (Fig. 5). Lipofuscin, an insoluble protein aggregate, accumulates due to elevated oxidative stress. Its buildup in lysosomes disrupts their function, ultimately leading to impaired autophagy [64, 73–77].

Research has shown that several natural compounds can slow down aging processes by affecting important cellular mechanisms [78]. For example, chitosan oligosaccharide (COS), a natural polysaccharide, demonstrated significant anti-aging properties when tested on mice with accelerated aging [79] found that COS effectively reduces oxidative stress, improves immune function, and strengthens the body's antioxidant defense system [80] revealed that COS

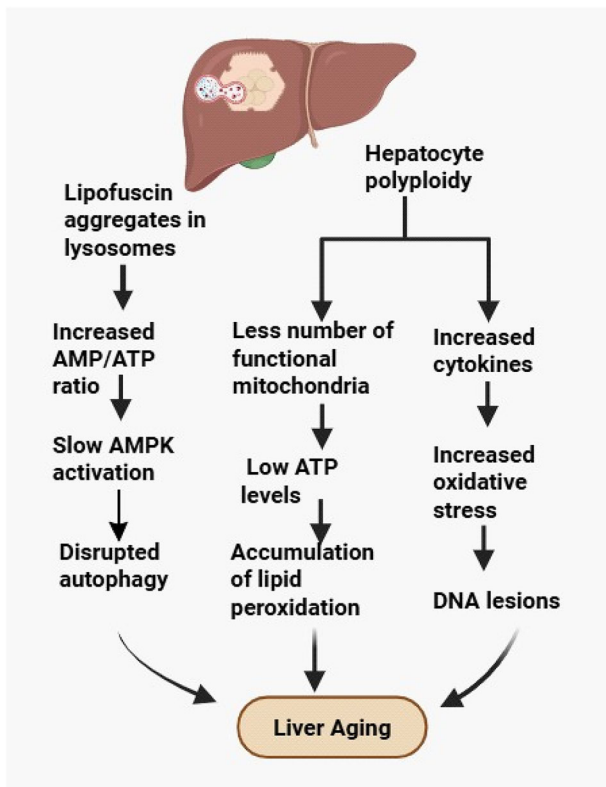


Fig. 5 Mechanisms involved in liver aging

mainly prevents age-related liver impairment through activation of the Nrf2 pathway. Activation of the Nrf2 pathway increases antioxidant gene expression such as NQO1, HO-1, and CAT which quenches toxic free radicals. Walnut extracts have also been found to be potential solutions to aging. Walnut kernel and walnut septum extract both significantly reversed liver and brain damage induced by D-galactose in mice. These extracts act by stimulating the Nrf2 pathway to control concentrations of free radicals, while phenolic constituents improve mitochondrial function and combat inflammation through NF- κ B downregulation [81]. Further studies by [11] established other useful natural substances with antiaging potential. *Aralia taibaiensis*, which is a medicinal herb, was shown to reverse aging impacts on several organs, mainly the liver. In the same manner, matrine isolated from *Sophora flavescens* effectively counteracted the overexpression of liver aging-related genes such as CDKN2D (P19), P16, and P21. These results cumulatively identify the promise of natural compounds in counteracting liver deterioration with aging via various synergistic mechanisms. In addition, it lowered the expression pattern of IL-6 and IL-1 β [82]. *Lycium ruthenicum* Murr. (LR), an edible berry, greatly controlled the levels of age-related serum markers, and amino acid metabolism and inhibited inflammation in aging induced by D-galactose in mice [30].

Skin

Skin, the initial protection barrier of the human body, is also associated with homeostasis maintenance [83]. As it is the outermost organ of the body, skin is targeted by intrinsic along with extrinsic factors. The intrinsic factors mainly comprise genetics and specific conditions like Diabetes and vascular diseases. On the other hand, extrinsic factors include environmental factors like exposure to sunlight and pollution [84]. Collectively, both factors contribute to the loss of structural integrity, wrinkles, elastosis, and pigmentation [85]. Skin aging is a complex process and lacks definitive universal biomarkers, especially genetic factors. However, the core molecular mechanisms responsible for skin aging include oxidative stress and autophagy [83].

Exposure to the sun is a key contributing factor that eventually results in skin deterioration and aging. Prolonged and repeated exposure to sunlight especially to ultraviolet (UV) radiations has proved to be age-inducing. The penetration of UV is dependent on the wavelength of its radiations. UVA penetrates the dermis while UVB only penetrates the epidermis layer of the skin. UVB radiations induce the development of cyclobutane pyrimidine dimers and other photoproducts. These changes disrupt the transcription and translation process primarily in the tumor suppressor gene (P53) thus inducing regular cell cycle modification. Ultimately, this results in skin tumors (Fig. 6). ROS generation, an intrinsic factor, is a by-product of aerobic mitochondrial metabolism. The extrinsic factor inducing ROS production is ultraviolet radiation (UVA), a main component of sunlight. ROS generation due to UVA causes DNA damage and activates the mitogen-activated protein kinase (MAPK) pathway. This in turn activates activator protein-1 (AP-1) and upregulates the expression of metalloproteinases (MMPs) as depicted in Fig. 6 [86, 87].

MMPs can restrict collagen synthesis and disintegrate dermal connective tissues [85, 88]. Overproduction of ROS is also responsible for triggering some inflammation pathways such as IL-1, IL-6, IL-3 and TNF- α . Constant release of the inflammatory cytokines leads to inflammation and ailments associated with age [89, 90]. Additionally, Autophagy is starvation-induced self-digestion that is used for degrading damaged cellular components [91, 92]. Autophagy declines with age and causes cellular senescence resulting from abnormal cellular homeostasis [93, 94].

To retard this physiological deterioration, natural neuroprotective products have been an area of interest in biogerontological research. In this respect, several vitamins, minerals, and micronutrients occurring naturally have proved to possess the potential. Vitamin C, an antioxidant, stimulates collagen synthesis, prevents UV-induced mutilation, enhances immunity, and possesses anti-inflammatory activity [95]. Vegetables and fruits that are available

