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Review Article

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Research Progress of Terpenoids in Anti-aging

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Abstract Terpenoids, as an important class of organic compounds, are widely distributed in nature and have many biological activities, such as antioxidant, anti-inflammatory, anti-cancer, anti-aging, antibacterial. Aging is an unavoidable natural phenomenon, intervened by factors such as oxidative stress, inflammation, and declining immune function. Anti-aging has been a hot research topic in recent decades, and as a result, more and more compounds have been studied and reported to have anti-aging properties. Among them, terpenoids are unique in many categories of compounds with their unique structures and functions. Therefore, the research progress of terpenoids in anti-aging in recent years is reviewed in this article.

Keywords Terpenoids, Anti-aging, Age-related Diseases, Oxidative stress, Inflammation

Introduction

Aging is an inevitable and multifactor-induced process in life, and it has been haunting people since the concept of aging came into being. Today's population ageing is a worldwide trend. With the continuous improvement of living standards and medical standards, the average life expectancy of contemporary human beings has been greatly extended. It is estimated that by 2050, the global elderly population over the age of 60 will exceed 2 billion [1]. Coupled with the fact that aging is a process that everyone has to go through, this shows that the strategy of delaying aging is undoubtedly a long-standing hot spot. The onset of senescence is usually accompanied by structural damage and functional decline of the cells, tissues and organs of the biological organism. In addition to being time-dependent, aging has been shown to accelerate by many factors, such as oxidative stress (OS), inflammation, immune dysfunction, cancer, etc. The researchers screened anti-aging compounds and anti-aging activities in model animal models (Drosophilas [2], Caenorhabditis elegans (C. elegans) [3, 4], Rats [5, 6], Mice [7-9], Yeasts [10], etc.) or various in vitro cell models [11-13] by targeting these factors that accelerate aging and using signaling pathways (including AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), sirtuin 1 (SIRT1), mammalian target of rapamycin (mTOR), nuclear factor-kappa B (NF-κB), etc. Their relationship is visible from Figure 1) associated with aging. A variety of compounds, including flavonoids [14], polyphenols [15], terpenoids [16], alkaloids [17, 18], lignans [19], etc., have been studied and proven to have anti-aging properties.

Terpenoids are an important class of secondary metabolites composed of isoprene as the basic unit, widely exert in nature, and are the main components of many plant essential oils, such as lemon oil, turpentine oil, peppermint oil and camphor oil. Terpenoids are found in almost all plants, as well as terpenoids in animals and fungi. Terpenoids, as one of the main sources of active ingredients in natural medicines, have been shown to have a variety of

biological activities, including antioxidant [20], anti-inflammatory [21], antibacterial [22], anti-aging[21, 22], anti-tumor [23], anti-diabetic [24], anti-Alzheimer's disease [24], etc., and are widely present in nature. Since terpenoids are currently rare in anti-aging reviews, this paper will review some of the natural terpenoids with anti-aging activities that have been studied in recent years.

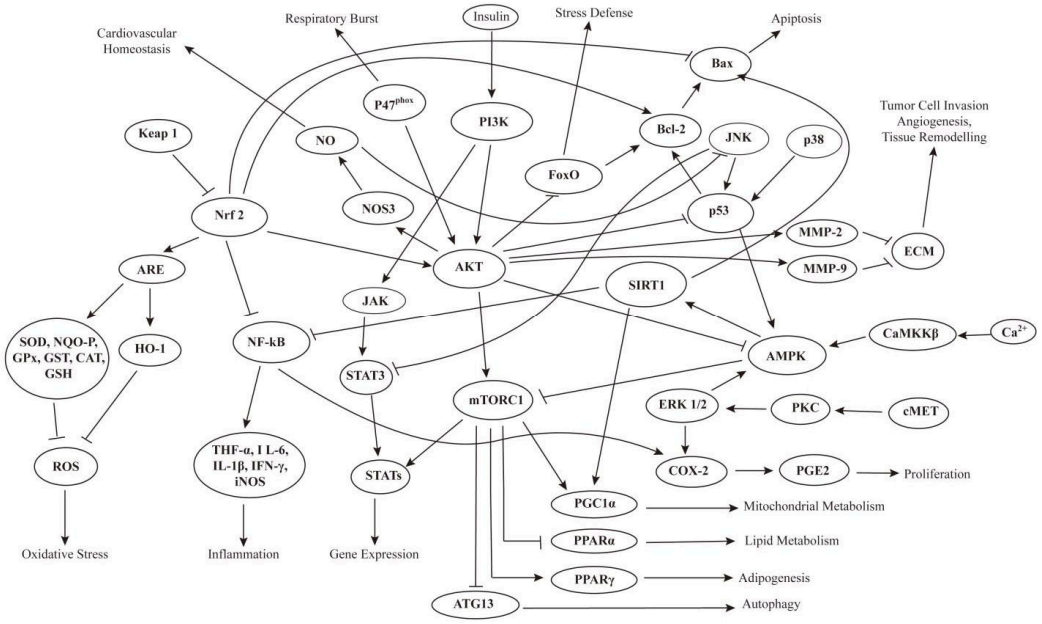


Figure 1: The Signaling Pathways for Terpenoids Associated with Aging

1. Monoterpenoids

Monoterpenoids consist of a structure with 10 carbon backbone (or 2 isoprene units) and can be divided into three categories: acyclic, monocyclic, and bicyclic. Within each class, monoterpenoids may be simple unsaturated hydrocarbons, or alcohols, aldehydes and ketones having functional groups. They are constituents of various volatile oils and are widely distributed in secretory tissues such as glands, oil chambers and resin tracts of higher plants. Because the oxygenated derivatives of monoterpenes (alcohols, aldehydes, ketones) have a strong aroma and biological activity such as antioxidant, anti-aging, antibacterial and anti-inflammatory activities, they have become important raw materials for the pharmaceutical, food and cosmetic industries. Recently, some monoterpenoids (see Figure 2) have been reported to have anti-aging effects. **Geraniol (GR**; **1)**, an unsaturated acyclic monoterpene alcohol derived from rose oil and citronella oil, is able to resist OS by upregulating the body's antioxidant capacity and treating inflammatory diseases by inhibiting NF-κB and upregulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway and the production of nitric oxide (NO) and prostaglandin E2 (PGE2) [7, 25]. In addition, GR can also regulate cellular metabolic processes by activating peroxisome proliferator-activated receptor α (PPARα)/peroxisome proliferator-activated receptor γ (PPARγ) [26]. **Citral (CT**; **2)** is an unsaturated acyclic monoterpene aldehyde, derived from lemongrass oil and citrus fruit's peel oil. CT prevents ultraviolet A (UVA) from becoming cancerous to the skin by lowering levels of OS and pro-inflammatory factors and promoting autophagy [27]. CT can also significantly inhibit hepatocyte carcinogenesis by restoring antioxidant and stage II xenoenzyme levels [28]. **Myrcene (MC**; **3)** is an acyclic monoterpene, derived from peppercorns, mangoes and lemongrass. MC treats intracutaneous oxidative and inflammatory damage in human dermal fibroblasts (HDFs) caused by ultraviolet B (UVB) radiation by reducing the production of reactive oxygen species (ROS), matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-3 (MMP-3), and interleukin-6 (IL-6) and increasing the secretion of transforming growth factor-β1 (TGF-β1) and type I procollagen, thereby exhibiting

photoprotective effects [11]. **Limoerknene (LM**; **4)** is a cyclic monoterpene, derived from lemon, orange, peppermint, and other essential oils. LM promotes the lifespan of C. elegans by modulating the transcription factor decay-accelerating factor 16 (DAF-16) and inhibiting OS [3], and can also reduce matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) mRNA expression levels by modulating the inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), PGE2, TGF-β1, and 1/2 signaling pathways in ulcerative colitis rat models [29]. LM has also been reported to have anti-diabetic and cardiovascular protective properties [30]. **Safranal (SF**; **5)** is an unsaturated cyclic monoterpene aldehyde, derived from *Aspalathus linearis* and *Cistus creticus*. SF can protect the brain and liver of senescent rats from oxidative damage by alleviating a variety of diseases caused by OS [31], such as improving lipid peroxidation and GSH levels associated with aging and reducing antioxidant enzyme activity [5, 6]. **Camphor (CP**; **6)** is a dicyclic monoterpene ketone, derived from *Cinnamomum camphora*. CP induces the proliferation of human primary HDFs in a dose-dependent manner through PI3K/AKT and extracellular regulated protein kinases (ERK) signaling pathways, and induced the expression of collagen IA, collagen IIIA, collagen IVA, and elastin in human primary dermal fibroblasts, thus having skin-protective properties [12].

