REVIEW

Current Perspective in the Discovery of Anti-aging Agents from Natural Products

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Abstract Aging is a process characterized by accumulating degenerative damages, resulting in the death of an organism ultimately. The main goal of aging research is to develop therapies that delay age-related diseases in human. Since signaling pathways in aging of Caenorhabditis elegans (C. elegans), fruit flies and mice are evolutionarily conserved, compounds extending lifespan of them by intervening pathways of aging may be useful in treating age-related diseases in human. Natural products have special resource advantage and with few side effect. Recently, many compounds or extracts from natural products slowing aging and extending lifespan have been reported. Here we summarized these compounds or extracts and their mechanisms in increasing longevity of C. elegans or other species, and the prospect in developing anti-aging medicine from natural products.

Keywords Aging · Natural products · Anti-aging · Drug screening

1 Introduction

Since realizing the inevitability of death, the fear of death and pursuit of immortality might have preoccupied with human beings. In the Epic of Gilgamesh, Gilgamesh (the Sumerian king of Uruk) was obsessed in pursuit of immortality herbal. About 200 BC, Qin Shi Huang (the first emperor of a unified China) feared death and desperately sought the fabled elixir of life. A more recent story was the Spanish explorer Ponce de Leon who was looking for the mythical fountain of youth. Unexpectedly, all these human activities of pursuing for immortality were failed. We now know that there is no such elixir of immortality placed in somewhere by god and waited for human to find it.

On the other hand, early medical practice was developed in Babylon, Egypt, Greece, India, and China. Along with the development of biology, chemistry, physics and math, the west medical tradition developed into modern medical science. Great success has been achieved in prevention and treatment of disease. Consequently, the longevity of human has been greatly extended. The aged population is growing...
rapidly in modern world. Aging is the most risk factor for many age-associated diseases, such as neurodegenerative disease, diabetes, stroke, and cancer. The aged people are often suffering from one or multiple aging associated diseases, which brings enormous social and economic burden. While current medicine is focused on treatment of individual disease, the aging people recovered for one disease would probably suffer from other disease soon later.

Two thousand years ago, a systematic theory and practice to achieve healthy aging with core idea of “preventive treatment of disease” was proposed in Huang Di Nei Jing (one of the most important classical texts of traditional Chinese medicine). Current geroscience research have revealed key molecular processes that underlie biological aging [1], and that delaying aging process could delay the onset and progress of age-associated diseases and the disability of aging people [2]. As the modern version of “the preventative treatment of disease”, anti-aging medicine could be the most effective way to combat the age-associated diseases and the disability of aging people. Currently, many compounds with anti-aging activity have been discovered. A large portion of these compounds are natural products. Therefore, we summarized these natural products or extracts that are reported to have anti-aging effects. We also discussed the prospect and challenges of natural products in development of anti-aging medicine.

2 Current Progress in Aging Research

Biological process was relying on the delicate interaction of biomolecules. These building blocks of organism were selected during the origin of life, and were imperfect and intrinsic to generation of damage in every biological process, such as in DNA replication, epigenetic modification, transcription and translation, protein post-translational modification, protein fold, and metabolic process. For some of the damages were endangering species survival, their correction mechanisms were evolved by natural selection, such as DNA repair, protein unfolding response, antioxidant mechanism, detoxification, autophagy, and proteasome. The failure of these protection processes would cause the occurrence of aging and pathological phenotypes, while enhancing these protection processes would delay aging and related phenotypes. Here we summarized how the dynamic interactions between various damages and errors occurred in biological process and their evoked response of correction mechanisms contribute to genome stability, proteostasis and metabolic homeostasis, to cellular homeostasis and finally to aging process (Figs. 1, 2).

For the detailed mechanisms of aging, we refer to the reviews elsewhere [1, 3–8].

2.1 Genome Stability and Aging

Accumulation of genome damage is one of the major causes of aging [9]. The intrinsic threats to DNA integrity, including DNA replication errors, spontaneous hydrolytic reactions, and reactive oxygen species (ROS), together with exogenous physical (e.g. UV/IR radiation), chemical and biological agents (e.g. virus) cause various genetic lesions, such as point mutations, translocations, chromosomal gains and losses, telomere shortening, and gene disruption. About 70,000 lesions per day were estimated to happen in each normal human cell [10]. Accordingly, a complex repair mechanisms, such as base excision repair (BER), nucleotide excision repair (NER), transcription-coupled repair (TCR), homologous recombination, non-homologous end-joining (NHEJ), and telomere elongation have been evolved in the organism. The deletion of genes for BER were lethal in mice [11], while mutations affecting NER and TCR were associated with numerous disorders and accelerated aging [12–14]. Mice with defected in NHEJ were subjected to early onset of aging [15]. The discovery of the causality between telomere shortening and cell replication limits, has led to the generation of telomere theory of aging [16]. Patients with inherited telomere syndrome presents greater overall telomere attrition and premature aging [16]. Compounds with improving telomerase activity or suppressing telomere shortening play distinct roles in anti-aging [17].

The epigenetic changes are one of the hallmarks of aging, including alterations in transcription factor binding, histone marks, DNA methylation, and nucleosome positioning [18]. These epigenetic changes can either happen spontaneously or modulated by environmental stimuli, nutrient signaling, and metabolic state, via multiple enzymatic systems including DNA methyltransferases, histone acetylases, deacetylases, methylases, demethylases, and other protein complex. These epigenetic changes can cause aberrant transcription and noncoding RNA expression and impair DNA integrity, affect cellular function and stress resistance, heavily influence the progression of aging. Diet or environment and genetic influencing epigenetic information could alter aging process [19]. Humans and mice with genetic defects in genome maintenance present accelerated aging symptoms, while enhancing DNA maintenance could delay aging [20].

2.2 Proteostasis and Aging

Errors happen on proteins including abnormally synthesized proteins, protein unfolding, abnormal cleavage, undesirable posttranslational modifications, can cause protein self-assembling into toxic oligomeric structures or aggregation into cytosolic inclusions. These damaged
proteins can be recognized by chaperones or heat shock proteins and delivered to degradation by the ubiquitin/proteasome system or the lysosomes/autophagy. Increased protein damages would compromise endo-reticulum (ER) homeostasis, lead to increased synthesis of ER chaperones and reduced protein translation to maintain proteostasis, this response is called the unfolding protein response (UPR) [21]. The ability to maintain the protein homeostasis decline with age, many age-related diseases, such as Alzheimer’s disease, Parkinson’s disease, and ALS are associated with intracellular accumulation of abnormal proteins in the form of protein inclusions and aggregates [22]. Chaperone defective could lead to accelerated aging [23], while activation of the master regulator of the heat-shock response, the transcription factor HSF-1, could upregulate heat-shock proteins and increase longevity in C. elegans and mice [24, 25].

2.3 Metabolic Homeostasis and Aging

Metabolism provides energy for cell activity, molecules attending signaling transmission, and building block of cell components. Genome instability, proteostasis failure, and environmental influence could lead to abnormal energy supply and metabolite production, such as excessive free oxygen radicals and toxic molecules. Free oxygen radicals including reactive oxygen species (ROS) and diffusible hydrogen peroxide (H₂O₂), could lead to accumulated oxidative damages, such as carbonylation, oxidized methionine, glycation, aggregation of proteins and DNA damage, and contribute to aging and age-related diseases [26]. This process was proposed by the famous free radical theory of aging. Many compounds increase longevity or improve age-related diseases via scavenging free radicals, such as resveratrol, astaxanthin and gallic acid [27–29].

JNK, a MAP kinase family member, activated by oxidative stress increases longevity in fruit flies and worms [30, 31]. Reduced function of electron transport chain (ETC) could dramatic extend the lifespan of C. elegans and Drosophila [32, 33]. Recently research shows that mitophagy modulates bioenergetics and survival in the neurodegenerative disease by reducing redox and damage [34].

The regulation of metabolism is closely coupled with nutrient sensing pathways, including insulin-like growth factor (IGF) signaling (IIS) pathway [35], target of rapamycin (TOR) signaling [36], adenosine monophosphate activated protein kinase (AMPK) pathway [37], and sirtuins [38]. These signaling pathways sense nutrient or metabolites to regulate the level of glucose, amino acid, cAMP and nicotinamide adenine dinucleotide (NAD⁺). These pathways regulate growth, metabolic and aging process. Genetic or pharmacological intervention of their components can extend lifespan and delay age-associated dysregulation [8].

Fig. 1 Aging mechanisms in different hierarchies
2.4 Cellular Homeostasis and Aging

Failure to maintain genome stability, proteostasis and metabolic homeostasis will lead to imbalance of cellular homeostasis and cellular senescence. Genome instability could lead to abnormality of nuclear structure, while excessive protein aggregation could cause ER malfunction. Genome damage, defective proteins, and excessive production of ROS could impair mitochondria. Mitochondria damage could induce rescue mechanisms: mitochondrial biogenesis, mitochondria specific unfolded protein response and mitophagy (macroautophagy that targets deficient mitochondria for proteolytic degradation) [39]. Recently research shows that mitophagy modulates bioenergetics and survival in the neurodegenerative disease by reducing redox and damage [34]. The increased damage and reduced repair response are important to aging process.

Senescent cells secret signaling molecules enriched in proinflammatory cytokines and matrix metalloproteinases, which could attract mast cells to clear the senescent cells through macrophage. But deficient clearance of senescent cells will induce inflammation, impair adjacent cells and tissue function, and lead to stem cell exhaustion, and finally contribute to aging [40]. Either genetic or pharmacological elimination of senescent cells could delay age-related pathologies [41, 42].