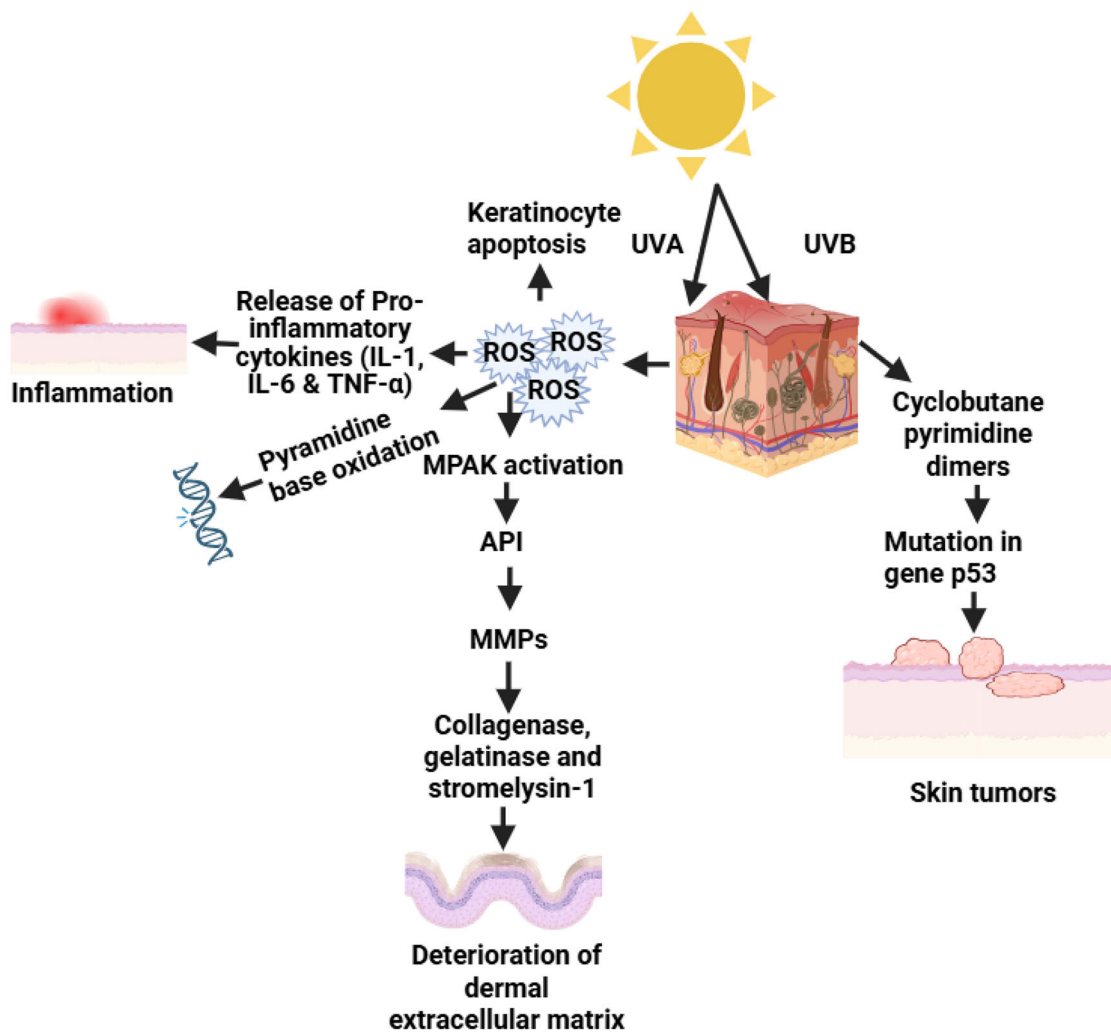


Fig. 6 Mechanisms involved in skin aging

throughout the years are natural sources of vitamin C. Some of these include Potatoes, Kiwi, strawberries, broccoli, and citrus fruit [96]. An increase in skin elasticity and smoothness was reported when treated with topical application of Vitamin C serum [97].

Other natural antioxidants, Vitamin E & A are found in nuts, grains, olive oil, and carrots. References [98, 99] documented that leaf extract of *Ginkgo biloba* prevents apoptosis and can be used against skin aging. Other medicinal plants that have been proved to combat skin aging include *Allium sativum*, *Aloe vera*, *Silybum marianum*, and *Amaryllideae* family [27, 100–102].

Immune System

Aging causes immunosenescence i.e., modifications in the immune function. With time, some functional aspects of the immune system become overactive while others deteriorate

or remain unchanged [103]. This includes alterations of both the innate and adaptive immune systems. The changes mainly include accumulation of potentially senescent immune cells, dysfunction of granulocytes, increased level of memory cells, and decreased number of immature T-lymphocytes. Along with these changes, persistent low inflammation in older people is also a contributing condition [103–105].

Lymphocytes (T and B cells) are the components of the adaptive immunity. However, with aging, the abundance and effectiveness of T cells decreases [106, 107]. With the rise in ROS, there is a decrease in ZAP70 phosphorylation, alteration in Ca^{2+} mobilization, and decline in T cell receptor (TCR/CD3 expression. This subsequently inhibits the TCR signaling as shown in Fig. 7. Elevated levels of $\text{TNF-}\alpha$ in plasma downregulate the CD28 expression leads to functional decline of the nuclear factor of activated T cells (NF-AT) and transcription factors NF- κB [108–110]. There is upregulation of Dual-specificity

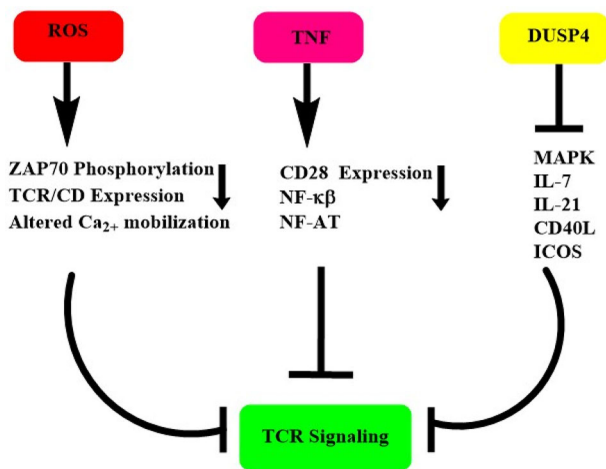


Fig. 7 Age-induced changes in T cells

phosphatase (DUSP4) which inactivates phosphorylation of MAPK and limits T cell activation. High levels of DUSP4 decrease the production of Interleukin-4(IL-4), Interleukin-21(IL-21) and Interleukin-17A (IL-17A) along with the downregulation of CD40 ligand now known as CD40L and inducible T cell co-stimulator also called as ICOS. This not only results in defective TCR signaling but affects the T cell dependent B cell response negatively [111–113].

B lymphocytes play a significant role in immunosenescence as they start to decrease in number and Proinflammatory B cells rise due to changes in hematopoiesis in bone marrow (BM). During aging peripheral B cells release very high amounts of TNF- α which leads to increased production of insulin-like growth factor binding protein 1 (IGFBP-1) [114–116]. Moreover, with age, repeated exposure to the same antigen reduces the quantity of switched memory B cells [117]. Tissue-resident B-lymphocytes respond to inflammation and begin to proliferate and play a role in triggering the Recombinant NLR Family, Pyrin Domain Containing Protein 3(Nlrp3) inflammasome, a controller of inflammation associated with age. These all changes contribute to the diminished ability of B cells to generate an antibody response [118].

The alteration in immune function leads to rise in inflammatory cytokines and subsequent high risk of developing age-related pathologies such as cancer, arthritis and diabetes [104]. Researchers are working on finding natural products/nutraceuticals that could be helpful in the declining efficiency of immune system. Evidences suggested the use of polyphenols, for targeting senescent cells (SC) by impairing their development and accumulation. Moreover, the use of polyphenols in combination with probiotics is another nutraceutical approach against age-related diseases [104, 119]. Polyphenols extracted from *Cassia auriculata* (CA) were found to have immunomodulatory potential [120]. Reference [121], in a case study,

reported lymphocyte growth and decline in inflammatory levels when Vitamin C, Vitamin E, Vitamin D, Zinc and nigra were used in combination. The study suggested the use of these nutraceuticals in low dosage for an extended period to decrease inflammation and avoid the risk of age-associated diseases. Dietary intake of fruits and vegetables increases the phenotype of innate immune cells and modulates immune response [122].

Micronutrients like Selenium, Copper, Iron and Zinc play a dynamic part in healthy aging of the immune system. Supplementation of Zinc has been reported to increase T-cell production, boost in natural killer cell toxicity and lower the incidence of infections [123]. Deficiency of copper and iron causes abnormally low levels of neutrophils and limited bactericidal activity of lymphocytes, respectively. Selenium exhibits antioxidant activities and controls redox status along with eliciting humoral and cell-mediated immune responses [124].

Plant-Derived Compounds as Safer Anti-Aging Strategies

Resveratrol

Bioactive compounds like polyphenols are being extensively explored for their potential health promoting effects. Resveratrol, a polyphenolic compound of natural origin, has shown numerous bioactivities including antioxidant, anti-inflammatory, immunomodulation and a potential to prevent and control age-related diseases [125–127]. This phenolic compound has three hydroxyl groups at positions 3, 5, and 4' with redox properties and a potential for delocalization of electrons. Out of which, hydroxyl group at the 4' position is the most reactive group and contributes majorly to their antioxidant potential. It also exerts antioxidant activity by metal ion chelation and fenton reaction and reduces ROS indirectly. Its unique chemical structure plays an intricate role in facilitating its specific interaction with certain cellular proteins like SIRT1 involved in aging. SIRT1 is a NAD⁺-dependent deacetylase that binds to resveratrol through its N-terminal domain (NTD) making an interaction between SIRT1 and its substrate [128]. Two molecules of resveratrol can bridge between NTD and its substrate while another one can simultaneously interact with its catalytic domain. The conformational changes in SIRT1 caused by binding enhance its deacetylase activity due to tighter substrate binding. This allosteric activation is substrate-specific and is influenced by presence of certain amino acids positioned adjacent to acetylated lysine. The ability of resveratrol to stabilize and activate SIRT1-substrate complex promotes mitochondrial biogenesis and mimics calorie-restriction- a well-known antiaging intervention [129].