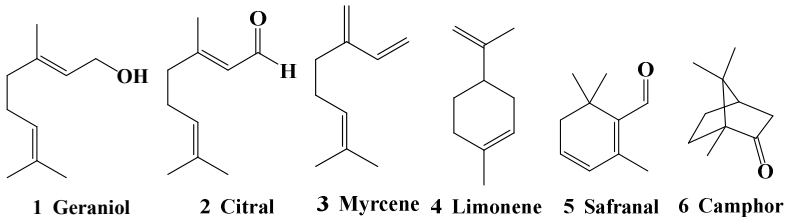


Figure 2: The Structures of Monoterpenoids

2. Iridoids

Iridoids, a special class of monoterpenes, are a class of active compounds that are widely present in plants. Nowadays, a variety of iridoids have been isolated, and most of them exist in the form of glycosides, such as aucubin, catalpol, gentiopicroside, etc. Iridoids exhibit a wide range of biological activities, containing neuroprotective, anti-inflammatory, anticancer, antioxidant, antibacterial and other properties. Recently, a number of iridoids (see Figure 3) have been reported to have anti-aging effects. **Aucubin (Au**; **7)** is an iridoid glycoside derived from *Verbascum lychnitis*. Au exerts cerebral neuroprotective in traumatic brain injury mouse models by activating the Nrf2-induced antioxidant system and inhibiting OS and inflammatory responses, and exerts an anti-osteoporosis effect in dexamethasone (Dex)/hydrogen peroxide (H_2O_2)-exposed MG63 cells and Dex-injected C57BL/6 mice with osteoporosis (OP) in Dex/H_2O_2-exposed MG63 cells and Dex-injected C57BL/6 mice with OP [8, 9]. Au significantly inhibits MMP-1 production and significantly reduces senescence-associated β-galactosidase activity [32]. **Catalpol (CTP**; **8)** is an iridoid glycoside, derived from *Verbascum lychnitis*. CTP can improve cognitive impairment in D-gal-induced senescent mice by enhancing endogenous antioxidant enzyme activity and inhibiting free radical production [33], and can also protect retinal pigment epithelium (RPE) cells from OS-induced damage by activating the kelch-like ECH-associated protein-1 (Keap1)/Nrf2/ARE pathway [13]. CTP can extend the lifespan of C. elegans and increase its stress tolerance through DAF-16/forkhead box O (FOXO) and skinhead-1 (SKN-1)/Nrf activation that rely on insulin/IGF signaling and JNK signaling [34]. In addition, CTP can also improve hepatic insulin resistance in HepG2 cells through acting on AMPK/NADPH oxidase type 4 (NOX4)/PI3K/AKT pathway [4]. **Geniposide (GP**; **9)** is an iridoid glycoside, derived from *Feretia apodanthera* and *Gardenia jasminoides*. GP is involved in upregulating PI3K/Nrf2 signaling and inducing the expression of the antioxidant enzyme HO-1 to protect primary hippocampal Neurons [35] and are able to antagonize OS caused by UVB radiation [36]. In addition, GP exerts a positive therapeutic effect on neuropathological impairment and cognitive deficit characteristics of Alzheimer's disease (AD) through downregulation of mTOR signaling and enhancement of autophagy of amyloid beta protein(Aβ) fibrils [37]. **Gentiopicroside (GTP**; **10)** is a secoiridoid glycoside, derived from *Gentiana davidii* and *Aster auriculatus*. GTP exhibits anti-aging properties because it can also prevent skin aging by promoting mitochondrial autophagy and anti-OS activity and prolonging yeast lifespan [7], as well as MMP inhibition and anti-transcriptional activity [38]. **Sweroside (SR**; **11)** is found in *Strychnos*

axillaris, *Fructus Corni* and *Lonicera japonica*. SR treats interleukin-1β (IL-1β)-induced osteoarthritis by inhibiting NF-κB and mechanistic target of rapamycin complex 1 (mTORC1) signaling in rats [39]. SR prevents myocardial ischemia-reperfusion injury by modulating the Keap1/Nrf2 pathway and then inhibiting OS and NLR family pyrin domain containing 3 (NLRP3) inflammasome-mediated bone degeneration [40]. **Swertiamarin (STM**; **12)** is a secoiridoid, derived from *Lonicera japonica* and *Swertia japonica*. STM has the potential to treat AD by modulating DAF-16 and nicotinic acetylcholine receptor (nAChR) and acetylcholinesterase (AChE) activity [41] and can also alleviate hepatic steatosis, inflammation, and insulin resistance caused by high-fat diets by inhibiting eWAT and activation of the p38 mitogen-activated protein kinase (MAPK) and NF-κB pathways in obese mice [42].