3 Natural Products with Anti-aging Activity

To date, there are about 5, 400 scientific research/review articles published under the terms of “anti-aging” and “anti-ageing” terms (obtained from Web of Science, May 2017; keywords restricted to the topics: anti-aging and anti-ageing, at the search domain of Science & Technology). These reports revealed more than 300 compounds with anti-aging activity. Here we summarized the compounds or natural product extracts with explicit anti-aging activity, including 185 compounds from natural products (Table 1), 55 complex or extracts from natural products (Table 2), 62 from clinical drugs (of which more than 50% are also from natural products or natural products analogues, Table 3), 35 from synthesized chemicals (Table 4). Some of them received popular interest and under vigorous investigation, present anti-aging activities in multiple aging models, such as resveratrol [28, 43–53], α-lipoic acid [54–56],
| CAS   | Chemicals      | Structure                  | Source                                      | Anti-aging activity and proposed anti-aging mechanism                                                                                                                                                                                                 |
|-------|----------------|----------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 501-36-0 | Resveratrol    | ![Resveratrol Structure](image) | *Polygonum cuspidatum* Sieb. et Zucc.       | In mice: 4.7% increase in mean lifespan; increasing insulin sensitivity, reducing insulin-like growth factor-1 (IGF-I) levels, increasing AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-gamma coactivator 1alpha (PGC-1alpha) activity, increasing mitochondrial number, and improving motor function [44, 46–51]. |
|        |                |                            |                                             | In *D. melanogaster*: extends mean lifespan of females fed the low sugar–high protein diet by ~15.0%, fed the high-fat diet by ~10.0%; modulating genetic pathways that can reduce cellular damage [45].                                                                                                         |
|        |                |                            |                                             | In *C. elegans*: 18.0% increase in mean lifespan; regulating AMPK, SIR-2.1, autophagy, and proteasomal degradation [28, 52, 53].                                                                                                                              |
|        |                |                            |                                             | In cell: increasing NAD(+) and the activity of AMPK and Sirt1, inhibiting PDE4, JAK2/STAT3 [89–92].                                                                                                                                                       |
|        |                |                            |                                             | In *S. cerevisiae*: 70.0% increase in mean lifespan; regulating Sir2 and SNF1 [93, 94].                                                                                                                                                                     |
|        |                |                            |                                             | In *Nothobranchius guentheri*: antioxidant [95].                                                                                                                                                                                                         |
| 62-46-4 | α-Lipoic acid  | ![α-Lipoic acid Structure](image) | Cell metabolite                             | In SAMP8 mice: improving memory and oxidative stress in extremely old SAMP8 mice, but decreasing lifespan [56].                                                                                                                                                 |
|        |                |                            |                                             | In *D. melanogaster*: 12.0% increase in mean lifespan and antioxidant [54].                                                                                                                                                                                 |
|        |                |                            |                                             | In *C. elegans*: 24.0% increase in mean lifespan and antioxidant, enhancing chemotaxis index [55].                                                                                                                                                        |
| CAS     | Chemicals          | Structure | Source                          | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|--------------------|-----------|---------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 472-61-7| Astaxanthin        | Carotenoid| In \(\text{D-galactose-induced brain aging in rats: antioxidant, upregulating BDNF expression}\) \[58, 59\] | In \(\text{D. melanogaster: antioxidant}\) \[57\] In \(\text{C. elegans: 29.0}\%\text{ increase in mean lifespan and regulating DAF-16}\) \[29\] |
| 154-23-4| Catechin           | Green tea, cocoa, grapes, and apples| In \(\text{D. melanogaster: 16.0}\%\text{ increase in mean lifespan and antioxidant}\) \[61, 96\]        | In \(\text{C. elegans: 13.0}\%\text{ increase in mean lifespan and antioxidant, regulating DAF-2, AKT-2, MEV-1, and NHR-8; decreasing insulin-like growth factor-1}\) \[60\] |
| 458-37-7| Curcumin           | Curcuma longa L. | In \(\text{C57BL6/N mice: antioxidant, increasing collagen and AGES}\) \[64\] | In \(\text{D. melanogaster: 25.8}\%\text{ increase in mean lifespan and antioxidant}\) \[65\] In \(\text{C. elegans: 25.0}\%\text{ increase in mean lifespan and antioxidant}\) \[63\] |
| 3351-86-8| Fucoxanthin       | Natural substances in human diet | In \(\text{hairless mice: lessening UVB-induced epidermal hypertrophy, VEGF, and MMP-13 expression}\) \[67\] | In \(\text{D. melanogaster: 33.0}\%\text{ increase in mean lifespan and antioxidant}\) \[66\] In \(\text{C. elegans: 14.0}\%\text{ increase in mean lifespan and antioxidant}\) \[66\] |
| 124-20-9| Spermidine         | Natural polyamine | In \(\text{D. melanogaster: 30.0}\%\text{ increase in mean lifespan and autophagy}\) \[68\] | In \(\text{C. elegans: 15.0}\%\text{ increase in mean lifespan and autophagy}\) \[68\] In \(\text{S. cerevisiae: autophagy}\) \[68, 69\] |
| CAS        | Chemicals            | Structure                                      | Source                                    | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|------------|----------------------|------------------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 480-44-4   | Acacetin             | ![Acacetin Structure](image)                   | Naturally occurring flavonoid            | In *D. melanogaster*: decreasing APP protein expression, BACE-1 activity, and Ab production [97]                      |
|            |                      |                                                |                                           | In *C. elegans*: 27.3% increase in mean lifespan and upregulating SOD-3 and GST-4 [98]                                 |
| 64-19-7    | Acetic acid          | ![Acetic acid Structure](image)                | Vinegars                                  | In *C. elegans*: 23.0% increase in mean lifespan and regulating insulin/IGF-1 pathway [99]                            |
|            |                      |                                                |                                           | In *S. cerevisiae*: stimulating growth signaling pathways, increasing oxidative stress and replication stress [100]   |
| 1005344-44-4 | Antcin M            | ![Antcin M Structure](image)                  | *Antrodia cinnamomea*                     | In cell: antioxidant, regulating Nrf2 and SIRT-1 [101]                                                              |
|            |                      |                                                |                                           | In *C. elegans* from oxidative stress: ~10.0% increase in mean lifespan and antioxidant [101]                           |
| 306-60-5   | Agmatine             | ![Agmatine Structure](image)                   | Generated by arginine decarboxylase      | In male sprague–dawley rats: suppressing age-related elevation in nitric oxide synthase activity in the dentate gyrus of the hippocampus and prefrontal cortex [102] |
|            |                      |                                                |                                           | In *C. elegans*: 16.0% increase in mean lifespan and needs further research [103]                                      |
| 328-50-7   | α-Ketoglutarate      | ![α-Ketoglutarate Structure](image)            | Tricarboxylic acid cycle intermediate    | In mice: decreasing TBARS level and the activity of superoxide dismutase, increasing glutathione peroxidase activity [104] |
|            |                      |                                                |                                           | In *C. elegans*: 50.0% increase in mean lifespan and inhibiting ATP synthase and TOR signaling [105]                   |
| CAS      | Chemicals                  | Structure                  | Source                                    | Anti-aging activity and proposed anti-aging mechanism |
|----------|----------------------------|----------------------------|-------------------------------------------|-------------------------------------------------------|
| 491-67-8 | Baicalein                  | ![Baicalein Structure](image) | Scutellaria baicalensis Lamiaceae         | In *C. elegans*: 24.0% increase in mean lifespan and antioxidant, regulating SKN-1 [106]  
|          |                            |                            |                                           | In PC12 cell: suppressing mitochondria dysfunction and apoptosis [107] |
| 107-43-7 | Betaine                    | ![Betaine Structure](image) | Nitrogen containing metabolite            | In aged rats: upregulating IKK/MAPKs, attenuating NF-κB activation [108, 109]  
|          |                            |                            |                                           | In *C. elegans*: 9.0% increase in mean lifespan and needs further research [103] |
| 331-39-5 | Caffeic acid               | ![Caffeic acid Structure](image) | Tomatoes, carrots, strawberries, blueberries and wheat | In Sprague–Dawley rats and intracerebroventricular streptozotocin induced experimental dementia in rats: antioxidant, restoring cholinergic functions [110, 111]  
|          |                            |                            |                                           | In *C. elegans*: 11.0% increase in mean lifespan and regulating OSR-1, SEK-1, SIR-2, UNC-43, and DAF-16 [112] |
| 305-84-0 | Carnosine                  | ![Carnosine Structure](image) | Endogenous dipeptide                      | In aged rats: preventing oxidative stress and apoptosis [113, 114]  
|          |                            |                            |                                           | In *D. melanogaster*: 26.0% increase in mean lifespan and antioxidant [115, 116] |
| 2415-24-9| Catalpol                   | ![Catalpol Structure](image) | Rehmannia glutinosa                       | In senescent mice induced by d-galactose: improving cholinergic function, reducing inflammatory cytokines; In rats: rebalancing E2 and P4 levels in aged rats [117, 118]  
|          |                            |                            |                                           | In *C. elegans*: 28.5% increase in mean lifespan and antioxidant, regulating SKN-1/Nrf and DAF-16 [119] |
| CAS     | Chemicals      | Structure          | Source                                         | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|----------------|--------------------|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 327-97-9| Chlorogenic acid| ![Structure](image) | Coffee and tea                                  | In d-galactose-induced mice: antioxidant, reducing tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) protein levels [120]<br> In C. elegans: 20.1% increase in mean lifespan and antioxidant, regulating IIS pathway [121] |
| 303-98-0| Coenzyme Q10   | ![Structure](image) | Mitochondrial respiratory chain component       | In mice: ameliorating age-related impairment, reducing protein oxidation [122]<br> In C. elegans: 18.0% increase in mean lifespan and scavenging reactive oxygen species [123] |
| 3416-24-8| D-Glucosamine  | ![Structure](image) | Hexosamine pathway                              | In mice: 6.0% increase in mean lifespan; enhancing expression of several murine amino-acid transporters, increasing amino-acid catabolism [124]<br> In C. elegans: 11.0% increase in mean lifespan and mimicking a low-carbohydrate diet by regulating AMPK and SKN-1 [124] |
| 75-18-3 | Dimethyl sulfide| ![Structure](image) | Metabolite of marine algae or fermentative bacteria | In D. melanogaster: 24.2% increase in mean lifespan and antioxidant [17]<br> In C. elegans: 24.3% increase in mean lifespan and antioxidant [17] |
| 490-46-0| (−)-Epicatechin | ![Structure](image) | Cocoa                                           | In obese diabetic mice: antioxidant, improving skeletal muscle stress output, reducing systematic inflammation and serum LDL cholesterol [61]<br> In D. melanogaster: ~8.0% increase in mean lifespan and needs further research [61] |
| CAS      | Chemicals              | Structure | Source                  | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|----------|------------------------|-----------|-------------------------|----------------------------------------------------------------------------------------------------------------------|
| 989-51-5 | Epigallocatechin gallate | ![Epigallocatechin Gallate Structure](image)  | Tea polyphenols                                                    | In D-galactose-induced mice: increasing oxidative stress and the expression of EGFR proteins [125]  
                                          |                                                      |                                                      | In C. elegans: 13.0% increase in mean lifespan and antioxidant, regulating IIS pathway [126] |
| 149-91-7 | Gallic acid            | ![Gallic Acid Structure](image)           | Beverages (red wines and green teas), plant leaves (berberis)     | In senescence accelerated mice: antioxidant [127]  
                                          |                                                      |                                                      | In C. elegans: 25.0% increase in mean lifespan and antioxidant [27] |
| 527-07-1 | Gluconate              | ![Gluconate Structure](image)            | Sugars metabolite                                                 | In D. melanogaster: 22.0% increase in mean lifespan and antioxidant [128]  
                                          |                                                      |                                                      | In lacking nitrogen on C. elegans: 16.0% increase in mean lifespan and antioxidant [103] |
| 56-81-5  | Glycerol               | ![Glycerol Structure](image)             | Sugars metabolite                                                 | In lacking nitrogen on C. elegans: 21.0% increase in mean lifespan and needs further research [103]  
                                          |                                                      |                                                      | In rotifer: 50.0% increase in mean lifespan; increasing resistance to starvation, heat, oxidation, and osmotic stress, but not UV stress [129] |
| CAS    | Chemicals   | Structure | Source            | Anti-aging activity and proposed anti-aging mechanism |
|--------|-------------|-----------|-------------------|------------------------------------------------------|
| 520-26-3 | Hesperidin  | ![Hesperidin](image) | Citrus genus       | In Murine model of sepsis: antioxidant [130]  
In S. cerevisiae: 37.0% increase in mean lifespan and antioxidant, regulating Sir2, UTH1 [131] |
| 489-32-7 | Icariin     | ![Icariin](image)   | Herba epimedi     | In mice: inducing antioxidant protein superoxide dismutase (SOD) activity, decreasing oxidative marker malondialdehyde (MDA) [132]  
In C. elegans: 20.7% increase in mean lifespan and regulating IIS pathway [133] |
| 74-79-3 | Arginine    | ![Arginine](image) | Amino acid        | In C. elegans: 27.0% increase in oxidative stress; 370% in heat stress and antioxidant, regulating insulin/IGF signaling pathway [103, 134]  
In Megalobrama amblycephala: antioxidant [134] |
| 50-21-5 | Lactate     | ![Lactate](image)   | Metabolite         | In D. melanogaster: 15.0% increase in mean lifespan and antioxidant [128]  
In C. elegans: 6.0% increase in mean lifespan and antioxidant [103] |
| CAS      | Chemicals              | Structure | Source                        | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|----------|------------------------|-----------|-------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 500-38-9 | Nordi-hydroguaiaretic acid | ![Structure](structure1.png) | Creosote plant (*Larrea tridentata*; *Zygophyllaceae*) | In mice: 12.0% increase in mean lifespan; decreasing the absorption or increasing the utilization of calories [135–138] In Mosquito: 64.0% increase in mean lifespan and needs further research [137] |
| 508-02-1 | Oleanolic acid         | ![Structure](structure2.png) | *Olea europaea*, *Viscum album* L., and *Aralia chinensis* L. | In *D*-galactose-induced mice: antioxidative, anti-glycative, and anti-apoptotic [139] In *C. elegans*: 16.6% increase in mean lifespan and antioxidant, regulating DAF-16 [140] |
| 851983-55-6 | Oligonol           | ![Structure](structure3.png) | Grape seed or lychee fruit | In mice: Regulating AMPK, SIRT1, autophagy, and increasing cell proliferation [141, 142] In *C. elegans*: regulating AMPK and autophagy [141] |
| 27208-80-6 | Polydatin            | ![Structure](structure4.png) | Grape juice | In mice: anti-oxidative, anti-inflammatory, and anti-apoptotic [143] In *C. elegans*: 30.0% increase in mean lifespan and regulating DAF-2, SIR-2.1, SKN-1, SOD-3, and DAF-16 [144] |
| CAS     | Chemicals       | Structure                           | Source                                      | Anti-aging activity and proposed anti-aging mechanism |
|---------|-----------------|-------------------------------------|---------------------------------------------|-------------------------------------------------------|
| 537-15-5| Rosmarinic acid | ![Structure](image)                   | Subfamily Nepetoideae of the Lamiaceae      | In aging mice: antioxidant [145]                      |
|         |                 |                                     |                                             | In C. elegans: 10.0% increase in mean lifespan and regulating SIR-2.1, OSR-1, SEK-1, UNC-43, and DAF-16 [112] |
| 607-80-7| Sesamin         | ![Structure](image)                   | Sesame seeds                                | In D. melanogaster: 12.0% increase in mean lifespan and antioxidant [146] |
|         |                 |                                     |                                             | In C. elegans: 14.0% increase in mean lifespan and regulating DAF-2, SKN-1, PMK-1, and DAF-16 [147] |
| 36062-04-1| Tetra-hydrocurcumin | ![Structure](image)                  | Biotransformed metabolite of curcumin contained in turmeric of Indian curry | In mice: 12.0% increase in mean lifespan; attenuating oxidative stress, hypertension, vascular dysfunction, and baroreflex dysfunction [148–151] |
|         |                 |                                     |                                             | In D. melanogaster: ~28.0% increase in mean lifespan and regulating Sir2 and FoxO [152] |
| 1143-70-0| Urolithin A     | ![Structure](image)                   | Pomegranate fruit, nuts and berries         | In mouse models of age-related decline of muscle function: improving exercise capacity [153] |
|         |                 |                                     |                                             | In C. elegans: 45.4% increase in mean lifespan and regulating mitochondrial function, mitophagy [153] |
Table 1 continued