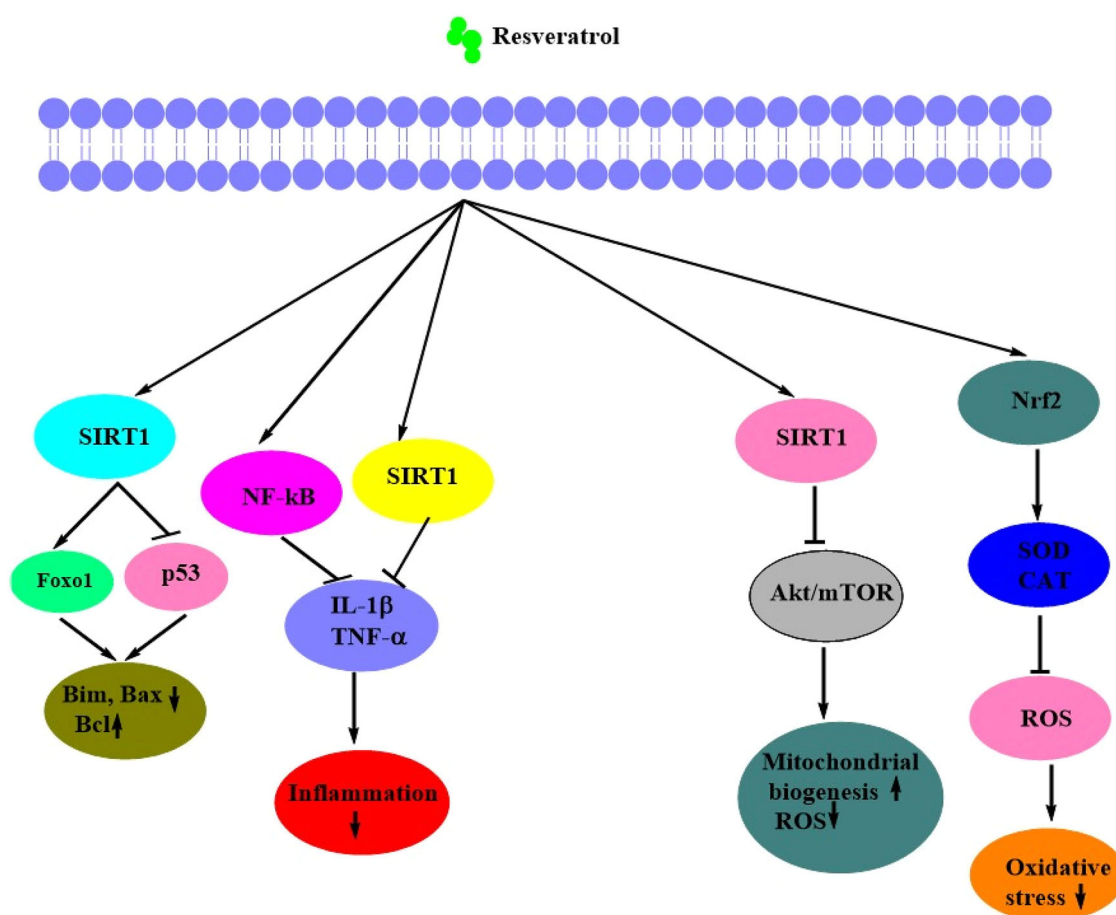


Fig. 8 Mechanism of resveratrol against aging

Table 1 Resveratrol and its mechanisms in different experimental models

Model of evaluation	Mechanism	Reference
Mice	IL-1 β ↓	[126]
Mice	SIRT1 ↑	[249]
Zebrafish Retina	Ampk/Sirt1/Pgc1 α ↑ Akt/mTOR pathway ↓	[127, 250]
Mice oocyte	SIRT1 Upregulation	
Mice	sirtuin1 ↑ TNF- α , L-1 β , NF κ B ↓	[126]
Rats	COX I ↑ Bcl-2/Bax ↑ Cytochrome C ↓	[251]
Mice	TNF- α , IL-1, IL-6 ↓	[252]
Rats	p53 deacetylation ↑ SIRT1 ↑	[134]

Because aging results as a buildup of oxidative stress, inflammation, mitochondrial dysfunction, and cell apoptosis, it is important to understand the mechanisms of resveratrol against these age-related processes (Fig. 8, Table 1). Resveratrol boosts the activity of antioxidant defense mechanism by increasing the activity of enzymes

such as superoxide dismutase (SOD) and catalase (CAT) via upregulation of Nrf2 pathway. This suppresses the generation of ROS, thus inhibits oxidative stress [130]. Reduction in oxidative stress not only inhibits mitochondrial dysfunction but also inhibits apoptosis resulting in holistic antiaging effect. In addition, the compound promotes mitochondrial production and efficiency by activating the longevity-related Sirt1 protein while stopping the Akt/mTOR signaling pathway at the same time. Resveratrol efficiently suppresses inflammation by lowering the levels of inflammatory molecules such as monocyte chemoattractant protein-1 (MCP-1), TNF- α and IL-1 β achieved through inhibition of NF- κ B and activation of Sirt1. Evidence shows that resveratrol-induced Sirt1 expression is responsible for several anti-aging activities, such as inhibition of NF- κ B-induced inflammation, promotion of mitochondrial activity by activating forkhead box protein O1 (Foxo1), and regulation of cell death pathways by control of pro-apoptotic proteins such as Bax and Bim and anti-apoptotic protein Bcl [131, 132]. Resveratrol upregulated the SIRT1, which inhibited neuronal apoptosis and hence protected the learning and memory capacity of the aged rats [133, 134].

Thus, as a positive regulator of AMPK and a potent activator of SIRT1, resveratrol positively affects the longevity of the model organisms. The possible mechanism involves inhibiting the mitochondrial ATP production and increasing the AMP-to-ATP ratio, thus activating the AMPK. AMPK activation promotes energy catabolism and elevates cellular NAD^+ levels subsequently leading to upregulation of SIRT1 activity. AMPK, as a suppressor of mTOR, induces autophagy and mitochondrial biogenesis. On the other hand, SIRT1 downregulates NF- κ B pathway, making broad-spectrum anti-aging effects [135]. Besides abundant preclinical studies on exploring its antiaging effect, resveratrol has been assessed for its effect on age-related conditions like cancer, cardiovascular diseases and obesity in limited clinical studies. In patients with Alzheimer's Disease (AD), a study spanning over 12 months was conducted where they were administered a dose of 500mg per day to 1000 mg per day. The results confirmed its neuroprotective role as it decreased the levels of matrix metalloproteinase-9 (MMP-9) in cerebrospinal fluid (CSF) [136]. Clinical trials have tested a dose range of 25–5000 mg orally while 100–500 mg is considered optimal dosage in terms of its safety and efficacy [137]. However, the clinical effectiveness is majorly compromised because of significantly low bioavailability because due to rapid metabolism. Even though the oral absorption of the compound is greatly high, its first pass rapid metabolism reduces the amount of active compound to just 1% of the administered dose [138, 139].

To enhance absorption and improve systemic availability, advanced formulations like nanoformulations and structurally modified derivatives are being tested. A formulation of resveratrol, SRT501 exhibited positive results but the side effects in the clinical trial hint towards searching other nanomaterials that exert same effect with good tolerance. Another nanoformulation of resveratrol loaded in nanocapsules was investigated in rat model and resulted in two fold increase in its bioavailability. On the other hand, a six fold increase was observed when resveratrol nanoparticles conjugated with folate and encapsulated in albumin were administered in the same animal model [140, 141]. In a clinical trial, resveratrol nanoemulsion loaded with vitamin E was administered to Alzheimer patients where it resulted in improving the endogenous antioxidant enzyme activity while loading the compound in zein nanoparticles improved the cellular antioxidant activity when compared to free resveratrol [142, 143].

However, a chronic resveratrol treatment resulted in substantial increase in the oxidative stress markers in the kidneys proposing that long-term usage may lead to nephrotoxicity [144].

Curcumin

Curcumin, a bioactive compound takes out from *Curcuma longa* (turmeric), has gained increasing attention in anti-aging research due to its diverse biological properties. The lipophilic nature of curcumin influences its pharmacological and biological properties. It disrupts the chain reaction at position 3' resulting in triggering of self-reaction (Diels–Alder reaction) to neutralize ROS [145]. The presence of β -diketone group and two phenolic rings donate electron and hydrogen atoms while methylenic hydrogen and o-methoxy phenolic groups play the central role in breaking down the reactive species [146]. The α,β -Unsaturated carbonyl group in heptadienone chain react with thiol in proteins, activating Nrf2 and inhibiting pro-inflammatory signaling [147]. Its unique structure allows curcumin to exist in tautomeric forms (keto and enol) that facilitate its interaction with certain biomolecules via hydrogen bonding and π - π stacking [148]. Curcumin directly interacts with AMPK pathway by forming a stable complex through allosteric regulatory site of AMPK and hydrogen bonds and π - π interactions of curcumin. This results in activation of AMPK leading to phosphorylation of its downstream targets. These events inhibit the mTORC1 signaling and activate ULK1 kinase promoting autophagy. These changes are linked to longevity and cellular homeostasis [149].