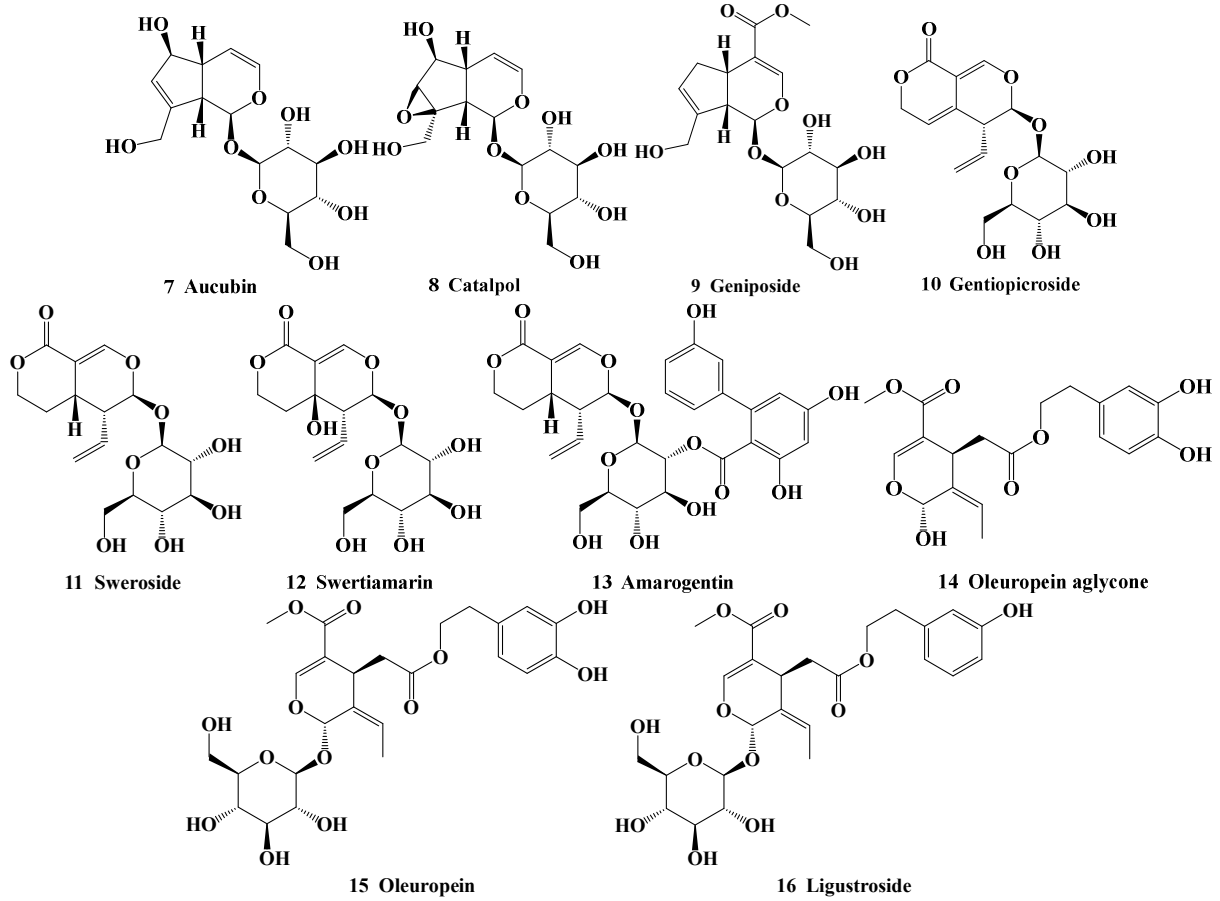


Figure 3: The Structures of Iridoids

Amarogentin (AG; **13)** is a secoiridoid glycoside and a monosaccharide derivative, derived from *Swertia japonica* and *Swertia chirayita*. AG resists OS damage in PC12 cells by increasing gene expression of superoxide dismutase 2 (SOD2), CAT, glutathione peroxidase (GPx), Nrf2, and Bcl-xl and significantly reducing ROS and malondialdehyde (MDA) levels, thereby demonstrating anti-aging and neuroprotective effects. In addition, AG exhibits neurogenerating activity in PC12 cells with potential to treat neurodegenerative diseases [43]. AG improves glucose homeostasis in diabetic rats by reversing the decrease in glucose transporter 4 level in skeletal muscle and reducing phosphoenolpyruvate carboxykinase (PEPCK) expression in type 1 diabetes mellitus (T1DM) rats' liver, while improving glucose homeostasis in diabetic rats by lowering homeostasis model assessment-insulin resistance (HOMA-IR) and increasing insulin sensitivity in type 2 diabetes mellitus (T2DM) rats [44]. AG also exhibits excellent potential for application as an anti-aging agent with the matrix metalloproteinases (MMPs) inhibitory and anti-transcriptional activities [38]. **Oleuropein Aglycone (OleA**; **14)**, a secoiridoid derived from olive oil, promotes glutamylcylase-catalyzed pyroglutamate-3 amyloid-beta (pE3-Aβ) generation of reductase expression and interferes

with Aß$_{42}$ and pE3-Aß aggregation. Even in mice in advanced pathology, OleA activates autophagy of neurons [45]. OleA promotes autophagy in cultured cells through the mutual activation of Ca^{2+} and calmodulin-dependent kinase kinase β (CaMKKβ)-AMPK. At the same time, the interaction of AMPK activation with mTOR inhibition promotes the activation of autophagy [46]. **Oleuropein (OLE**; **15)**, a secoiridoid glycoside derived from *Olea europaea*, inhibits human islet amyloid polypeptide and other amyloid polypeptide aggregations associated with amyloidosis, reducing the risk of developing T2DM and neurodegenerative diseases [47]. OLE exhibits moderate inhibition of collagenase and elastase activity and has shown cytoprotective effects by improving OS-induced human skin fibroblast cell damage [48]. **Ligustroside (LGT**; **16)**, a secoiridoid glycoside derived from *Ligustrum vulgare*, has shown significant activity against mitochondrial dysfunction in cell models of early AD and mouse senescence models, but its mechanism may not interfere with the production of Aβ [49]. LGT can also significantly inhibit the production of NO in RAW264.7 macrophages activated by lipopolysaccharide (LPS).

3. Sesquiterpenoids

Sesquiterpenes refer to terpenes containing three isoprene carbon backbones and their derivatives in the structure and derived from the active precursor farnesyl pyrophosphate (FPP) through double bond shifts or cyclics at different locations, widely present in the plant kingdom. Recently, some sesquiterpenes (see Figure 4) have been reported to have anti-aging effects. **Farnesol (FN**; **17)** is an acyclic sesquiterpene alcohol, derived from *Cinnamomum tenuipilum* and *Eriobotrya japonica Thunb.*, Lemongrass oil and Citronella oil. FN promotes repair after skin sunburn caused by UVB radiation via increasing collagen synthesis and exerting anti-inflammatory effects [50], and can also effectively inhibit DMH-induced Wistar rat colonic mucosal damage by promoting antioxidant enzyme expression and reducing Caspase-3 activity in colon tissue [51]. **Albicanol (AB**; **18)**, a drimane-type sesquiterpenoid derived from *Dryopteris fragrans*, can alleviate OS-induced mouse senescence by modulating the Keap1/Nrf2 signaling pathway, while also significantly reducing the expression of IL-1β and tumor necrosis factor-α (TNF-α) to have some anti-inflammatory properties [52]. AB could inhibit the profenofos-induced genotoxicity of L8824 cells by inhibiting oxidative stress and the tumor suppressor protein 53 (p53) pathway [53]. **β-Caryophyllene (BCP**; **19)**, a bicyclic sesquiterpene derived from Clove oil, regulates oxidative and thermal stress, balances intracellular ROS, and thus maintains cellular redox homeostasis. At the same time, BCP modulated transcription factors, namely SKN-1, SIR-2.1, DAF-16, heat shock factor 1 (HSF-1), defective pharyngeal development protein 4 (PHA-4), and stress-regulating target genes superoxide dismutase 3 (SOD3), SOD2, GST-4, GST-7, heat shock protein 70 (HSP70), and decay-accelerating factor 9 (DAF-9) [54]. BCP can inhibit the production of aging-related interleukin-23 (IL-23), reversing age-related damage in memory [55].

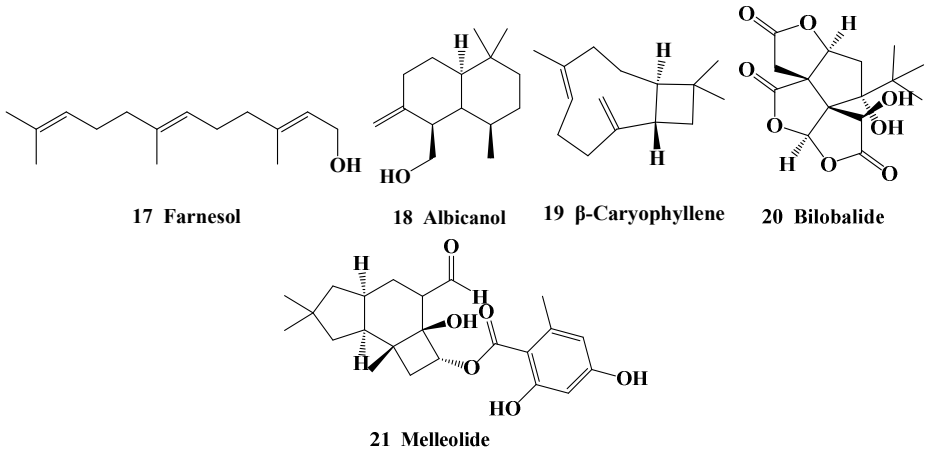


Figure 4: The Structures of Sesquiterpenoids

Bilobalide (BB; **20)**, a terpenoid trilactone found in extracts of *Ginkgo biloba*, can prevent $A\beta_{1-42}$ and H_2O_2-induced cellar damage of SH-SY5Y cells by modulating the PI3K/AKT pathway [56], and can also treat neuronal damage in Aβ-induced AD by promoting the expression of Aβ-degrading enzymes in astrocytes [57]. In addition, BB can also prevent oxidative damage during cerebral ischemia by activating the AKT/Nrf2 pathway [58]. **Melleolide (ML**; **21)** is a sesquiterpenoid and a benzoate ester, derived from *Desarmillaria tabescens*, *Armillaria ostoyae*, and *Armillaria tabescens*. ML can prolong the distinct lifespan of yeast [59], but its mechanism for exerting anti-aging properties has not been reported.