| CAS      | Chemicals       | Structure | Source          | Anti-aging activity and proposed anti-aging mechanism                          |
|----------|-----------------|-----------|-----------------|---------------------------------------------------------------------------------|
| 3681-93-4 | Vitexin         | ![Vitexin Structure](image) | *Vigna angularis* | In D-galactose-aged mice: antioxidant [154]                                      |
|          |                 |           |                 | In *C. elegans*: 17.0% increase in mean lifespan and antioxidant [155]           |
|          |                 |           |                 | With anti-aging activities in rats or mice                                       |
| 118-00-3 | Guanosine       | ![Guanosine Structure](image) | Endogenous nucleoside | In Wistar rats: antioxidant [156]                                                |
| 70579-26-9 | Porphyra-334  | ![Porphyra-334 Structure](image) | Red alga *Porphyra rosengurttii* | In mice skin: antioxidant, Hsp70 [157]                                           |
| 73112-73-9 | Shinorine      | ![Shinorine Structure](image) | Red alga *Porphyra rosengurttii* | In mice skin: antioxidant, Hsp70 [157]                                           |
| CAS          | Chemicals                          | Structure | Source                  | Anti-aging activity and proposed anti-aging mechanism |
|--------------|------------------------------------|-----------|-------------------------|-------------------------------------------------------|
| 70363-87-0   | Sargaquinoic acid                  | ![Structure](image1) | Sargassum sagamianum    | In mice skin: inducing apoptosis [158]                 |
| 70363-89-2   | Sargachromenol                     | ![Structure](image2) | Sargassum sagamianum    | In mice skin: inducing apoptosis [158]                 |
| 1094-61-7    | β-Nicotinamide mononucleotide      | ![Structure](image3) | Turnover of the oxidized form of nicotinamide adenine dinucleotide (NAD⁺) | In rats: increasing NAD⁺ level [159]                  |
| 1339070-29-9 | TA-65                              | ![Structure](image4) | Root of Astragalus membranaceus | In mice: activating telomerase [160]                   |
| 34157-83-0   | Celastrol                          | ![Structure](image5) | Traditional Chinese medicinal herbs of the Celastraceae family | In transgenic mouse model of amyotrophic lateral sclerosis: 13.0% increase in mean lifespan and regulating HSP70, blocking neuronal cell death [161] |
| CAS       | Chemicals     | Structure  | Source                             | Anti-aging activity and proposed anti-aging mechanism |
|-----------|--------------|------------|------------------------------------|------------------------------------------------------|
| 57-00-1   | Creatine     | ![Creatine Structure](image) | Natural ergogenic compound          | In mice: 9.0% increase in mean lifespan and upregulating genes implicated in neuronal growth, neuroprotection, and learning [162] |
| 42553-65-1| Crocin       | ![Crocin Structure](image) | Kashmiri saffron (Crocus sativus) | In mice: 44.0% increase in mean lifespan and impacting on hematological parameters [163] |
| 61276-17-3| Acteoside    | ![Acteoside Structure](image) | Roots of Incarvillea younghusbandii Sprague | In senescent mouse model induced by a combination of d-gal and AlCl3: decreasing nitric oxide, the activity of nitric oxide synthase and the expression of caspase-3 [164] |
| 11096-26-7| Erythropoietin| Glycoprotein | Glycoprotein hormone               | In rats: antioxidant, regulating ERK/Nrf2-ARE [165] |
| 62499-27-8| Gastrodin    | ![Gastrodin Structure](image) | A number of plants and herbs       | In vascular dementia rats induced by chronic ischemia: antioxidant, regulating ADH7, GPX2, GPX3 and NFE2L2 [166] |
| CAS     | Chemicals           | Structure | Source                  | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|---------------------|-----------|-------------------------|----------------------------------------------------------------------------------------------------------------------|
| 22427-39-0 | Ginsenoside Rg1 | ![Ginsenoside Rg1](image) | *Panax ginseng* | In d-galactose-induced mice: antioxidant, regulating the level of proinflammatory cytokines and telomerase system, activating the Wnt/β-catenin signaling [167, 168] |
| 87-89-8   | Chiro-inositol     | ![Chiro-inositol](image)    | Inositol family | 16.7% increase in mean lifespan and antioxidant, regulating dFOXO [169]                                             |
| 526-95-4 | Gluconic acid      | ![Gluconic acid](image)     | Glucose catabolism | 22.0% increase in mean lifespan and antioxidant [128]                                                               |
|          | Glycoside acteoside | ![Glycoside acteoside](image) | Roots of *Incarvillea younghusbandii* Sprague | 15.0% increase in mean lifespan and antioxidant [170]                                                              |
| CAS       | Chemicals            | Structure | Source                                      | Anti-aging activity and proposed anti-aging mechanism                  |
|-----------|----------------------|-----------|---------------------------------------------|------------------------------------------------------------------------|
| 127-40-2  | Lutein               | ![Lutein Structure](image) | Major carotenoids in most fruits and vegetables | 11.0% increase in mean lifespan and antioxidant [171]                 |
| 1004313-10-3 | S,S-Trolox-carnosine | ![S,S-Trolox-carnosine Structure](image) | Trolox acylated derivatives | 36.0% increase in mean lifespan and antioxidant [116]                 |
| 4670-05-7 | Theaflavins          | ![Theaflavins Structure](image) | Black tea | 10.0% increase in mean lifespan and antioxidant [172]                 |
| 353-09-3  | β-Guani-dinopropionic acid | ![β-Guani-dinopropionic acid Structure](image) | Metabolites | 13.0% in female, 90% in male increase in mean lifespan and regulating AMPK-Atg1-autophagy signaling [173] |
| 19545-26-7 | Wortmannin           | ![Wortmannin Structure](image) | Penicillium funiculosum | 5.0% increase in mean lifespan and inhibiting PI3K [174] |
| CAS     | Chemicals          | Structure | Source                     | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|--------------------|-----------|---------------------------|----------------------------------------------------------------------------------------------------------------------|
| 139-85-5| 3,4-Dihydroxybenzaldehyde | ![Structure](image1.png) | *Sasa senanensis* leaves | 23.0% increase in mean lifespan and inhibiting the 2-oxoglutarate binding sites of prolyl 4-hydroxylase [175] |
| 57-91-0 | β-Estradiol        | ![Structure](image2.png) | Hormone                   | 7.0% increase in mean lifespan and antioxidant [176]                                                                  |
| 1406-65-1| Chlorophyll | ![Structure](image3.png) | Green vegetables          | 25.0% increase in mean lifespan and antioxidant [177]                                                                  |
| 730-08-5| Dipeptide Tyr-Ala  | ![Structure](image4.png) | Hydrolyzed maize protein  | 12.4% increase in mean lifespan and antioxidant [178]                                                                  |
| CAS       | Chemicals                       | Structure                           | Source                          | Anti-aging activity and proposed anti-aging mechanism                                      |
|-----------|---------------------------------|-------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------|
| 934822-64-7 | Ferulsinaic acid                 | ![Structure](image1.png)            | Sesquiterpene coumarins from the genus Ferula | 20.0% increase in mean lifespan and antioxidant [179]                                         |
| 446-72-0   | Genistein                        | ![Structure](image2.png)            | Vigna angularis                 | 27.9% increase in mean lifespan and antioxidant [180, 181]                                     |
|           | Quercetin 3-O-β-D-glucopyranoside | ![Structure](image3.png)            | Onion                           | 12.4% increase in mean lifespan and antioxidant [182]                                         |
| 69-72-7    | Salicylic acid                   | ![Structure](image4.png)            | Plant hormone                   | 14.0% increase in mean lifespan and antioxidant [183]                                         |
| 72514-90-0 | Specioside                       | ![Structure](image5.png)            | Stereospermum suaveolens        | 15.5% increase in mean lifespan and antioxidant [184]                                         |
| CAS     | Chemicals       | Structure           | Source                  | Anti-aging activity and proposed anti-aging mechanism                      |
|---------|----------------|---------------------|-------------------------|--------------------------------------------------------------------------------|
| 480-18-2| Taxifolin      | ![Taxifolin structure](image) | Citrus fruits and onion | 51.0% increase in mean lifespan and antioxidant [185]                        |
| 3081-61-6| Theanine      | ![Theanine structure](image)          | *Camellia sinensis*      | ~5.0% increase in mean lifespan and antioxidant [186]                        |
| 6829-55-6| Tocotrienols  | ![Tocotrienols structure](image)       | Vitamin E members        | ~20.0% increase in mean lifespan and antioxidant [187]                        |
| 53188-07-1| Trolox        | ![Trolox structure](image)            | Vitamin E analog         | 31.0% increase in mean lifespan and antioxidant [185]                        |
| 528-48-3 | Fisetin        | ![Fisetin structure](image)           | Apples, onions and grapes and many more herbal edibles | 6.0% increase in mean lifespan of thermal stress and antioxidant, regulating DAF-16 [188] |
| CAS          | Chemicals                  | Structure | Source               | Anti-aging activity and proposed anti-aging mechanism                                      |
|--------------|----------------------------|-----------|----------------------|------------------------------------------------------------------------------------------|
| 215112-16-6  | 4-Hydroxy-E-globularinin   | ![Structure](image1) | *Premna integrifolia* | 18.8% increase in mean lifespan and antioxidant, regulating DAF-16 [189]                 |
| 521-48-2     | Iso-xanthohumol             | ![Structure](image2) | *Humulus lupulus* L. | 10.2% increase in mean lifespan and antioxidant, regulating DAF-16 [190]                |
| 520-18-3     | Kaempferol                  | ![Structure](image3) | Apples, onions and grapes and many more herbal edibles | 10.0% increase in mean lifespan and antioxidant, regulating DAF-16 [188]                |
| 117-39-5     | Quercetin                   | ![Structure](image4) | Onions, apples, and broccoli as well as in red wine, tea, and extracts of *Ginkgo biloba* | 15.0% increase in mean lifespan and antioxidant, regulating DAF-16 [191]                |
| CAS   | Chemicals         | Structure | Source                        | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-------|-------------------|-----------|-------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 50932-19-9 | Verminoside | ![Verminoside](image1) | Stereospermum suaveolens | 20.8% increase in mean lifespan and antioxidant, regulating DAF-16 [192]                                              |
| 113558-15-9 | Icarin II       | ![Icarin II](image2) | Icarin active metabolite     | 20.0% increase in mean lifespan and regulating IIS signaling [133]                                                   |
| 99-20-7   | Trehalose        | ![Trehalose](image3) | Disaccharide of glucose      | 32.0% increase in mean lifespan and regulating IIS signaling [193]                                                   |
| 32911-62-9 | Withanamide A   | ![Withanamide A](image4) | Ayurvedic                    | 29.7% increase in mean lifespan and regulating IIS pathway and neural activity [194]                              |
| CAS      | Chemicals    | Structure                          | Source            | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|----------|--------------|------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------|
| 501-94-0 | Tyrosol      | ![Tyrosol Structure](image)         | Extra virgin olive oil | 10.8% increase in mean lifespan and regulating IIS pathway and heat shock response [195–197]                    |
| 4339-71-3| Piceatannol  | ![Piceatannol Structure](image)     | Grapes and white tea | ~18.3% increase in mean lifespan and regulating IIS pathway and SIR-2.1 [198]                                  |
| 52-89-1  | Cysteine     | ![Cysteine Structure](image)        | Amino acids        | 16.0% increase in mean lifespan and regulating AMPK and DAF-16 [103]                                           |
| 6537-80-0| Chicoric acid| ![Chicoric acid Structure](image)   | Caffeoyl derivative | 21.0% increase in mean lifespan and regulating AMPK [199]                                                      |