Its neuroprotective, anti-inflammatory, and antioxidant effects contribute to its ability to downregulate the process of aging. Curcumin counteracts age-related changes by suppressing pro-aging proteins such as NF- κ B and mTOR while activating protective proteins like sirtuins and AMPK. Among these, SIRT1 is particularly important, as it regulates DNA repair, inflammation, and metabolic functions associated with aging [150]. Research by [151] indicates that curcumin enhances cellular longevity and resilience by stimulating SIRT1 activity. Curcumin's anti-aging activity is mainly manifested through strong antioxidant potential. The study proves curcumin has the ability to neutralize ROS efficiently, hence preventing oxidative stress—a universal factor in aging and age-related disease [152, 153]. Curcumin also has the ability to increase the efficiency of important antioxidant enzymes such as superoxide dismutase and catalase, which is very important in shielding cellular structures against oxidative damage. Apart from antioxidant activity, curcumin exhibits high anti-inflammatory action. The compound suppresses NF- κ B activation and decreases inflammatory cytokine levels like TNF- α , IL-6 and IL1 β [153–155]. This regulation of inflammatory pathways has the potential to slow the development of age-related conditions, especially cognitive impairment and cardiac diseases. Large-scale studies validate curcumin's neuroprotective effects [156–158].

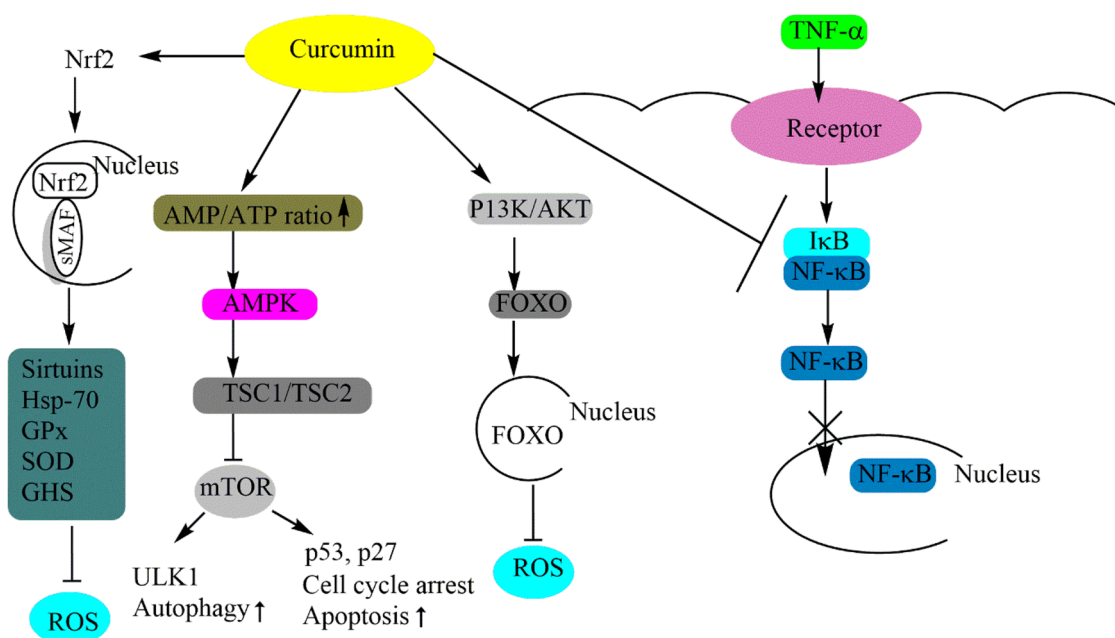


Fig. 9 Mechanism of curcumin against aging

Table 2 Curcumin and its mechanisms in different experimental models

Model of Evaluation	Mechanism	Reference
<i>Drosophila melanogaster</i>	Enhanced the cellular stress response, Modified the gene expression of mth, thor, InR, and JNK	[253]
<i>Caenorhabditis elegans</i>	Enhanced oxidative stress resistance Inhibited MAPK signaling pathway Enhanced mitochondrial DNA (mtDNA) replication	[165]
<i>Caenorhabditis elegans</i>	Triggering of the DAF-16 transcription factor and consequent upregulation of antioxidative genes	[254]
<i>Caenorhabditis elegans</i>	Inhibition of activity of AhR (aryl hydrocarbon receptor) Nrf2/SKN-1 activation Protection against the accumulation of aggregation-prone proteins	[255]
Human primary endothelial cells	Enhanced the migratory capacity of cells.	[255]
<i>Saccharomyces cerevisiae</i>	Triggered protective cellular responses	[256]

Research shows that curcumin enhances cognitive performance in animal models and prevents the amyloid plaque deposition [159–161].

Its capacity to penetrate the blood-brain barrier and modulate microglial activity as well as alleviate neuro-inflammation makes curcumin an attractive candidate in the treatment of age-related cognitive decline [162, 163]. In the context of longevity, studies involving *Caenorhabditis elegans* have confirmed that curcumin increases the resistance to oxidative stress, extending lifespan through pathways that include the MAPK pathway. The compound reduces ROS levels after stress induction and enhances replication of mitochondrial DNA, suggesting its significance in longevity promotion through both antioxidant

and metabolic modulation as depicted in Fig. 9 and Table 2 [164, 165]. Curcumin also has dermatological advantages. Its use in skincare products is due to its free radical scavenging capacity, which can possibly inhibit ultraviolet radiation-induced skin damage and photoaging and hence preserve young skin appearance [166].

Aside these promising qualities, curcumin has encountered great bioavailability problems through limited solubility and extensive metabolism. Current progress in delivery systems, such as nanocarrier systems, has revealed noteworthy enhancement in curcumin bioavailability [167–170]. Studies by [171] recorded remarkable improvements in bioavailability by synthesizing curcumin nanoparticles. Modern nanotechnology strategies, such as

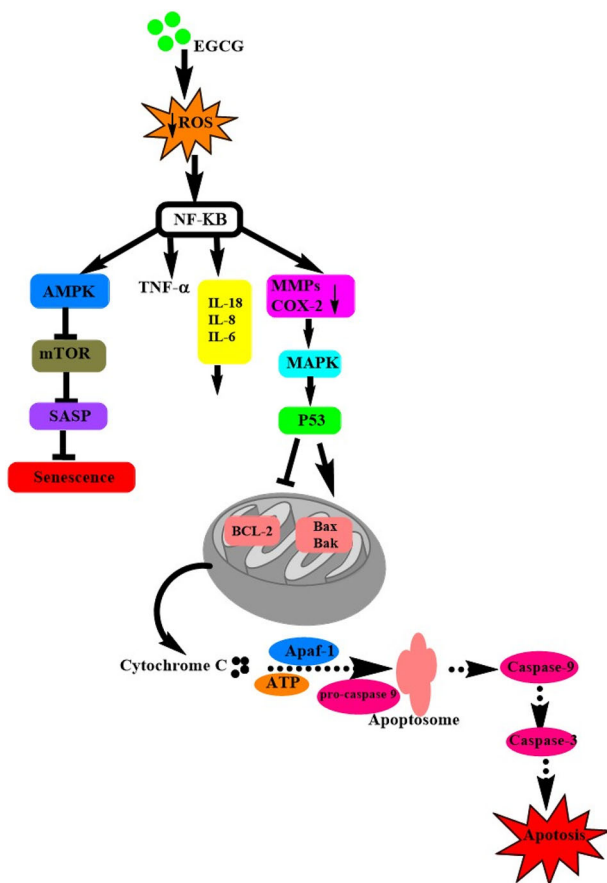


Fig. 10 Mechanism of EGCG against aging

encapsulation of liposomes and preparation of nanoparticle, have shown promising preclinical results that could improve curcumin's clinical effectiveness for the treatment of aging and diseases associated with age [168].

Epigallocatechin Gallate (EGCG)

Catechins represent a class of flavanols primarily derived from *Camellia sinensis* leaves and constitute a major component of green tea. These polyphenolic compounds also appear in various other plant-based foods including apples, berries, persimmons, and grapes. Extensive research has established numerous health benefits associated with catechins, primarily attributed to their antioxidative, anti-inflammatory, and immunoregulatory properties. Among various catechins, epigallocatechin gallate (EGCG) has received the most scientific attention [172, 173]. The presence of galliccatechol rings in the EGCG are capable of directly scavenging the free radicals and is responsible for its antioxidant properties [174]. Molecular simulation studies reveal two possible mechanisms of EGCG to scavenge free radicals. They either dissociate phenolic O–H bonds via single electron transfer or hydrogen atom transfer. The

presence of hydroxyl group at position 5' on ring B is the most reactive site to eliminate ROS [175]. Besides that multiple hydroxyl groups attached to ester-linked gallate group associated with catechin core participate in metal ion chelation and protect against Fenton reaction-mediated oxidative damage including the inhibition of enzymes involved in aging [176]. Aromatic rings and conjugated double bonds allow it to interact with certain proteins including epidermal growth factor receptor (EGFR) and help regulate signaling pathways involved in autophagy, cell survival and aging [177].