4. Diterpenoids

Diterpenoids can be seen as natural terpenoids formed by the polymerization of 4 molecules of isoprene and containing 20 C atoms in the molecule. Due to the large molecular weight of diterpenoids and poor volatility, most of them cannot be distilled with water vapor and are rarely found in volatile oils, and the diterpene components found in individual volatile oils are mostly in the high-boiling fractions. Diterpene compounds mostly exist in nature in the form of resin, lactone or glycoside. Recently, a number of diterpenoids (see Figure 5) have been reported to have anti-aging effects. **Crocetin (CCT**; **22)** is a 20-carbon dicarboxylic acid which is a diterpenoid and natural carotenoid, found in the crocus flower. CCT protects ARPE19 cells from tert-butyl hydroperoxide-induced OS by protecting the cellular energy production pathway and activating the ERK1 / 2 pathway, which may therefore delay the progression of age-related macular degeneration (AMD) [60]. CTT can also improve Aβ accumulation-induced learning and memory deficits in AD transgenic mice through its anti-inflammatory and anti-apoptotic abilities [61]. CCT exhibits excellent anti-inflammatory activity in LPS-stimulated RAW264.7 cells via modulating the crosstalk between the NF-κB/iNOS pathway and the Nrf2/HO-1 pathway [62]. **Andrographolide (ANDRO**; **23)**, a labdane diterpenoid, is found in the leaves and roots of *Andrographis paniculata*. By regulating tumor suppressor protein 53 (p53) and hepatocyte nuclear factor alpha (HNF4A), ANDRO upregulates the microRNA, HO-1, glutathione (GSH), and thioxin systems, thus playing a beneficial role in regulating OS-induced diseases, such as diabetes, aging [63]. In addition, ANDRO produces antidepressant-like and anti-inflammatory effects in chronic unpredictable mild stress (CUMS)-induced mice through upregulation of autophagy [64]. In aging Octodon degus, ANDRO can restore spatial memory and synaptic basal transmission while reducing phosphorylated tau protein and Aβ aggregation thus having a neuroprotective effect [65]. **14-Deoxyandrographolide (14DAP**; **24)**, **14-Deoxy-11,12-Didehydroandrographolide (DEAND**; **25)** and **Neoandrographolide (NEO**; **26)** are diterpene lactones and derivatives of ANDRO，derived from *Andrographis paniculata*. All of them can inhibit ROS production and TNF-α expression in HaCaT under pro-oxidant and pro-inflammatory conditions, respectively [66]. In addition, 14DAP can mediate adenylate cyclase-cAMP signaling activation leading to upregulation of constitutive nitric oxide synthase (cNOS), thereby reducing OS [67]. DEAND can induce redox-mediated cell death in THP-1 cells while activating procaspase-3 [68]. **Carnosic acid (CA**; **27)**, an abietane diterpenoid found from rosemary and common sage, promotes the healthy lifespan of C. elegans by increasing SOD3 expression and regulating MAPK and HSF-1 [69]. CA activates endogenous antioxidant phase 2 genes by activating the Nrf2 transcription pathway, thereby improving oxidative-related diseases of the retina [70]. **Carnosol (CN**; **28)**, a naturally occurring phenolic diterpene found in rosemary, is a Nrf2 activator, and can improve endothelial barrier function through anti-OS [71], and can also alleviate bleomycin-induced biochemical and histological changes by inhibiting fibrosis, OS, and inflammation in rats [72]. **Rosmanol (RM**; **29)** is also a naturally occurring phenolic diterpene found in *Salvia tomentosa* and *Lepechinia salviae*. RM downregulates inflammatory iNOS and COX-2 gene expression by interfering with the activation of PI3K/AKT and MAPK signals [73], and can also be synergistically treated with CN by inhibiting the TLR4/NF-κB/MAPK pathway [74]. **Triptolide (TPL**; **30)** is an organic heteroheptacyclic compound and a natural diterpenoid isolated from *Tripterygium wilfordii Hook F*. TPL inhibits inflammatory and oxidative response by activating the Nrf2 pathway and inhibiting NF-κB activity, and improves neurobehavioral function, thereby alleviating anxiety-like behavior, working memory, spatial learning, and memory in deep hypothermia circulatory arrest (DHCA) rats [75]. TPL can alleviate cerebral ischaemia/reperfusion (CI/R) damage in rats by inhibiting the expression of wnt family member 1 (Wnt1), β-catenin, c-Myc, and Cyclin-D1 [76]. TPL can significantly reduce the

expression of TGF-β1, SMAD Family Member 3 (SMAD3), alpha-smooth muscle actin (α-SMA), vimentin and increase the expression of Smad7 in rats with diabetic nephropathy, and the effect shows significant concentration dependence [77]. In addition, TPL can inhibit the proliferation and growth of tumor cells in vitro and in vivo, accelerate cell senescence and G0/G1 stage stagnant cells. TPL has been shown to promote anti-cancer activity of HepG2 cell senescence through both the AKT pathway and the human telomerase reverse transcriptase pathway [78]. **Ginkgolide A (GA**; **31)**, **Ginkgolide B (GB**; **32)**, and **Ginkgolide J (GJ**; **33)** are three natural products found in *Ginkgo biloba*. Among them, GA can reduce renal inflammation by upregulating microRNA-25 (miR-25) targeting NOX4 [79] and can also improve LPS-stimulated inflammation by down-regulating NF-κB and MAPKs (p38 MAPK and ERK) [80]. GB can exert neuroprotective effects on the cognitive function of SAM8 mice through autophagic degradation of the NLRP3 infammasome [81] and can also reverse OS-induced OP [82]. GJ prevents $A\beta_{1-42}$ induced inhibition of long-term potentiation in the CA1 region of mice hippocampal slices to improve cell death of hippocampal slices, making it a drug candidate for the treatment of AD [83].