| 328-42-7 | Oxaloacetate | ![Oxaloacetate Structure](image)    | Citric acid cycle metabolite | 25.0% increase in mean lifespan and regulating AMPK [200]                                                   |
| CAS       | Chemicals                             | Structure                          | Source                                | Anti-aging activity and proposed anti-aging mechanism                                      |
|-----------|---------------------------------------|------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------------|
| 29700-22-9| Oxy-resveratrol                       | ![Structure](image1.png)           | Isomer of hydroxylated resveratrol    | 31.1% increase in mean lifespan and regulating calorie restriction, AMPK, and SIR-2.1 [201]   |
|           | β-Dihydro-agarofuran-type sesquiterpenes| ![Structure](image2.png)           | Seeds of *Celastrus monospermus*      | 38.0% increase in mean lifespan and rapamycin mimetics [202]                              |
| 13095-47-1| (R)-2-Hydroxyglutarate                | ![Structure](image3.png)           | Oncometabolite                        | 43.0% increase in mean lifespan and inhibiting ATP synthase and mTOR signaling [203]       |
| 13095-48-2| (S)-2-Hydroxyglutarate                | ![Structure](image4.png)           | Oncometabolite                        | 32.0% increase in mean lifespan and inhibiting ATP synthase and mTOR signaling [203]       |
| 765-01-5  | 10-Hydroxy-2-decenoic acid            | ![Structure](image5.png)           | Major lipid component of Royal Jelly  | 10.0% increase in mean lifespan and regulating dietary restriction and mTOR signaling [204]|
| Ascr#2    |                                       | ![Structure](image6.png)           | Pheromone                             | 14.0% increase in mean lifespan and regulating SIR-2.1 [205]                              |
| Ascr#3    |                                       | ![Structure](image7.png)           | Pheromone                             | 14.0% increase in mean lifespan and regulating SIR-2.1 [205]                              |
| CAS    | Chemicals                      | Structure        | Source                                | Anti-aging activity and proposed anti-aging mechanism                                      |
|--------|--------------------------------|------------------|---------------------------------------|------------------------------------------------------------------------------------------|
| 1740-19-8 | Dehydro-abietic acid         | ![Dehydro-abietic acid](image1) | *P. densiflora,* *P. sylvestris,* *Abies grandis* | 15.5% increase in mean lifespan and regulating SIR-2.1 [206]                              |
| 7783-06-4 | Hydrogen sulfide             | ![Hydrogen sulfide](image2) | Naturally produced in animal cells | 74.0% increase in mean lifespan and antioxidant, regulating SIR-2.1 [207, 208]              |
| 932-30-9  | Salicylamine                  | ![Salicylamine](image3)   | Phenolic amines                        | 56.0% increase in mean lifespan and regulating SIR-2.1 and ETS-7 [209]                     |
| 481-39-0  | Juglone                       | ![Juglone](image4)      | Roots, leaves, woods and fruits of *Juglandaceae* walnut trees | 29.0% increase in mean lifespan and regulating SIR-2.1 and DAF-16 [210]                     |
| 53-84-9   | Nicotinamide adenine dinucleotide | ![Nicotinamide adenine dinucleotide](image5) | Porphyrin-peptide | 19.1% increase in mean lifespan and regulating SIR-2.1 and DAF-16 [211]                     |
| 149-61-1  | Malate                        | ![Malate](image6)     | Tricarboxylic acid cycle metabolite    | 14.0% increase in mean lifespan and regulating dietary restriction, SIR-2.1, and DAF-16 [213] |
| CAS     | Chemicals                  | Structure                  | Source                | Anti-aging activity and proposed anti-aging mechanism                                      |
|---------|----------------------------|----------------------------|-----------------------|------------------------------------------------------------------------------------------------|
| 70-47-3 | Asparagine                 | ![Asparagine structure](image1) | Amino acid            | 5.0% increase in mean lifespan and regulating SKN-1 [103]                                      |
| 2050-87-5 | Diallyl trisulfide       | ![Diallyl trisulfide structure](image2) | Garlic               | 12.6% increase in mean lifespan and regulating SKN-1 [214]                                    |
| 481-42-5 | Plumbagin                 | ![Plumbagin structure](image3) | Plumbago zeylanica L. | 15.0% increase in mean lifespan and regulating SKN-1 [215]                                    |
| 77-59-8 | Tomatidine                | ![Tomatidine structure](image4) | Unripe tomato fruits, leaves and stems | 7.0% increase in mean lifespan and regulating SKN-1/Nrf2 pathway, mitophagy [216]             |
| 21593-77-1 | S-Allylcysteine       | ![S-Allylcysteine structure](image5) | Allium sativum L.    | 17.0% increase in mean lifespan and antioxidant, regulating SKN-1 [217]                      |
| 2281-22-3 | S-Allylmercapto-cysteine | ![S-Allylmercapto-cysteine structure](image6) | Allium sativum L.    | 20.9% increase in mean lifespan and antioxidant, regulating SKN-1 [217]                      |
| 61-90-5 | Leucine                  | ![Leucine structure](image7) | Amino acids           | 16.0% increase in mean lifespan and regulating SKN-1 and DAF-16 [103]                         |
| CAS      | Chemicals     | Structure | Source         | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|----------|---------------|-----------|----------------|------------------------------------------------------------------------------------------------------------------|
| 62333-08-8 | Isolappao A   | ![Structure of Isolappao A](structure.png) | A. lappa seeds | 11.0% increase in mean lifespan and regulating JNK-1 and DAF-16 [218]                                              |
| 64855-00-1 | Lappaol C     | ![Structure of Lappaol C](structure.png) | A. lappa seeds | 12.0% increase in mean lifespan and regulating JNK-1 and DAF-16 [218]                                              |
| 69394-17-8 | Lappaol F     | ![Structure of Lappaol F](structure.png) | A. lappa seeds | 13.0% increase in mean lifespan and regulating JNK-1 and DAF-16 [218]                                              |
| 580-72-3  | Matairesinol  | ![Structure of Matairesinol](structure.png) | Arctium lappa | 25.0% increase in mean lifespan and regulating JNK-1 and DAF-16 [218]                                              |
| 7770-78-7 | Arctigenin    | ![Structure of Arctigenin](structure.png) | Arctium lappa | 14.0% increase in mean lifespan and antioxidant, regulating JNK-1 and DAF-16 [218]                                |
| CAS      | Chemicals | Structure | Source            | Anti-aging activity and proposed anti-aging mechanism                                          |
|----------|-----------|-----------|-------------------|-------------------------------------------------------------------------------------------------|
| 20362-31-6 | Arctii | ![Arctiin structure](image) | *Arctium lappa* | 15.0% increase in mean lifespan and antioxidant, regulating JNK-1 and DAF-16 [218]             |
| 484-68-4   | Pinitol   | ![Pinitol structure](image) | Fine wood, alfalfa, and legumes | 13.0% increase in mean lifespan and regulating JNK, S6K, and DAF-16 [169]                     |
| 56-41-7    | Alanine   | ![Alanine structure](image) | Amino acid | 11.0% increase in mean lifespan and regulating AAK-2, SKN-1, and DAF-16 [103]                   |
| 56-87-1    | Lysine    | ![Lysine structure](image) | Amino acids | 8.0% increase in mean lifespan and regulating AAK-2, SKN-1, and DAF-16 [103]                   |
| 338-69-2   | d-Alanine | ![d-Alanine structure](image) | Amino acids | 16.0% increase in mean lifespan and regulating AAK-2, SIR-2.1, and DAF-16 [103]                |
| 56-85-9    | Glutamine | ![Glutamine structure](image) | Amino acids | 16.0% increase in mean lifespan and regulating EAT-2, AAK-2, and SKN-1 [103]                   |
| CAS       | Chemicals                                      | Structure                                      | Source                                      | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-----------|-----------------------------------------------|------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| 87-44-5   | β-Caryophyllene                               | ![Structure](image1)                            | Edible plants                              | 22.0% increase in mean lifespan and regulating SIR-2.1, SKN-1 and DAF-16 [219]                                       |
| 60-18-4   | Tyrosine                                      | ![Structure](image2)                            | Amino acids                                | 10.0% increase in mean lifespan and regulating SIR-2.1, SKN-1, and DAF-16 [105]                                       |
| 107-95-9  | β-Alanine                                     | ![Structure](image3)                            | Amino acid                                 | 13.0% increase in mean lifespan and regulating AAK-2, SIR-2.1, SKN-1, and DAF-16                                    |
|           | Acacetin 7-O-α-1-rhamnopyranosyl (1-2) β-α-xylopyranoside | ![Structure](image4)                            | *Premna integrifolia*                      | 39.0% increase in mean lifespan and regulating EAT-2, SIR-2.1, SKN-1, HSF-1, MEV-1, and DAF-16 [220]               |
| 15502-74-6| Arsenite                                      | ![Structure](image5)                            | Natural and anthropogenic sources          | (10 μM) 10.0% increase in mean lifespan, (>100 μM) 12.0% decrease and antioxidant, regulating SKN-1, MTL-2, TIN-9, and DAF-16 [221, 222]|
| 625-72-9  | D-β-Hydroxybutyrate                           | ![Structure](image6)                            | Ketone body                                | 26.0% increase in mean lifespan and regulating AAK-2, SIR-2.1, SKN-1, and DAF-16; inhibiting histone deacetylase [225]|
| 71-00-1   | Histidine                                     | ![Structure](image7)                            | Amino acids                                | 12.0% increase in mean lifespan and regulating EAT-2, AAK-2, SIR-2.1, SKN-1, BEC-1, HIF-1, GAS-1, IFE-2, GCN-2, and DAF-16 [103] |
| CAS         | Chemicals   | Structure     | Source         | Anti-aging activity and proposed anti-aging mechanism |
|-------------|-------------|---------------|----------------|-------------------------------------------------------|
| 37159-97-0  | Proline     | ![Proline Structure](image) | Amino acids    | 19.0% increase in mean lifespan and regulating EAT-2, AAK-2, SIR-2.1, SKN-1, BEC-1, and DAF-16 [103] |
| 56-45-1     | Serine      | ![Serine Structure](image) | Amino acids    | 22.0% increase in mean lifespan and regulating EAT-2, AAK-2, SIR-2.1, SKN-1, HIF-1, BEC-1, and DAF-16 [103] |
| 73-22-3     | Tryptophan  | ![Tryptophan Structure](image) | Amino acids    | 14.0% increase in mean lifespan and regulating EAT-2, AAK-2, SIR-2.1, SKN-1, BEC-1, GCN-2, and DAF-16 [103] |
| 1405-87-4   | Bacitracin  | ![Bacitracin Structure](image) | *Bacillus subtilis* var Tracy | 59.0% increase in mean lifespan and regulating CBP-1, improving proteotoxicity [224] |
| 142-42-7    | Fumarate    | ![Fumarate Structure](image) | Tricarboxylic acid (TCA) cycle metabolite | 16.0% increase in mean lifespan and increasing the amount of oxidized NAD and FAD cofactors [213] |
| 63-68-3     | Methionine  | ![Methionine Structure](image) | Amino acids    | 14.0% increase in mean lifespan and regulating mitochondrial unfolded protein response [103] |
| CAS     | Chemicals                  | Structure | Source                                           | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|----------------------------|-----------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 62-75-9 | N-Nitrosodimethylamine     | ![Structure](image1) | Ubiquitously distributed organic xenobiotic compounds | 6.0% increase in mean lifespan and reducing transcription of many stress response genes [225]                           |
| 25166-14-7 | 2,3-Dehydrosily-bin A/B | ![Structure](image2) | Potential active components of silymarin          | 16.1% increase in mean lifespan and antioxidant, regulating FGT-1, improving proteotoxic stress [226]                     |
| 476-66-4 | Ellagic acid               | ![Structure](image3) | Strawberry and raspberry                         | ~10.0% increase in mean lifespan and antioxidant, CR mimetics, antimicrobial [27]                                       |
| 1259-86-5 | Glau-carubinone            | ![Structure](image4) | Different species of the tropical plant family Simaroubaceae | ~80.0% increase in mean lifespan and promoting mitochondrial metabolism, reducing body fat [227]                         |
| 529-44-2 | Myricetin                  | ![Structure](image5) | Tea, different vegetables, onions, berries, grapes and medical plants | 34.3% increase in mean lifespan and regulating DAF-16; enhanced quality of life during aging [63, 228]                      |
Table 1 continued