Contemporary research has illuminated EGCG's significant anti-aging capabilities. This compound demonstrates substantial protective effects against oxidative stress, a primary driver of cellular aging. EGCG inhibits key senescence markers in human dermal fibroblasts, including p53 and p21, thereby preventing the accumulation of senescent cells—a universal factor in age-related degenerative conditions [178, 179]. The activation of the Nrf2/HO1 signaling pathway by catechins effectively counteracts oxidative damage and cellular aging through increased production of antioxidant enzymes (Fig. 10). These enzymes typically respond to elevated ROS levels, a common feature of the aging [180, 181]. Mitochondrial dysfunction represents another significant age-related characteristic that typically results in diminished energy production and increased cellular oxidative stress (Table 3). Research indicates that EGCG enhances respiratory function and stimulates mitochondrial biogenesis, thereby maintaining cellular energy homeostasis and mitigating age-related decline. In vitro study by [182], using HepG2 cells have demonstrated that the combined action of EGCG and kaempferol significantly increases the action of antioxidant enzymes such as GPx, SOD and catalase. These enzymes provide protection against oxidative damage by limiting intracellular ROS accumulation and preserving mitochondrial potential—particularly significant as mitochondria constitute the center of cellular homeostasis and metabolic activity related to energy generation [183–185].

Research conducted by [186] and [187] with rodent models has demonstrated EGCG's capacity to extend lifespan in obese subjects through improvements in hepatic and renal function, along with enhanced metabolic efficiency. EGCG effectively counteracts the adverse effects of high-fat diets by modulating primary metabolic pathways, regulating free fatty acid metabolism, and reducing inflammatory marker levels. EGCG's interaction with significant metabolic regulators appears particularly noteworthy, especially regarding SIRT1—a catecholamine-activated enzyme involved in stress resistance and DNA repair through deacetylation of forkhead box O1 transcription factors (FOXO1). These transcription factors play vital parts in regulating metabolism and oxidative stress response genes.

Table 3 EGCG and its mechanisms in different experimental models

Model of Evaluation	Mechanism	Reference
Human dermal fibroblasts	Reduces oxidative stress by regulating senescence markers (p53 and p21)	[257]
Rodent model (Rats)	Prolongs lifespan by improving metabolic processes and reducing inflammatory markers	[189]
<i>Drosophila melanogaster</i>	Promotes longevity and delays age-related decline	[258]
Mice	Lifespan extended via suppression of the p38MAPK/NF-κB/Cox-2 pathway, AMPK inhibition, upregulation of cell cycle inhibitors (p53/p21)	[183]
PC12 cells	Alleviates oxidative stress via the SIRT1/PGC-1α signaling pathway	[259]
<i>Caenorhabditis elegans</i>	Activates antioxidant pathways such as GSH-Px and SOD, decreases Aβ deposition,	[260]
Human Skin Fibroblasts	Promoted TGF-β1 secretion, prevented cell cycle arrest	[261]
Senescent 3T3-L1 preadipocytes	reduced IL-6 secretion, reduced CDKN1a expression	[178]

This mechanism signifies the role catechins contributes to lifespan increase and enhanced global health through metabolic imbalances abrogation implicated in aging [188, 189]. Reference [190] documented that there was a decrease in intracellular hydrogen peroxide (H_2O_2) levels in *Caenorhabditis elegans* for both the wild-type strain and the transgenic strain. This decrease could be attributed to downregulation of stress protein-induced proteins like hsp-16.2. For the same animal model, research by [191] reported that EGCG prolonged lifespan by inducing mitohormesis. EGCG inhibited the insulin/IGF-1 signaling resulting in activation of DAF-16, the sole forkhead box transcription factors class O (FoxO) homolog in *Caenorhabditis elegans* and critical for the lifespan extension [21, 192]. Moreover, further researches revealed that green tea extract prolonged the life of *Drosophila melanogaster* and delayed the development of senescence in transgenic models of Alzheimer's disease. According to [193], EGCG exhibited neuroprotective effects through antioxidant activity. This is achieved by either activating the SIRT1/PGC-1α pathway, which lowered the levels of oxidative stress in PC12 cells that could potentially be advantageous for the therapeutic management of Parkinson's disease. This implies that catechins may expand their potential benefits for cognitive health, particularly as people age [194]. It has been found that catechins impact endothelial function, which is critical in vascular aging, by potentially minimizing arterial stiffness and improving NO bioavailability [195, 196]. This broad impact on vascular health is significant since endothelial dysfunction is linked to cardiovascular disorders and is common in elders. In a study involving aged Wistar rats [197], reported protective effect of EGCG against cardiovascular aging. EGCG treatment reduced the hypertrophy and collagen deposition as well as lowered the low-density lipoprotein (LDL), triglycerides, and total cholesterol. The possible mechanism involves suppression of ROS-dependent activation of TGFβ, TNFα, and NF-κB pathways, which are known to control fibrosis and apoptosis.

Furthermore, catechins have the ability to regulate chronic inflammation in related to aging by suppressing the NLRP3 inflammasome, which is associated with inflammatory conditions linked to aging [176, 198].

Lipofuscin, an age pigment that contains carbonyl-amino cross-linked protein residues, deposits as we age. Studies using D-galactose-induced aging animals and MDA-modified human serum albumin in vitro models demonstrated that EGCG prevents the production of lipofuscin. It was found that EGCG neutralizes amino-carbonyl cross-linking processes, traps reactive unsaturated aldehydes, and effectively lowers the buildup of age pigments. This multidimensional approach towards functional decline demonstrates the broad spectrum of health benefits that catechins provide. EGCG (400 mg per day) was administered to men with elevated risk of prostate cancer for a period of one year, showed no adverse effects and overall improved metabolic parameters. However, a dose of above 800 mg/day showed signs of hepatotoxicity [199, 200]. EGCG shows low systemic bioavailability with 4.9–6.7% in rodents which can potentially be enhanced by combining it with nutrients like vitamins and minerals and by encapsulation [199]. When EGCG was loaded into polymeric nanoparticles, it resulted in two-fold increase in its bioavailability [201].

Quercetin

Quercetum is the term for quercetin, a flavonoid originated from the Latin word for oak forest. Even though the human body cannot synthesize this flavonoid, it is reported to have multiple therapeutic benefits such as curing cancer, inflammatory diseases, allergic diseases, arthritis, and cardiovascular diseases. Their biological effects are noteworthy since they influence mitochondrial biogenesis, lipid peroxidation, and platelet aggregation [202]. Recent research has confirmed the efficiency of quercetin in curing and alleviating age-related diseases because of its potent in vivo and in vitro antioxidant action.