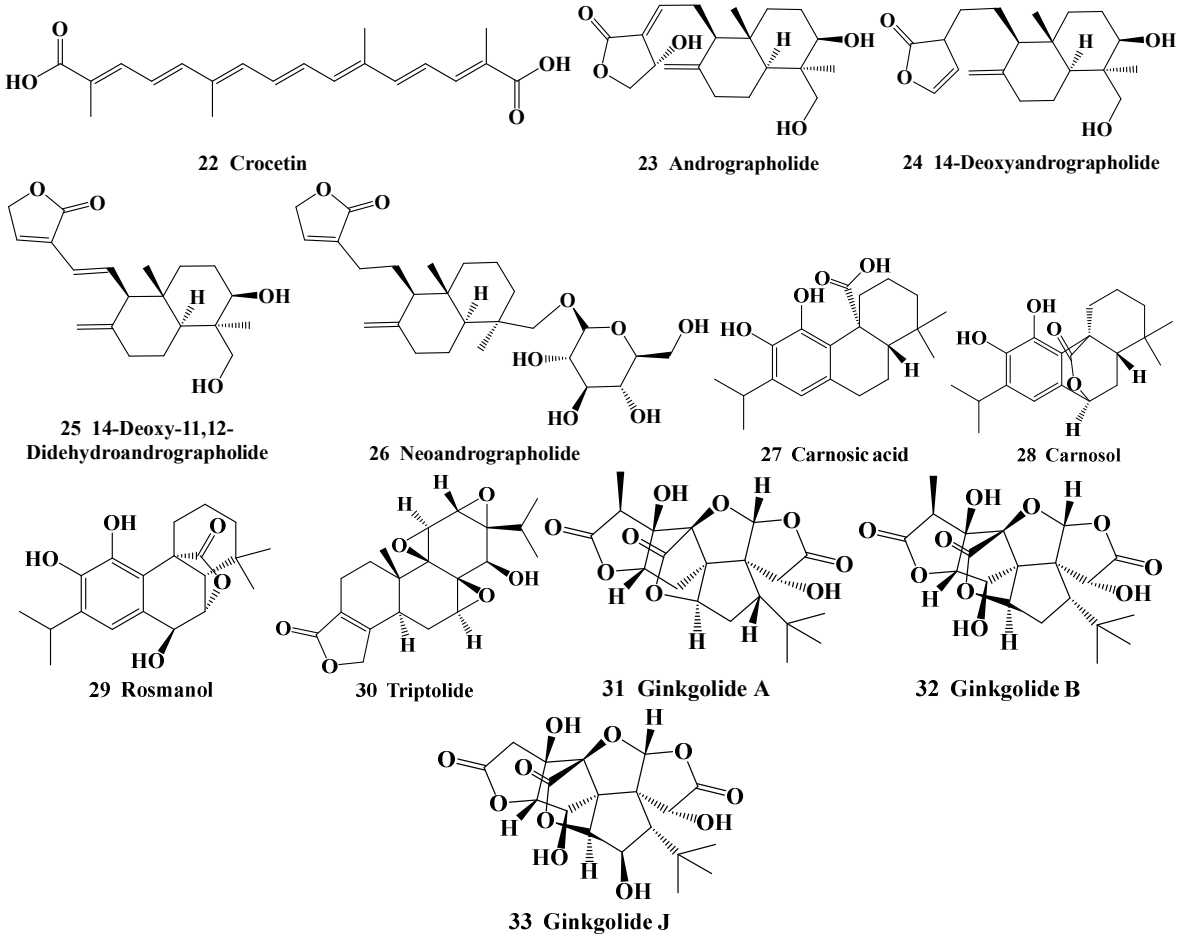


Figure 5: The Structures of Diterpenoids

5. Triterpenoids

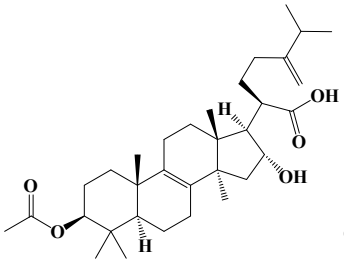
Triterpenoids are a class of terpenoids consisting of 30 carbon atoms in a basic parent nucleus, present in plants in free form or in the form of glycosides or esters combined with sugars, and have a variety of biochemical activities, including anti-inflammation, antibacterial, immunomodulation, anti-aging and antitumor. It is generally classified according to the presence or absence of carbon rings of triterpenoid components. Most of the triterpenoids, which have anti-aging activities, have been found are tetracyclic triterpenes and pentacyclic triterpenes (see Figure 6).

Pachymic acid (PA; **34)**, a lanostrane-type triterpenoid from *Fomitopsis pinicol*, can significantly increase cerebral blood flow in rats after I/R, reduced infarction volume, and significantly reduced post-I/R neuronal injury in rats through activation of the PI3K/AKT signaling pathway [84]. PA inhibits the expression of inflammatory cytokines in serum of pneumonia rats through the NF-κB and MAPK pathways, inhibiting inflammation in lung tissue [85]. **Antcin C (AC**; **35)** and **Antcin M (AM**; **36**) are natural products found in *Taiwanofungus camphoratus*. Among them, AC protects hepatocytes from OS-induced cellar damage through activation of the c-Jun N-terminal kinase (JNK)/PI3K signal-mediated Nrf2/ARE pathway, while also preventing cell death through regulation of B-cell lymphoma-2 (Bcl-2) and Bcl-2 associated X protein (Bax) [86]. AC controls microglial inflammation through the toll-like receptor 4 (TLR-4) pathway and prevents intracerebral hemorrhage injury [87]. AM promotes antioxidant defense and SIRT1 stability in HDFs and endothelial cells induced by hyperglycemia in vitro, thereby minimizing cellular senescence and growth arrest, and can improve OS resistance and prolong C. elegans lifespan in vivo [88]. **Ginsenoside Compound K (CK**; **37)** is an active metabolite of diol-type ginsenosides in the human intestine. CK improves skin barrier function in UVB-irradiated and 1-Chloro-2,4-dinitrobenzene-induced atopic dermatitis-like models with serine peptidase inhibitor kazal type 5 (SPINK5) [89]. CK inhibits TNF-α-induced MMP-1 expression by downregulating MMP-1 activity and inhibiting the production of collagen type 1 (Col-1) protein in UVA-irradiated fibroblasts, and can also inhibit skin photoaging by inactivating the c-Src/epidermal growth factor receptor (EGFR)-dependent Extracellular signal regulated kinase/Activator protein-1 (ERK/AP-1) signaling pathway, thereby inhibiting collagen degradation in human fibroblasts [90, 91]. **Ginsenoside Rb1 (Rb1**; **38)**, a ginsenoside found in *Panax ginseng*, may play an anti-aging role in stem cell antigen 1^+ hematopoietic stem/progenitor cells (Sca-1^+HSC/HPC) sequential transplantation by regulating cell cycle regulating molecule expression. Rg1 can also conduct anti-aging function of Sca-1^+HSC/HPC cells in D-galactose (D-gal)-induced senescent models by modulating mitochondrial pathway and activating the sirtuin 3 (SIRT3)/SOD2 signaling pathway [92]. Rb1 protects the skin by clearing ROS and lowering MMP-2 levels, enhancing the antioxidant activity of keratinocytes under UVB irradiation [93]. In addition, Rg1 can also improve cognitive abilities, protect neural stem cells/progenitor cells (NSCs/NPCs), and promote neurogenesis by enhancing antioxidant and anti-inflammatory abilities in the hippocampus[94], and can also antagonize spleen and thymus gland damage in D-gal-induced aging rats by mitigating OS damage and downregulating the expression of aging-related proteins to improve the body's immunity [95]. **Mogroside V (MV**; **39)**, a natural cucurbitane glycoside found in *Siraitia grosvenorii* and *Siraitia siamensis*, can reduce H_2O_2-induced OS and enhance endogenous antioxidant activity in skin fibroblasts [96].

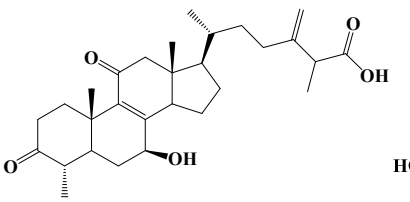
Cycloastragenol (CAG; **40)** is a sapogenin, a pentacyclic triterpenoid from *Astragalus membranaceus*. AD-associated neurodegeneration can be reduced by CAG via inhibiting OS, neurotrophic factors, MAPK signaling, and apoptosis-related markers [97]. CAG can alleviate the inhibition of osteogenesis differentiation induced by Dex in vitro and in vivo by activating telomerase [98], or by inducing the expression of osteoactivin, alleviating age-related bone loss, improving bone microstructure and biomechanical properties, and thus becoming a compound for treating the OP potential associated with aging [99]. **Lupeol (LP**; **41)**, is a lupane-type triterpene found in *Bombax ceiba*, can alleviate LPS/D-galactosamine (D-GalN)-induced liver damage by reducing infiltration of inflammatory cells and reducing pro-inflammatory cytokines. In addition, LP can also protect injured livers from OS by downregulating the expression of TGFβ1 and upregulating Nrf2 [100], and inhibit cellar senescence through inhibiting MMP-1, -2, -3 as well as SA-β-gal activity in repeated UVA-irradiated senescent fibroblast models, therefore suggesting that LP may be useful as an anti-aging agent [101]. **Arjunolic acid (AA**; **42)**, a pentacyclic triterpenoid isolated from *Symplocos lancifolia* and *Juglans sinensis*, regulates oxidative phosphorylation in mitochondria and subsequently inhibits ROS production by eliminating $p47^{phox}$-Ser345 phosphorylation in myocardial infarction (MI) neutrophils [102]. AA protects retinal cells from streptozotocin-induced OS and inflammation through autophagy pathways regulated by AMPK/mTOR/HO-1 [103]. **Hederagenin (HE**; **43)**, is a pentacyclic triterpenoid, a dihydroxy monocarboxylic acid and a sapogenin isolated from Araliaceae. HE attenuates CI/R-induced apoptosis and inflammatory cytokine expression in the infarct region by inhibiting the activation of the mixed lineage kinase 3 (MLK3) signaling pathway [104]. HE also exerts anti-inflammatory activity by reducing LPS-induced levels of iNOS and COX-2 and the mRNA levels of the cytokines described above in a dose-dependent manner [105].