| CAS          | Chemicals                        | Structure | Source                        | Anti-aging activity and proposed anti-aging mechanism |
|--------------|----------------------------------|-----------|-------------------------------|-------------------------------------------------------|
| 106758-54-7  | Otophylloside B                  | ![Structure](image1) | Cynanchum otophyllum         | 11.3% increase in mean lifespan and regulating DAF-2, SIR-2.1, CLK-1, and DAF-16 [229] |
| 14937-32-7   | Pentagalloyl glucose             | ![Structure](image2) | Eucalyptus leaves            | 18.0% increase in mean lifespan and regulating dietary restriction, IIS pathway, SIR-2.1 and mitochondrial electron transport chain [230] |
| 7512-17-6    | N-Acetyl-glucosamine            | ![Structure](image3) | Hexosamine Pathway Metabolite | 50.0% increase in mean lifespan and enhancing autophagy, ER-associated protein degradation, and proteasomal activity [231] |
|              | Quercetin 3'-O-β-D-glucopyranoside | ![Structure](image4) | Onion                        | 20.9% increase in mean lifespan and regulating DAF-2, OLD-1, OSR-1, and AEK-1 [182] |
| CAS     | Chemicals | Structure | Source          | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|-----------|-----------|----------------|----------------------------------------------------------------------------------------------------------------------|
| 50-70-4 | Sorbitol  | ![Sorbitol Structure](image) | *S. cerevisiae* | 3.5% increase in mean lifespan and regulating DR and osmotic response [232]                                             |
| 1401-55-4 | Tannic acid | ![Tannic Acid Structure](image) | Grapes and green tea | 19.0% increase in mean lifespan and regulating TGF-β, p38 MAPK pathways, and DAF-12 [233, 234]                       |
| 77-92-9 | Citrate   | ![Citrate Structure](image) | Tricarboxylic acid cycle intermediate | 13.0% increase in mean lifespan and inducing ER stress response [103]                                                   |
| 107-35-7 | Taurine   | ![Taurine Structure](image) | Nitrogen containing metabolites | 11.0% increase in mean lifespan and inducing ER stress response [103]                                                   |
Table 1 continued