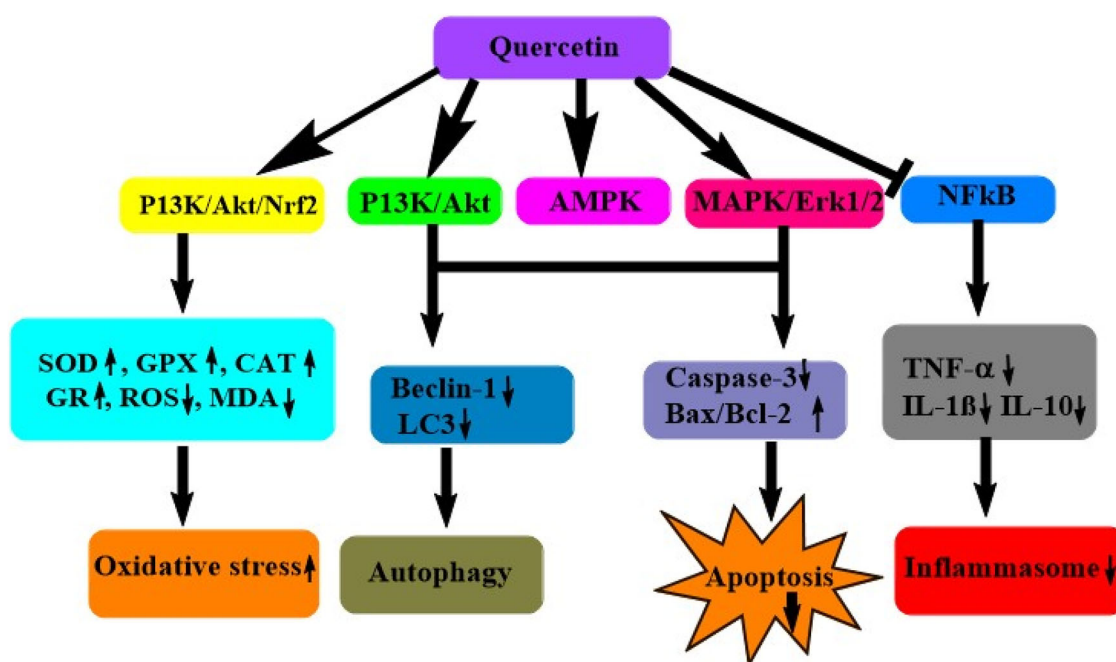


Fig. 11 Mechanism of quercetin against aging

Table 4 Quercetin and its mechanisms in different experimental models

Model of Evaluation	Mechanism	Reference
<i>Simocephalus vetulus</i>	AMPK ↑ Glycometabolism ↑	[262]
Mice	Amyloid-β (Aβ) aggregation ↓ Tau phosphorylation ↓	[263]
<i>Drosophila</i>	Oxidative stress ↓ Inflammation ↓ Mitochondrial function ↑ Autophagy ↑	[214]
Mice	p16 ^{INK4a} ↓ IL-6 ↓ MMP13 ↓	[264]
Oocytes from aged mice	SIRT3- mediated deacetylation (↑SOD2 activity) ↓ ROS via SOD2 activation	[265]
Mice	↓ TBARS Total Glutathione (GSH) Levels ↑	[266]
Mice	↑ Sirtuin1 ↓ NLRP3 and ASC	[11]
Human erythrocytes	↓ TBARS ↓ Glycated Hemoglobin (A1c)	[215]

Polyphenols, particularly quercetin, are important modulators of oxidative stress -an imbalance of the body between the levels of antioxidants and ROS production [203]. Oxidative stress-related cellular damage emerges initially in nucleic acids followed by lipids and proteins. Polyphenols have the ability to interact with reactive oxygen and nitrogen species prior to the oxidative chain

damages the cellular viability [204, 205]. The hydroxyl groups on quercetin's structure, contribute to its antioxidant capacity. Owing to the unique chemical structure, quercetin exhibits strong antioxidant properties. Presence of hydroxyl group specifically at positions 3 and 5 readily interact with the oxidizing agent to neutralize the ROS [206]. The presence of the functional group, catechol group (o-dihydroxyl groups) on B ring along with 4-oxo group and C2 = C3 double bond enhance the oxidative strength of the compound [207]. B group is also involved in inhibiting enzymes like matrix metalloproteinases (MMPs) that are responsible for collagen breakdown. 3-Hydroxyl Group on C-ring is involved in hydrogen bonding and electron delocalization making radicals stable and enhancing its antioxidant activity. This hydroxyl group is also important for modulation of signaling pathways involved in cellular senescence like NF-κB and MAPK. Moreover, 4-Keto Group and 2,3-Double Bond in C-ring create a planar structure of the compound that boosts radical stabilization and allows it to bind to protein like sirtuins and kinases, involved in aging pathways [208, 209].

The most distinctive property of quercetin is its dual action as an antioxidant and a pro-oxidant, based on the concentration. Quercetin significantly lowers the indices of oxidative stress, as shown by recent research (Fig. 11, Table 4). While high quantities of quercetin may generate pro-oxidative activities that hinder tumor growth, low amounts of the component have a strong antioxidative effect [210]. For example, it has been observed by [211] that the presence of these flavonoids in red human blood cells lowers

MDA levels and upsurges glutathione (GSH) and membrane sulfhydryl groups. The mechanism of quercetin includes the inhibition of nuclear factor kappa B (NF- κ B), additionally involved in inflammation. Quercetin activates the Nrf2 pathway to scavenge ROS and induces antioxidant enzymes that has been demonstrated to have preventive benefits against age-related diseases [212]. Quercetin has been found to reduce reactive oxygen species via the Keap1-Nrf2 pathway and alteration of the AKT1-FoxO1 pathway in experimental models, both in vitro and in vivo [213] reported the lifespan extension and improved mobility via insulin-like signaling (ILS) and p38-MAPK pathways, mediated by transcription factors such as SKN-1 and DAF-16 in *Caenorhabditis elegans*, after quercetin feeding. Quercetin upregulates SIRT1 by signaling pathways like SIRT1/NLRP3 and SIRT1/Keap1/Nrf2 in aging related diseases thus mitigating the oxidative damage, neuroinflammation, and mitochondrial decay, as reported by [214]. In cellular models involving D-galactose induced aged human erythrocytes, Band 3 protein (B3p) function was altered, ameliorating the lipid peroxidation and exhibiting potential as a protective agent against cell aging effects [215]. Because of its broad range of effects, quercetin can be promising natural product for preventing aging and maintaining health.

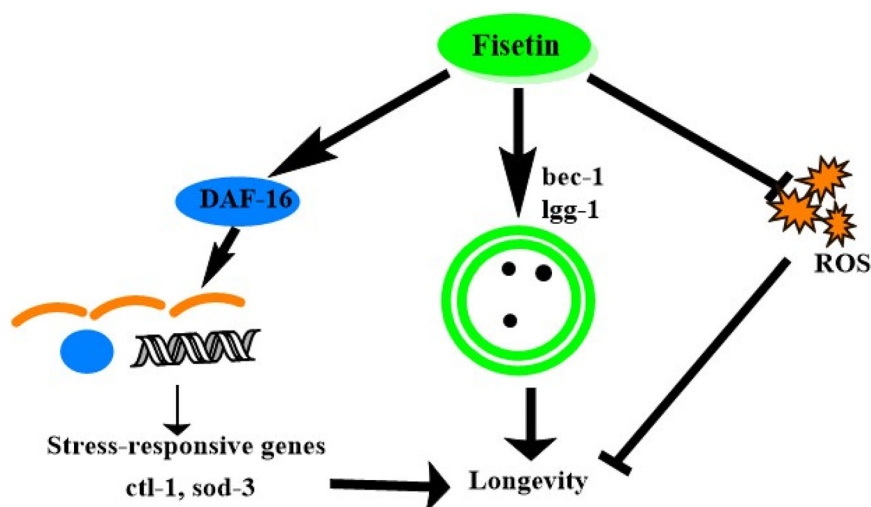
Quercetin as a senolytic drug is being investigated in human adults that have been through cancer in their childhood. The results showed a positive improvement in overall health of the survivors. When quercetin was combined with dasatinib, it improved frailty and cognitive health. In human studies a dose of 500 mg–1250 mg/day was administered and declared safe. However, the therapeutic efficacy of quercetin is compromised because of its low oral bioavailability and limited plasma concentrations. To address this issue, nanoformulations and its encapsulation with nanomaterials are being investigated [216]. When alloxan-induced diabetic mice were treated with quercetin loaded nanorods, it improved the activity of endogenous antioxidant enzyme system and reduced lipid peroxidation. A similar response was observed when its nanoformulation was used to treat mice with induced nephrotoxicity and cardiotoxicity [217].

Fisetin

Targetting cell senescence, a hallmark of aging, can diminish the severity or postpone progression of multiple age-related co-morbidities concurrently. Senolytics are substances that eliminate damaged tissues in the body to reduce the impact of aging and diseases associated with age [218]. The biological activities of fisetin are attributed to its electrophilic nature towards oxidative species. The presence of Catechol moiety on the B ring is involved in electron

delocalization while conjugation of C2 = C3 double bond with 4-oxo group in the C ring further enhance the redox activity of the compound [219]. The key functional group responsible for its interaction with cellular proteins is 3-Hydroxyl group on C-ring that regulate cellular senescence and inflammation. Catechol group, similar to quercetin enhances its metal chelation ability and protect the cell from oxidative stress. Structure planarity and electron delocalization is due to 4-Keto Group and 2,3-Double Bond in C-ring that supports radical scavenging activity and facilitates protein bonding [220]. The additional Hydroxyl Group at 7-Position in A-ring modulate the signaling pathways responsible for autophagy and apoptosis-key regulator of aging process [221]. Fisetin, a flavonoid polyphenol has been assessed for senotherapeutic efficiency in mice and human adipose tissues. Fisetin lowered senescence markers in progeroid and aged wild-type mice tissues and in a particular subset of cell types in adipose tissues [218, 222] used fisetin as an active senolytic remedy to reverse enhanced aging phenotypes in telomerase knockout mice. Fisetin supplementation was found to significantly repress the overexpression of age markers p16INK4a and p21CIP1, and lesser collagen fiber buildup that had listed a considerable increase prior to the cure. The probable mechanism defined for this involves blocking the Akt signaling pathway by suppressing the Stc1 expression, which leads to the programmed cell death of the senescent cells (Fig. 12, Table 5). Lifespan prolongation through DAF-16-induced stress response and autophagy and delay of age-dependent reduction in motility was found with fisetin supplementation in *Caenorhabditis elegans* by [220]. Fisetin inhibits topoisomerase activity and increases longevity by downregulating the PI3K/AKT/mTOR pathway [218]. Studies by [223] and [220] showed that fisetin prevents aging by downregulating and expression of p16, p53 and p21 in tissues of human and mice. Since cellular senescence is associated with phosphatase and tension homolog deleted on chromosome ten (PTEN) damage and mTOR pathway activation, the study by [224] targeted PTEN and mTORC2 during Vascular smooth muscle cells (VSMCs) senescence. The study highlighted that fisetin administration effectively alleviated VSMC senescence by decreasing the mTORC2 protein levels while elevating the PTEN expression. Fisetin in age accelerated rat brain increased the expression of autophagy genes such as Beclin-1 and Atg-3, sirtuin-1 and neuronal markers as Ngb and NSE.