Oleanolic acid (OA; **44)**, a pentacyclic triterpenoid of the leaves of *Olea europaea* and *Viscum album L.*, is a telomerase activator that delays DNA damage-induced cellular senescence [106] and can also promote autophagy and ultrastructural integrity of mitochondria through mitophagy receptors FUN14 domain containing 1 (FUNDC1)-mediated mechanisms. to alleviate cardiac remodeling and systolic dysfunction in aging [107]. In addition, OA protects reproductive function by inhibiting the NF-κB, p53, and p38 signaling pathways by reducing germ cell DNA damage and apoptosis [108]. **Asiatic acid (ASA**; **45)**, a pentacyclic triterpenoid found in *Centella asiatica*, enhances SIRT1 expression, reduces NF-κB p65 acetylation, and inhibits NF-κB activation after LPS stimulation, thereby inhibiting BV2 microglia neuroinflammation [109]. ASA protects dopaminergic neurons from mitochondrial ROS by directly downregulating mitochondrial ROS, and improves mitochondrial dysfunction in SH-SY5Y cells, inhibits NLRP3 inflammatory body activation in microglia, and directly protects dopaminergic neurons from neuroinflammation [110]. ASA can inhibit osteoclast formation and reduce bone resorption through receptor activator of NF-κB ligand-activated NF-κB or nuclear factor of activated T cells 1 (NFATc1) signaling [111]. **Asiaticoside (AHS**; **46)**, a trisaccaride triterpene from *Centella asiatica*, prevents spatial learning and memory decline by upregulating antioxidant enzyme activity and lowering Aβ levels, improving synaptic plasticity dysfunction, and reversing abnormal changes in acetylcholine (ACh) levels and AChE activity [112]. AHS is able to protect the skin by activating TGF-β receptor type I (TβRI) kinase-non-dependent Smad signaling and promoting Col-1 protein synthesis [113]. **Madecassoside (MAD**; **47)**, a triterpenoid saponin found in *Centella asiatica*, induces collagen expression and regulates inflammatory mediators that can restore damage to the skin's elastomeric fibrous network after prolonged sunburn [114]. MAD can also inhibit the proliferation and invasion of hepatocyte growth factor (HGF)-activated HCC cells by modulating the cellular-mesenchymal epithelial transition factor (cMET)-protein kinase C (PKC)-ERK1/2-COX-2-PGE2 pathway [115]. **Ursolic Acid (UA**; **48)** is a ubiquitous pentacyclic triterpene found in various fruits, vegetables and medicinal herbs. It can improve OP by inhibiting autophagy-mediated osteoclast differentiation [116] and can also attenuate UVB radiation-induced cellular photo-oxidative damage by interfering with ROS-mediated apoptosis and photo-aging senescence [117]. In addition, UA has therapeutic potential for neurodegenerative diseases such as AD and Parkinson's disease (PD), as well as for mental disorders with certain neurobiological mechanisms (OS, neuroinflammation, impaired signaling pathways, and neuroplasticity) [118]. UA may improve aging-related IR and inflammatory and metabolic diseases in adipose tissue, including hypertension, coronary heart disease, and obesity [119]. **Corosolic acid (CRA**; **49)**, a pentacyclic triterpenoid extracted from *Ternstroemia gymnanthera* and *Cunila lythrifolia*, with anti-hyperlipidemia and anti-hepatic steatosis activity, the mechanism of which may be through AMPK/sterol regulated element-binding proteins (SREBPs) and NF-κB/MAPK signaling pathway inhibits lipid production and cholesterol synthesis, as well as inflammatory responses [120]. CRA has multi-targeted activity in cancer cells and also have the potential to treat metabolic syndromes [121]. **Ziyuglycoside I (ZI**; **50)**, one of the major active ingredients in *Sanguisorba officinalis*, can resist photo-aging caused by UVB exposure by down-regulating the expression of the inflammatory cytokines IL-1β, MMP-2, MMP-9 and inhibiting the expression of the MMP-2 protein [122]. **Celastrol (51)**, a pentacyclic triterpenoid derived from *Tripterygium wilfordii Hook. F.*, regulates bone marrow mesenchymal stem cells and bone-fat balance in OP and bone aging by stimulating peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) [123], and also exhibits neuroprotective effects against early brain injury after subarachnoid hemorrhage [124]. **18α-Glycyrrhetinic acid (18α-GA**; **52)**, a bioactive triterpenoid found in *Glycyrrhiza glabra* and *Glycyrrhiza uralensis*, further demonstrates a SKN-1- and proteasome activation-dependent life extension in C. elegans through activation of proteasomes, and can reduce paralysis in various AD nematode models, accompanied by a decrease in Aβ deposits, which ultimately slows the progression of the AD phenotype [125]. Another anti-aging function of 18α-GA can be demonstrated by activating Nrf2 to relieve OS and DNA damage [126]. **18β-Glycyrrhetinic acid (18β-GA**; **53)**, a pentacyclic triterpenoid found in the *Glycyrrhiza glabra*, significantly attenuates ultraviolet (UV)-induced skin photoaging by its antioxidant and anti-inflammatory properties and interference with the expression of MMP-1 and MMP-3 [127]. **Glycyrrhizic acid (GA**; **54)**, the major active constituent of licorice, can attenuate renal glycative stress in diabetic mice by reducing the declining polyol pathway, enhancing the glyoxalase pathway, and inhibiting the NF-κB and MAPK pathways [128]. In addition, GA can prevent UVB-induced cellular DNA damage

by inducing autophagy [129] and can also induce cell cycle arrest to inhibit gastric cancer cells proliferation by inhibiting phosphorylation of PI3K and AKT [130].



34 Pachymic acid



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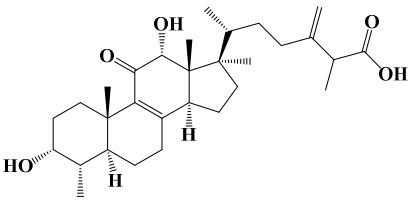

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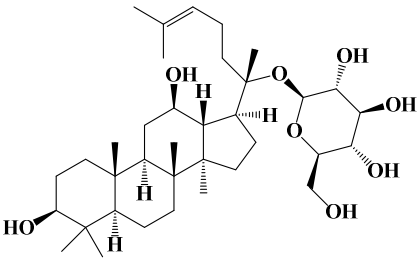

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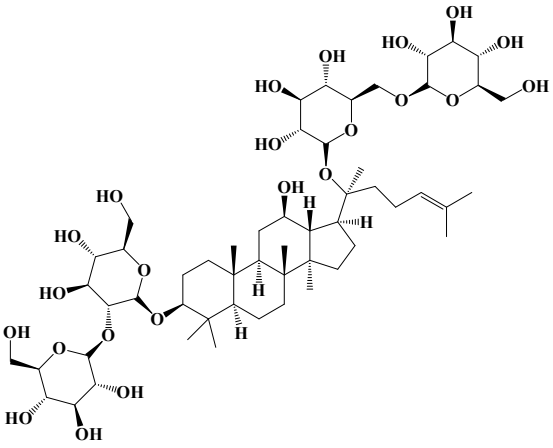
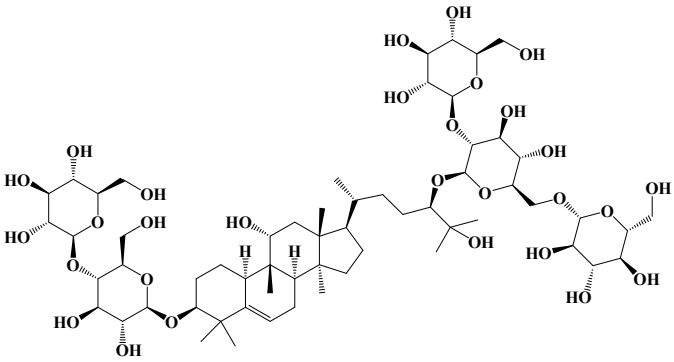
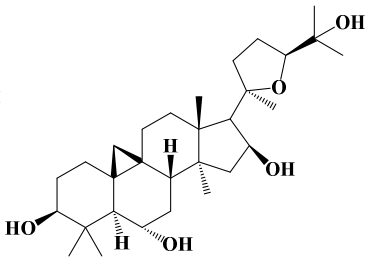