| CAS         | Chemicals          | Structure | Source                        | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-------------|--------------------|-----------|-------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 38748-32-2  | Triptolide         | ![Triptolide structure](image1.png) | Tripterygium willdii          | 20.1% increase in mean lifespan and antioxidant, regulating HSP6.2 and SOD-3 [235]                                     |
| 67-97-0     | Vitamin D3         | ![Vitamin D3 structure](image2.png) |                               | 39.0% increase in mean lifespan and regulating SKN-1, IRE-1, XBP-1, DAF-16, and proteostasis [236]                   |
| 57-88-5     | Cholesterol        | ![Cholesterol structure](image3.png) | Cyclo-pentanoperhydro-phenanthrene ring | Regulating cholesterol-binding protein NSBP-1, and DAF-16 [237]                                                      |
| 94900-12-0  | Dafachronic acid   | ![Dafachronic acid structure](image4.png) |                                | 17.0% increase in mean lifespan and “antiaging” in the germ-line longevity pathway [238]                              |
| CAS        | Chemicals                  | Structure | Source     | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|------------|---------------------------|-----------|------------|---------------------------------------------------------------------------------------------------------------|
| 145-13-1   | Pregnenolone              | ![Pregnenolone](image) | Hormonal steroids | 20.0% increase in mean lifespan and relating to germline-defective regulated longevity [239]                    |
| 1315285-41-6 | Royalactin Glycoprotein | ![Royalactin Glycoprotein](image) | Royal jelly | 34.0% increase in mean lifespan and regulating EGF signaling [240]                                                |
| 104594-70-9 | Caffeic acid phenethyl ester | ![Caffeic acid phenethyl ester](image) | Propolis | 9.0% increase in mean lifespan and regulating DAF-16 [241]                                                        |
| 64-17-5    | Ethanol                   | ![Ethanol](image) | Metabolites | Serving as a carbon and energy source and/or by inducing a stress response [242]                                |
|            |                           |           |            | Garlic as and primary metabolic product of SeMet                                                                 |
|            |                           |           |            | Antioxidant, regulating selenoprotein TRXR-1 [243]                                                              |
| 74-81-7    | Caprylate                 | ![Caprylate](image) | Metabolites | In lacking nitrogen on C. elegans: 7.0% increase in mean lifespan and needs further research [51]               |
| 6893-26-1  | D-Glutamate               | ![D-Glutamate](image) | Amino acids | 18.0–114.0% increase in mean lifespan and needs more research [103]                                               |
| CAS       | Chemicals            | Structure          | Source                  | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-----------|----------------------|--------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------|
| 10257-28-0 | Galact-opyranose     | ![Galact-opyranose](image) | Sugars metabolites      | In lacking nitrogen on *C. elegans*: 6.0% increase in mean lifespan and needs more research [103]                  |
| 56-40-6    | Glycine              | ![Glycine](image)   | Amino acids             | 10.0% increase in mean lifespan and needs more research [103]                                                      |
| 6027-13-0  | Homocysteine         | ![Homocysteine](image) | Nitrogen containing metabolites | 13.0% increase in mean lifespan and needs more research [103]                                                       |
| 87-89-8    | Inositol             | ![Inositol](image)  | Metabolites             | In lacking nitrogen on *C. elegans*: 17.0% increase in mean lifespan and needs more research [103]                  |
| 320-77-4   | Isocitrate           | ![Isocitrate](image) | TCA cycle intermediate  | 13.0% increase in mean lifespan and needs more research [103]                                                       |
| 7004-09-3  | Isoleucine           | ![Isoleucine](image) | Amino acids             | 3.0% increase in mean lifespan and needs more research [103]                                                        |
| CAS     | Chemicals         | Structure                                                                 | Source                  | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|-------------------|---------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------------|
| 70-26-8 | Ornithine         | ![Ornithine Structure](image)                                             | Amino acids             | 8.0% increase in mean lifespan and needs more research [103]                                                        |
| 138-08-9| Phosphoenol-pyruvate| ![Phosphoenol-pyruvate Structure](image)                                | Metabolites             | In lacking nitrogen on *C. elegans*: 12.0% increase in mean lifespan and needs more research [103]                   |
| 98-98-6 | Picolinic acid    | ![Picolinic acid Structure](image)                                       | Endogenous metabolite of the kynurenine pathway | 7.0% increase in mean lifespan and needs further research [103]                                                        |
| 10257-32-6| Ribopyranose   | ![Ribopyranose Structure](image)                                        | Sugars metabolites      | In lacking nitrogen on *C. elegans*: 9.0% increase in mean lifespan and needs more research [103]                   |
| 56-14-4 | Succinate         | ![Succinate Structure](image)                                            | TCA cycle intermediates | 11.0% increase in mean lifespan and needs more research [103]                                                         |
| 72-19-5 | Threonine         | ![Threonine Structure](image)                                           | Amino acids             | 8.0% increase in mean lifespan and needs more research [103]                                                         |
| 72-18-4 | Valine            | ![Valine Structure](image)                                               | Amino acids             | 13.0% increase in mean lifespan and needs more research [103]                                                         |
| CAS       | Chemicals                  | Structure | Source               | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-----------|----------------------------|-----------|----------------------|---------------------------------------------------------------------------------------------------------------------|
| 58-86-6   | Xylose                     | ![XYLOSE](xylose.png) | Sugars metabolites   | In lacking nitrogen on *C. elegans*: 6.0% increase in mean lifespan and needs more research [103]                      |
| 32619-42-4 | Oleuropein                 | ![OLEuropein](oleuropein.png) | *Olea europaea* leaf | In cell: 15.0% increase in mean lifespan; and increasing proteasome-mediated degradation rates, retaining proteasome function and Nrf2/heme oxygenase-1 pathway [244] |
| 84605-18-5 | Cyclo-astragenol           | ![Cyclo-astragenol](cyclo-astragenol.png) | *Astragalus membranaceus* | In PC12 cells and primary neurons: inducing telomerase activity and cAMP response element binding (CREB) [245]         |
| 528-58-5   | Cyanidin                   | ![Cyanidin](cyanidin.png) | Fruits and vegetables | In cell: antioxidant, decreasing expressions of nuclear factor-kappaB, cyclooxygenase-2, and nitric oxide synthase [246] |
| CAS          | Chemicals                  | Structure                                                                 | Source                          | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-------------|---------------------------|---------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 88095-77-6  | Dieckol                   | ![Dieckol Structure](image)                                               | Eckloina cava                   | In radiation-induced cell damages: protecting effects on UV-B [247]                                                  |
| 1229519-12-3| HDTIC-1                   | ![HDTIC-1 Structure](image)                                               | Herb *Astragalus membranaceus* var. *mongholicus* | In cell: antioxidant, improving proliferation, inhibiting glycation end product formation, slowing down telomere shortening rate [248, 249] |
| 1229519-13-4| HDTIC-2                   | ![HDTIC-2 Structure](image)                                               | Herb *Astragalus membranaceus* var. *mongholicus* | In cell: antioxidant, improving proliferation, inhibiting glycation end product formation, slowing down telomere shortening rate [248, 249] |
| 87798-94-5  | Quercetin caprylate       | ![Quercetin caprylate Structure](image)                                  | Quercetin derivative            | In cell: antioxidant, proteasome activator [250]                                                                  |
| 501334-35-6 | Collemin A                | ![Collemin A Structure](image)                                            | Lichenized ascomycete *Collema cristatum* | In cell and human skin: preventing pyrimidine dimer formation and UV-B induced erythema [251] |
| CAS       | Chemicals          | Structure | Source                              | Anti-aging activity and proposed anti-aging mechanism                                      |
|-----------|--------------------|-----------|-------------------------------------|------------------------------------------------------------------------------------------|
| 87425-34-1| Nolinospirose F    | ![Structure](image1) | *Ophiopogon japonicus*              | In *S. cerevisiae*: 23.0% increase in mean lifespan and antioxidant [252, 253]               |
| 57103-57-8| (-)-Glyceollin I   | ![Structure](image2) | Soybeans                            | In *S. cerevisiae*: calorie restriction mimetic [254]                                       |
| 487-52-5  | Butein             | ![Structure](image3) | *Toxicodendron verniciflum*         | In *S. cerevisiae*: 31.0% increase in mean lifespan and regulating Sir2 [255]               |
| 1341-23-7 | Nicotinamide riboside | ![Structure](image4) | NAD(+) precursor                    | In *S. cerevisiae*: 20.0% increase in mean lifespan and increasing net NAD(+) synthesis and Sir2 function [252, 253] |
| CAS     | Chemicals          | Structure | Source                                           | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|--------------------|-----------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 434-13-9 | Lithocholic acid   | ![Lithocholic acid](image.png) | Major bile acids excreted by mammals | In *S. cerevisiae*: 100.0% increase in mean lifespan and modulating housekeeping longevity assurance processes [256, 257] |
| 57-94-3 | Curare             | ![Curare](image.png)          | Chondrodendron tomentosum, Menispermaceae or Strychnos | In *Asplanchna brightwelli*: 34.0% increase in mean lifespan and needs further research [258]                         |
| Complex or extracts | Source | Anti-aging activity and proposed anti-aging mechanism |
|---------------------|--------|-----------------------------------------------------|
| **With anti-aging activities in two aging models** | | |
| Green tea extract | Green tea | In mice: 7.0% increase in mean lifespan and antioxidant [44] |
| Korean mistletoe water extract | Viscum album coloratum | In *D. melanogaster*: 20.0% increase in mean lifespan and regulating Sir2 [259] In *C. elegans*: 10.0% increase in mean lifespan and antioxidant [259] |
| **With anti-aging activities in rats or mice** | | |
| A-type proanthocyanidin-rich cranberry extract | Cranberry | In mice: antioxidant [260] |
| *Fungus Phellinus* sp. polysaccharide | *Fungus Phellinus* sp. | In mice: antioxidant [261] |
| Polysaccharides of *Diplodia chinensis* (L.) Juss | *Diplodia chinensis* (L.) Juss | In mice: scavenging free radical and antioxidant [262] |
| Polysaccharides of *Urtica* | *Urtica* | In n-galactose-induced mice: antioxidant [263] |
| Coca polyphenolic extract | Acticoa powder | In rats: 11.0% increase in mean lifespan and retarding age-related brain impairments [264] |
| *Nigella Sativa* fixed oil | *Nigella Sativa* | In mice: reducing lipid peroxidation, Bax/Bcl2, and caspase-3 [265] |
| Exopolysaccharides of *Agrocybe* | *Agrocybe clyndracea* | In n-galactose-induced mice: antioxidant, reducing the contents of malonaldehyde (MDA) and total cholesterol (TC) [266] |
| Neem leaves extract | Neem | In UVB-irradiated NHDFs, hairless mice: increasing TGF-β1, decreasing AP-1, ROS, and MAPK [267] |
| **With anti-aging activities in *Drosophila melanogaster*** | | |
| APPLE polyphenols | Apple | 10.0% increase in mean lifespan and antioxidant [268] |
| Cocoa | | ~14.0% increase in mean lifespan and antioxidant [269] |
| *Cordyceps sinensis* oral liquid | Traditional Chinese medicine | 32.0% increase in mean lifespan and antioxidant [270] |
| *Cynomorium songaricum* Rup | Traditional Chinese medicine | 15.0% increase in mean lifespan and antioxidant [271] |
| *Embllica officinalis* (fruit) | *Embllica officinalis* | 6.0% increase in mean lifespan and antioxidant [272] |
| Rhizome powder of *Rhodiola rosea* | *Rhodiola rosea* | 17.0% increase in mean lifespan and antioxidant [273] |
| *Curcuma longa* (rhizome) | *Curcuma longa* | 18.0% increase in mean lifespan and antioxidant [272] |
| Oregano and cranberry extracts | Oregano and cranberry | ~43.0% in male and ~62.0% in female (full diet +2% OC) increase in mean lifespan and partly through DR-independent pathways [274] |
| Cinnamon extract | Cinnamon | 17.0% in male, 37.0% in female increase in mean lifespan and regulating insulin signaling [275] |
| *Ludwiga octovalvis* extract | *Ludwiga octovalvis* | 24.0% increase in mean lifespan and regulating AMPK [276] |
| Jujube fruit | Jujube | 11.1% increase in mean lifespan and regulating FoxO [277] |
| Black tea extract | Black tea | 21.4% increase in mean lifespan and inhibiting the ageing-related accumulation of iron [278] |
| Cranberry anthocyanin extract | Cranberry | 10.0% increase in mean lifespan and up-regulation of SOD1 and down-regulation of MTH, InR, TOR and PEPCK [279] |
| *Rosa damascena* extract | *Rosa damascena* | 32.0% increase in mean lifespan and increasing sensitivity to heat [280] |
| **With anti-aging activities in *Caenorhabditis elegans*** | | |
| *Acanthopanax sessiliflorus* stem extract | *Acanthopanax sessiliflorus* stem | 16.8% increase in mean lifespan and antioxidant [281] |
| *Angelica sinensis* peptides | *Angelica sinensis* | ~20.0% increase in mean lifespan and antioxidant [282] |
| Apple procyanidins | Apple | 12.1% increase in mean lifespan and antioxidant [283] |
| Blueberry polyphenols | Blueberry | 28.0% increase in mean lifespan and antioxidant [284] |
| Extract from seed of *Platycladus orientalis* | *Platycladus orientalis* | 24.5% increase in mean lifespan and antioxidant [285] |
astaxanthin [29, 57–59], catechin [60–62], curcumin [63–65], fucoxanthin [66, 67], spermidine [68, 69], metformin [70–72], caffeine [73–75], and rapamycin [76–84], all show anti-aging activity in both D. melanogaster and C. elegans, as well as in other aging models (Table 1). There are 39 compounds present anti-aging activity in two aging models, 32 of them with anti-aging activity in C. elegans. 19 of the 39 compounds are antioxidant (including acacetin, antcin M, agmatine, baicalein, caffeic acid, carnosine, chlorogenic acid, coenzyme Q10, dimethyl sulfide, gallic acid, gluconate, glycerol, hesperidin, icariin, lactate, oleanolic acid, minocycline, vitamin E, and vitexin). Compound betaine, catalpol, (-)-epicatechin, huperzine A and polydatin regulate inflammation. 11 compounds act through energy sensing pathway, including acetic acid, a-ketoglutarate, D-glucosamine, epigallocatechin gallate, nordihydroguaiaretic acid, oligonol, polydatin, rosmarinic acid, sesamin, aspirin, and tetrahydrocurcumin. There are