Fisetin treatment is being extensively researched for its role as senolytic drug to remove senescent cells. In this regard, a pilot study was conducted in humans where a dose of 500 mg fisetin was administered once a week every month for a period of 6 months and showed inconsistent results. This hints towards the need of

Fig. 12 Mechanism of fisetin against aging**Table 5** Fisetin and its mechanisms in different experimental models

Model of Evaluation	Mechanism	Reference
Mouse model with telomerase deficiency (G3 Tert ^{-/-} mice)	Akt signaling pathway inhibition, Stc1 expression suppression	[222]
<i>C. elegans</i>	Autophagy induction, DAF-16-induced stress response, Oxidative stress reduction	[220]
APP ^{swe} /PS1 ^{dE9} double transgenic AD mice	anti-inflammatory, neurotrophic activation, glutathione boost	[267]
Human epidermal keratinocytes	Telomerase activation, CDKN1B suppression, ceramide synthase gene expression increase	[268]
Rats	autophagy gene upregulation, mitochondrial protection, apoptotic cell death reduction, neuro-inflammation suppression	[269]
Smooth muscle cells	PTEN activation, mTORC2-Akt (Ser473) pathway regulation, Senescence marker reduction (SA-β-gal, p53-p21 pathway)	[224]
Mice	reduced vascular cell senescence and SASP factors	[270]
Mice oocyte model	Sirt1 upregulation, GSH increase, ROS inhibition, H3K9me3 expression reduction.	[271]
Vascular smooth muscle cells	inhibition of PTEN-PKCδ-NOX1-ROS signaling pathway, decreased PTEN expression	[272]

Table 6 Comparative overview of key natural compounds in anti-aging therapy

Compound	Targeted pathway	Organ affected	Bioavailability issue	Available Nanoform	References
Quercetin	SIRT1, Nrf2, NF-κB, mTOR	Brain, Skin, Liver	Poor, metabolized fast	Quercetin NPs, Liposomes	[214, 273]
Curcumin	mTOR, AMPK, NF-κB	Skin, Liver, GI tract	Poor water solubility	Curcumin SLNs, Micelles	[274, 275]
EGCG	SIRT1, PI3K/Akt, FOXO	Brain, Heart	Moderate, unstable	EGCG Nanoparticles	[276]
Resveratrol	SIRT1, AMPK, Autophagy	Brain, Kidney, Heart	Low oral bioavailability	Nanoemulsion, Liposomes	[277]

conducting trials on larger scale. A dose of 20 mg per Kg body weight per day has also reported to show good tolerance with no adverse effects [225]. Fisetin shows limited oral bioavailability because of rapid metabolism. There is ongoing research involving the use of nanoparticle-based delivery system to enhance its bioavailability. Fisetin nanoparticles with poly(vinylpyrrolidone) (PVP) encapsulation slowed the drug release due to high surface-area-to-volume ratio. The

systemic bioavailability was increased by 24 folds when fisetin was used in nanocrystal form as compared to fisetin in its standard form [226].

Comparative Overview of Key Natural Compounds in Anti-Aging Therapy

Comparative overview of key natural compounds in anti-aging therapy is summarized in Table 6.

Clinical Studies on Natural Therapeutics and Their Limitations

Modern healthcare is adopting traditional plant and herbal medicines despite varying clinical evidence behind each one. Various obstacles prevent the widespread medical utilization of therapeutic drugs primarily because of bioavailability problems. Natural products are chemically complex because they are usually a mixture of different active components rather than a single well-defined compound, making it difficult to assess their pharmacokinetics and bioavailability. Moreover, the lack of standardized method to evaluate pharmacokinetics poses a challenge to their clinical application. However, there are certain studies regarding human bioavailability that reveal different rates of excretion for different components [227]. For example, quercetin exhibits low availability while catechin in green tea show relatively higher bioavailability but this compound demonstrates restricted absorption throughout the blood system thus creating potential hepatic toxicity risks after taking excessive doses [228]. Moreover, a significant portion of polyphenols is broken down in the body and is not excreted in the urine. Alkaloid-based natural therapeutics have also been assessed for their bioavailability in clinical settings but the results show certain limitations like poor absorption. A reason for their poor gastrointestinal absorption is their low aqueous solubility and their metabolic breakdown by hepatic enzymes like CYP3A4, limiting their efficacy by restricting their reach to systemic circulation [229]. Research indicates quercetin fails to express anti-senescent effects due to its low solubility together with its pro-oxidant characteristics at elevated concentrations. Research on fisetin's senotherapeutic effects depends primarily on animal-based trials since there is limited evidence from human clinical tests and no accepted dosing recommendation exists [218, 230]. Monoterpenoids, a class of phytochemicals exhibit broad spectrum biological activities including anti-inflammatory and antioxidant properties. Animal studies revealed that administration of carvacrol resulted in poor accumulation in the body while linalool showed better results when administered as a part of essential oil, hinting towards exploring the idea of synergy of these compounds [231]. The chemical complexity of natural products makes it difficult to isolate and quantify their dose. Also, plant species vary in their composition based on their geography and cultivation method, another reason contributing to inconsistent clinical outcomes. In silico studies can help in screening the phytocompounds with strong binding affinities and targeted interaction for modulate the signaling proteins involved in aging [232].

Implementing nature-based treatments in evidence-based healthcare calls for advanced formulation approaches together with robust clinical evaluation before

establishing official health treatment protocols. For example, formulating lipid-based prodrug designs can increase solubility and stability through encapsulation. Moreover, to tackle variability in results, using a personalized approach and tailoring formulation specific to individual's pharmacokinetic profile can be adopted. To fully harness therapeutic potential of natural products, addressing the low bioavailability and standardization gaps are the most important challenges.

Role of Nanotechnology

Use of nanotechnology is considered to be an effective strategy to use in antiaging applications to enhance the efficacy of existing antiaging treatments as well as a novel separate therapy. In this regard, both organic and inorganic nanoparticles are being explored to investigate their antiaging properties. Nanoparticles are known to target both cellular and molecular pathways to exert their effect [233]. When bioactive compounds are loaded onto nanoparticles it prevents their degradation, helping them reach systemic circulation safely. Nanomaterials can be manipulated based on their surface chemistry to release the bioactive at desired site. It is quite an important aspect of nanotechnology to drive the targeted release of the bioactive in specific tissues and body sites. Tuning the nanomaterials by modifying their chemical composition, morphology and size can allow the controlled release of the bioactives [234, 235]. Flavonoids are reported to play key role in improving cellular survival mechanism by reducing oxidative stress but face the challenge of rapid metabolism and poor bioavailability that can be addressed by modifying their structure and using nanoparticles delivery system [236]. Hence, use of nanodelivery systems can benefit over conventional formulations because of their enhanced stability, solubility and bioavailability properties. Nanodelivery is being extensively explored in age-related diseases like cardiovascular diseases, type 2 diabetes, tumors and certain neurodegenerative diseases [217].

By utilizing liposomes and nanoemulsions alongside nano capsules nanotechnology enhances herbal medicine because it helps improve stability and enhances bioavailability and raises solubility rates. The revolutionary delivery systems enable plant medicinal compounds to achieve better target application along with preserving them against rapid body breakdown [237, 238]. The anti-aging properties of resveratrol prove the potential effectiveness of this approach when studied through an exemplary analysis. The polyphenolic compound reaches various biological mechanisms through sirtuin activation as well as oxidative stress modulation and inflammatory cytokine regulation. Skin tissue that receives resveratrol consumption experiences increased

collagen production and better elastic tissue which results in reduced wrinkle appearance [239]. As an antioxidant agent resveratrol enables better blood vessel health while stopping arterial stiffness from developing. Resveratrol brings about protective neural effects through two mechanisms which decrease oxidative stress and elevate mitochondrial function. Through nanotechnology the dissolution and stability levels of resveratrol therapy increases, creating effective treatments by building delivery frameworks which target specific body parts [240].