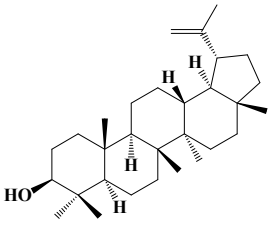
38 Ginsenoside Rb1



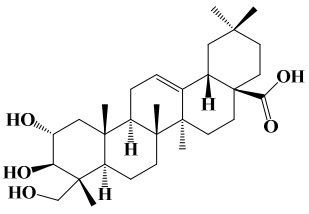
39 Mogroside V



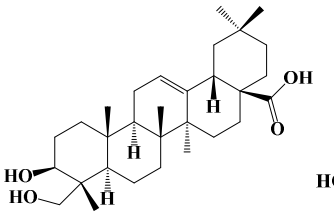
40 Cycloastragenol



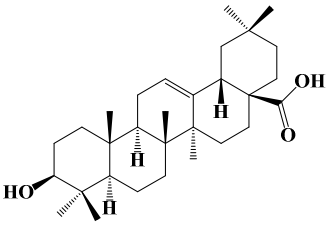
41 Lupeol



42 Arjunolic acid



43 Hederagenin



44 Oleanolic acid

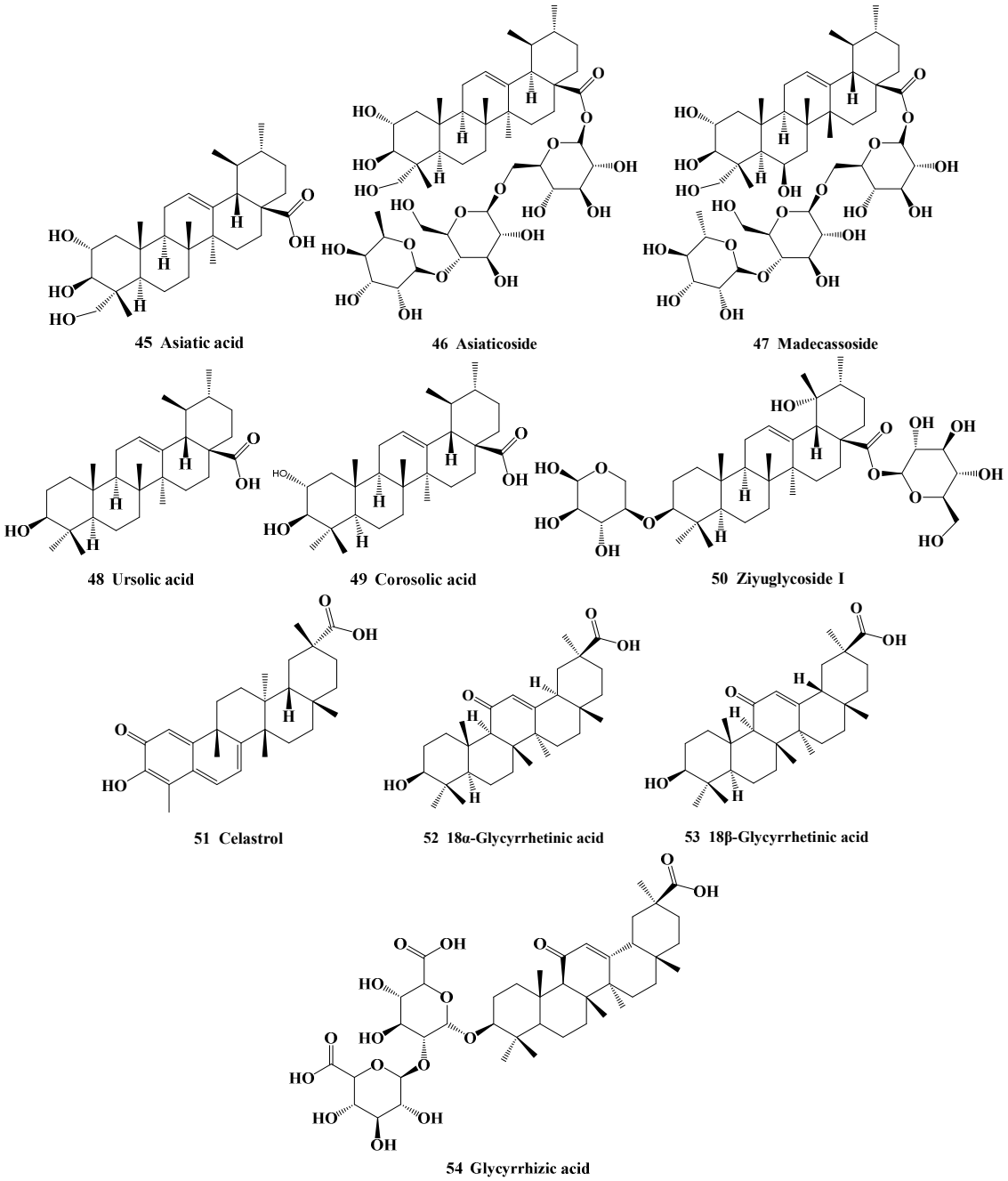


Figure 6: The Structures of Triterpenoids

6. Tetraterpenoids

Tetraterpenoids consist of 8 isoprene units containing 40 carbon atoms of terpenoids. Carotene pigments are the most common tetraterpenoids, which are fat-soluble pigments, and a series of conjugated double bond chromophores exist in their molecules, which gives them strong antioxidant activity and anti-aging potential. Recently, some tetraterpenoids (see Figure 7) have been reported to have anti-aging effects. **Lycopene (LY**; **55)**, a lipophilic red-colored carotenoid pigment from tomatoes, can reactivate SIRT1 and improve insulin resistance, thereby reversing vascular senescence [131]. LY possesses a powerful antioxidant activity which inhibits aging, cardiovascular disease, and T2DM caused by OS and the accumulation of ROS and NO [132]. And LY has therapeutic potential to treat metabolic disorders such as diabetes and obesity, which may be associated with some