| Table 2 continued |
| Source |
| Anti-aging activity and proposed anti-aging mechanism |
| Ginkgo biloba extract | Ginkgo biloba | 8.0–25.0% increase in mean lifespan and antioxidant [286] |
| HonTsai Tai extract | HonTsai Tai | 8.0% increase in mean lifespan and antioxidant [287] |
| KPG-7 | Herb mixture | 12.0% increase in mean lifespan and antioxidant [288] |
| Panax notoginseng Polysaccharides | Panax notoginseng | 21.0% increase in mean lifespan and antioxidant [289] |
| Tenebrio molitor extracts | Tenebrio molitor | 30.6% increase in mean lifespan and antioxidant [290] |
| Erchen wan | Traditional Chinese medicine | 22.0% increase in mean lifespan and antioxidant [291] |
| Huanshao dan | Traditional Chinese medicine | 38.0% increase in mean lifespan and antioxidant [291] |
| Liuweihuang wan | Traditional Chinese medicine | 13.0% increase in mean lifespan and antioxidant [291] |
| Shengmai yin | Traditional Chinese medicine | 47.0% increase in mean lifespan and antioxidant [291] |
| Shiquan dabu wan | Traditional Chinese medicine | 15.0% increase in mean lifespan and antioxidant [291] |
| Bletilla striata polysaccharide | Bletilla striata | ~20.0% increase in mean lifespan and regulating IIS pathway [292] |
| Ethylacetate fraction from Ribes fasciculatum | Ribes fasciculatum | 16.3% increase in mean lifespan and regulating IIS pathway and SIR-2.1 [293] |
| Peptides from sesame cake | Sesame cake | 15.6% increase in mean lifespan and regulating SKN-1 signaling [294] |
| Astragalus membranaceus polysaccharide | Astragalus membranaceus | 24.0% increase in mean lifespan and regulating DAF-16 [295] |
| Garlic extract | Garlic extract | 21.0% increase in mean lifespan and regulating DAF-16 [296] |
| Reishi mushroom polysaccharide | Reishi mushroom | ~20.0% increase in mean lifespan and regulating TIR-1 and DAF-16 [99] |
| Royal Jelly | Honeybeee | 18.0% increase in mean lifespan and DAF-16 dependent [297, 298] |
| Ayurvedic polyherbal extract | Ayurvedic | 16.1% increase in mean lifespan and regulating DAF-2, SKN-1, SOD-3, GST-4, and DAF-16 [299] |
| Dammacanthus officinarum leaf extract | Dammacanthus officinarum | 19.0% increase in mean lifespan and regulating neuroprotective activity [300] |
| Deuterohemin peptide | Peptides | 21.0% increase in mean lifespan and antioxidant, regulating DR [301] |
| Eleutherococcus senticosus root extract | Eleutherococcus senticosus | 16.0% increase in mean lifespan and antioxidant, regulating DAF-16 [302] |
| Lowbush cranberry | Lowbush cranberry | 22.0% increase in mean lifespan and altering mechanosensory neuron aging [303] |
| Mulberry leaf polyphenols | Mulberry leaf | 23.0% increase in mean lifespan and regulating DAF-12, PHA-4, NHR-80, and DAF-16 [304] |
| Dauer-inducing Pheromone | Worms | 27.0% increase in mean lifespan and needs more research [305] |
| With anti-aging activities in other aging models |
| Annurca apple extracts | Annurca apple | In S. cerevisiae: antioxidant, antiapoptotic [306] |
| Red algal extracts | Red algal | In Brachionus manjavacas: 9.0% increase in mean lifespan and needs further research [307] |
### Table 3 Clinical medicine with anti-aging activities