Nanoherbal medicine applications deliver strong therapeutic benefits to cancer patients by enabling targeted cancer pathway disruption and better stability performance and enhanced penetration effects. The development of nanoherbal delivery systems with resveratrol multi-organ benefits brings forth fresh possibilities to treat medical issues which commonly occur in aging adults. Multiple significant barriers to progress remain despite the strong advantages of uniting nanotechnology with herbal medicine because extraction techniques remain inconsistent and there are safety concerns about nanoparticles while production costs are high and regulatory practices differ between markets [241]. Sustainable production systems need to be combined with organized international safety frameworks to overcome existing production challenges and safety obstacles while implementing international regulatory unification. The scientific community requires additional investigation to resolve existing problems in this hybrid research modality that merges herbal medicine with nanotechnology for therapeutic development [242].

Certain biocompatible polysaccharides like Hyaluronic acid (HA) or Folic acid (FA) are being used for targeted delivery of herbal drugs that enhances their therapeutic efficacy by improving drug stability, solubility, extended circulation time, and site-specific drug release. These coatings facilitate receptor-mediated endocytosis and active targeting, reducing the possible off-target adverse effect. HA and FA coated systems target CD44, RHAMM and Folate receptor (FR), respectively [243, 244].

HA coated Solid Lipid Nanoparticles (SLNs) loaded with herbal drugs by electrostatic coating. The charged interaction between negatively charged HA and positively charged pre-formed nanoparticles assist the formation of these HA-coated systems. This method ensures entrapment efficiency (>95%) of drug and significantly enhances drug uptake by CD44+ cancer cells. Similar systems prepared by niosomes were reported to have improved anticancer and anti-inflammatory drug delivery. HA-coated nanocrystals showed pH-responsive release and increased apoptosis in cancer cells by simultaneously reducing the toxicity to normal cells via regulating the Bax/Bcl-2 ratios [245]. The transdermal delivery of

anti-aging actives by HA-coated nanoparticles increased the encapsulation efficiency and loading capacity of antioxidants. The hygroscopic properties of HA facilitates the penetration of actives through stratum corneum and prolongs the retention of bioactive agents in the dermis, enabling the controlled release of dermal antiaging compounds. HA itself has anti-oxidative properties and combining it with plant extracts (e.g., *Penthorium chinense*, *Gynostemma pentaphyllum*) amplifies its antioxidant and anti-inflammatory synergy [246].

Similarly, Folic Acid (FA) coated systems have been employed due to its target-specific delivery, enhanced cellular uptake and specific cytotoxicity in cancer cells without affecting normal cells. FA-conjugated micelles improved the doxorubicin delivery and were reported to exhibit increased tumor uptake by 2–3 × when compared to non-conjugated system [247]. Nano curcumin conjugated with folate as ligand allowed specific targeting of cancer cells because of receptor's increased expression in affected cells and could be a promising approach to overcome major limitations including poor solubility and limited bioavailability [248]. FA can be conjugated to nanoparticles or liposomes for targeted nanodelivery of antioxidants by exploiting the overexpression of folate receptors in certain cells that enhance their cellular uptake resulting in better protection against oxidative stress- a major driver in aging [217]. These technologies improve the therapeutic potential of herbal agents and antioxidant actives by serving as targeted ligands. Figure 13 depicts the targeted delivery of herbal drugs using a nano-carrier coated with Hyaluronic Acid (HA) or Folic Acid (FA).

Future Perspective

Phytochemicals of plants are well recognized as potential antiaging agents because of their high activity and low toxicity, suggesting their role in preventing age related disorders. Despite the significant progress, several gaps in gerontology require thorough assessment to fully understand their therapeutic potential. A crucial aspect includes determining specific compound of phytochemical responsible for attributed effects of phytochemicals while considering their synergistic interactions of these compounds to develop an effective targeted therapeutic strategy. The variables like bioavailability and bio-efficacy of these phytochemicals along with their potential interaction with drug must be investigated. Moreover, there is need to establish accessible and predictive biomarkers to accurately assess the antiaging potential of the phytochemicals. Eventually, extensive and well-controlled clinical trials should be carried out to recommend their usage by human population.

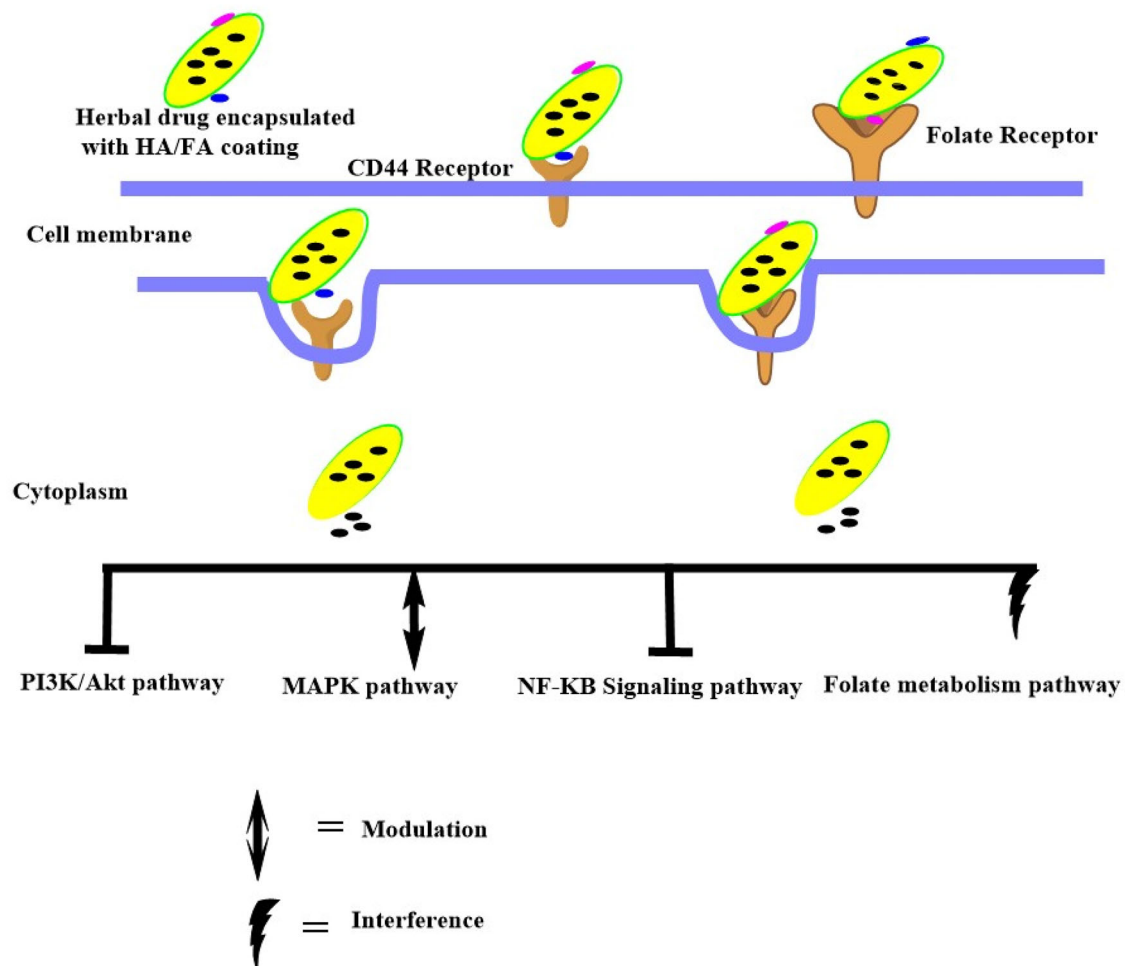


Fig. 13 Mechanism of targeted delivery of herbal drugs using a nanocarrier coated with Hyaluronic Acid (HA) or Folic Acid (FA)

Data Availability

No datasets were generated or analysed during the current study.

Author Contributions R.A. wrote and edited the manuscript and did the software work. S.A. edited and evaluated the manuscript. M.S. edited the manuscript and help in data acquisition regarding mechanism of action. H.T. proofread and edited the manuscript.

Compliance with ethical standards

Conflict of Interest The authors declare no competing interests.

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