mechanisms, including JNK/MAPK, PI3K/AKT, SIRT1/FOXO1/PPARγ signaling pathways and AChE activity [133]. **Zeaxanthin (ZEA**; **56)**, a common carotenoid alcohols found in nature, can repair age-related AD through a decrease in Aβ levels and the regulatory function of neurotransmitters [134]. ZEA can improve the body's anti-OS ability by downregulating myelodidase and MDA levels, upregulating superoxide dismutase (SOD) and catalase (CAT) activity, and increasing GSH levels. At the same time, ZEA exerts anti-inflammatory properties by inhibiting TNF-α, interferon-gamma (IFN-γ), IL-6, IL-1β, and NF-κB levels, and inhibiting nitric oxide synthase (NOS) and COX-2 protein expression [135]. **Lutein (LT**; **57)**, a xanthophyll carotenoid, with its superior antioxidant properties, protects cells from OS-induced cellular senescence, so it is able to treat age-related macular degeneration and OS-associated retinal diseases [136]. LT can extend the lifespan of Drosophila melanogafly through upregulation of endogenous antioxidant enzymes (SOD, SOD1 and SOD2). In addition, LT has beneficial effects on brain function and brain structure in older adults. 12 months of 10 mg LT intake can selectively affect brain activity and the total gray matter volume in the elderly prefrontal cortex of older adults [137]. **Fucoxanthin (FCT**; **58)**, an epoxycarotenol derived from brown seaweed, inhibits the production of pro-inflammatory cytokines, eotaxin and ROS in inflammatory human tracheal epithelial BEAS-2B cells, Increasing GSH and SOD levels in the lungs of asthmatic mice and reducing MDA levels can improve pathological changes associated with asthma in mice [138]. FCT can increase the expression levels of genes associated with the Nrf2/ARE pathway and can also alter cellular processes such as ribosome biogenesis, lipid metabolism, and cell cycle regulation, including some age-related signaling pathways, including Wnt, janus kinase (JAK)/signal transducer and activator of transcription (STAT), and FOXO signaling pathways [139]. FCT can significantly inhibit ROS production in OS-induced RPE damage, reduce MDA concentration and improve mitochondrial metabolic rate. Pathological changes in RPE in aging, including Aβ deposition, beta-site amyloid precursor protein-cleaving enzyme 1 expression, and tight junction disruption, are improved after FCT treatment [140]. **Astaxanthin (ATX**; **59)**, a widely distributed keto-carotenoid, is a promising anti-aging agent, which exerts a variety of biological activities through the participation of Nrf2, including antioxidant, anti-inflammatory, anti-aging, anti-diabetic, anti-cancer, and protective effects on cardiovascular, nervous, skin, lung, and liver [141]. Elevated levels of interleukin-2 (IL-2), immunoglobulin M (IgM), and immunoglobulin G (IgG) after ATX treatment suggest that ATX can modulate cellular immunity and humoral immunity to attenuate immune aging. ATX can improve OS and immune damage in rat models of D-gal-induced aging by upregulating Nrf2 and downregulating Keap1, lowering IL-1β and IL-6 levels, and expression of NF-κB p65 and IκB alpha proteins [142]. In addition, ATX also regulates OS and the aging process by modulating insulin signaling pathways around DAF-16. In addition to insulin signaling pathways, other pathways including dietary restriction, AMPK, and mTOR also rely on DAF-16 [143]. In addition, ATX may alleviate UV exposure-induced skin photoaging [144]. In addition, ATX can improve learning, cognition, and memory in mice by modulating expression of synaptic proteins in mouse hippocampus through the sirtuin 1/PGC-1α signaling pathway [145]. **Crocin (CC**; **60)**, a rare water-soluble carotenoid in nature, was able to significantly reverse age-related OS and neuroinflammation markers. At the same time, high concentrations of CC significantly improve cholinergic and mitochondrial function, as well as enhance cognitive effects, and promote the delay of the aging process in the brain [146]. CC is able to enhance memory function in D-gal aging models through its anti-glycation and antioxidant properties, and can also prevent age-related brain disease via increasing activities of PI3K/AKT and ERK/MAPK pathway and inhibiting production of inflammatory mediators (IL-1, TNF and NF-κB) in the brain [147]. CC improves cell proliferation inhibited by UVB irradiation and prevents cell cycle arrest. In addition, CC reduces UVB-induced ROS by increasing GPX-1 expression and other direct neutralizing effects while promoting expression of the extracellular matrix protein Col-1 [148]. CC can also downregulate protein levels of cyclin-dependent kinase 5 (CDK5) and reduce PPARγ phosphorylation through activation of AMPK, thereby creating a protective effect against glucose and lipid metabolic dysfunction [149].

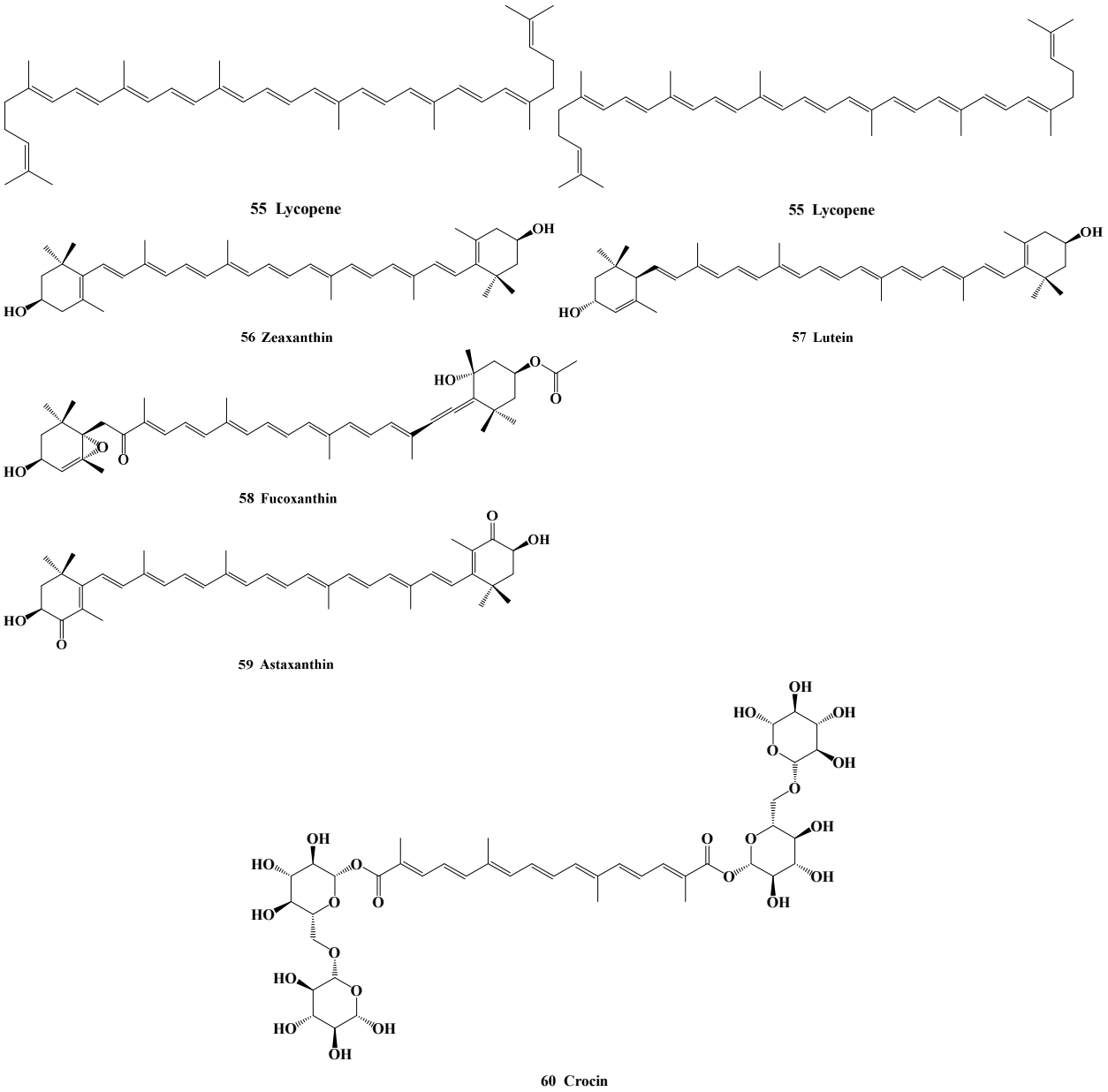


Figure 7: The Structures of Tetraterpenoids

Conclusion and Prospect

In this paper, 60 terpenoids from different sources and their role in anti-aging activity are classified and reviewed. Their anti-aging activity is associated with a number of signaling pathways, including AMPK, SIRT1, PI3K/AKT, NF-κB, mTOR, etc., and can also directly neutralize and eliminate ROS by relying on its own excellent antioxidant properties or otherwise exert anti-aging functions. Terpenoids are widely distributed in nature and have a wide range of quantities and types, but at present, there are more studies on anti-aging activities of compounds such as flavonoids and polyphenols, and the research on terpenoids is not extensive. Therefore, the research of anti-aging terpenoids is very promising. In short, terpenoids are an important branch of anti-aging drugs, and more terpenoids will be issued and eligible for clinical application.

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