| CAS       | Chemicals | Structure | Clinical application                                                                 | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-----------|-----------|-----------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| 58-08-2   | Caffeine  | ![Caffeine](image) | Psychoactive drug                                                                   | In rats: antioxidant, alleviating neuroinflammation and neurodegeneration [75]                                          |
|           |           |           |                                                                                     | In *zebrafish*: 29.4% increase in mean lifespan and regulating proteostasis [74]                                         |
|           |           |           |                                                                                     | In *C. elegans*: 29.4% increase in mean lifespan and regulating IIS pathway and proteostasis [73]                        |
| 657-24-9  | Metformin | ![Metformin](image) | Treatment of type 2 diabetes and polycystic ovary syndrome                           | In rats: altering erythrocyte redox status [70]                                                                        |
|           |           |           |                                                                                     | In *D. melanogaster*: has not effect on fecundity or lifespan and activating AMPK, reducing lipid stores [72]           |
|           |           |           |                                                                                     | In *C. elegans*: 40.0% increase in mean lifespan and regulating AMPK, LKB1, and SKN-1 [71]                              |
| 53123-88-9| Rapamycin | ![Rapamycin](image) | Used to coat coronary stents, prevent organ transplant rejection and to treat a rare lung disease called lymphangioleiomyomatosis | In mice: 14.0% increase in mean lifespan for females and 9% for males and reducing mTOR activity [76–82]              |
|           |           |           |                                                                                     | In *D. melanogaster*: 13.0% increase in mean lifespan and regulating TORC1 branch of the TOR pathway, through alterations to both autophagy and translation [83] |
|           |           |           |                                                                                     | In *C. elegans*: 19.0% increase in mean lifespan and regulating TOR, SKN-1 and DAF-16 [84]                             |
| 50-78-2   | Aspirin   | ![Aspirin](image) | Used to treat pain, fever, and inflammation                                           | In genetically heterogeneous male mice: 8.0% increase in mean lifespan and needs further research [135]                |
|           |           |           |                                                                                     | In *C. elegans*: 30.0% increase in mean lifespan and antioxidant, regulating AMPK and insulin-like signaling pathway [183, 308] |
| CAS      | Chemicals     | Structure | Clinical application                                                                 | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|----------|---------------|-----------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| 2086-83-1| Berberine     | ![Berberine Structure](image) | Used to treat bacillary dysentery and gastroenteritis                               | In aged mice: suppressing neuroinflammation, reducing vascular stiffness in aged mice through suppression of TRPV4 [309, 310] |
|          |               |           |                                                                                     | In *D. melanogaster*: 46.0% increase in mean lifespan and inhibiting kynurenine (KYN) formation from tryptophan (TRP) [311] |
| 102518-79-6| Huperzine A   | ![Huperzine A Structure](image) | Treatment for neurological conditions such as Alzheimer's disease                   | In *D*-galactose-induced mice: inhibiting DAMPs-mediated NF-κB nuclear localization and activation [312] |
|          |               |           |                                                                                     | In *C. elegans*: 14.0% increase in mean lifespan and needs further research [285]                                          |
| 10118-90-8| Minocycline   | ![Minocycline Structure](image) | Antibiotic                                                                          | In *D. melanogaster*: 63.0% increase in mean lifespan and antioxidant [313] |
|          |               |           |                                                                                     | In *C. elegans*: 29.0% increase in mean lifespan and antioxidant [176]                                                  |
| 114-86-3 | Phenformin    | ![Phenformin Structure](image) | Antidiabetic                                                                         | In mice: 21.0% increase in mean lifespan and decreasing the body weight, slowing down the age-related decline of the reproductive function in female rats [314] |
|          |               |           |                                                                                     | In *C. elegans*: 29.0% increase in mean lifespan and needs further research [315]                                          |
| CAS     | Chemicals   | Structure | Clinical application                                                                 | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|---------|-------------|-----------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 59-02-9 | Vitamin E   | ![Vitamin E structure](image) | Vitamins                                                                              | In rats: reducing the oxidative stress increased in old age [316, 317]  
In *C. elegans*: 23.0% increase in mean lifespan and antioxidant [318] |
|         |             |           | With anti-aging activities in rats or mice                                              |                                                                                                                     |
| 692-13-7 | Buformin    | ![Buformin structure](image) | Antidiabetic                                                                           | In rats: 7.0% increase in mean lifespan in female and decreasing the body weight, slowing down the age-related decline of the reproductive function in female rats [314] |
| 73-31-4 | Melatonin   | ![Melatonin structure](image) | Regulating sleep and wakefulness                                                         | In male Wistar: restoring rSocs1 rhythms and levels in various tissues [319]                                             |
| 155974-00-8 | Ivabradine | ![Ivabradine structure](image) | Used for the symptomatic management of stable heart related chest pain and heart failure | In C57BL/6 J mice: 6.0% increase in mean lifespan and reducing heart rate [320]                                          |
| 56180-94-0 | Acarbose   | ![Acarbose structure](image) | Antidiabetic                                                                           | In SAMP8 mice and male mice: 22.0% increase in mean lifespan and changing in the insulin system and the levels of BDNF, IGF-1R, and the pre-synaptic proteins Syt1 and Stx1 [321, 322] |
| 51384-51-1 | Metoprolol | ![Metoprolol structure](image) | Used to treat high blood pressure, chest pain due to poor blood flow to the heart, and a number of conditions involving an abnormally fast heart rate | In mice: 10.0% increase in mean lifespan and needs further research [323]                                              |
| CAS          | Chemicals       | Structure | Clinical application               | Anti-aging activity and proposed anti-aging mechanism |
|--------------|-----------------|-----------|------------------------------------|------------------------------------------------------|
| 99200-09-6   | Nebivolol       | ![Structure of Nebivolol](image) | Treatment of hypertension                 | In mice: 6.4% increase in mean lifespan and needs further research [323] |
| 13123-37-0   | Riboflavin      | ![Structure of Riboflavin](image) | Vitamin                          | 14.1% increase in mean lifespan and increasing SOD1 and CAT, inhibiting LF [324] |
| 84057-84-1   | Lamotrigine     | ![Structure of Lamotrigine](image) | Anticonvulsant                   | 17.0% increase in mean lifespan and reducing locomotor activity and metabolic rate [325] |
| 1716-12-7    | 4-Phenyl-butyrate| ![Structure of 4-Phenyl-butyrate](image) | Used to treat urea cycle disorder | 40.0% increase in mean lifespan and increasing histone acetylation [326] |
| 52757-95-6   | Sevelamer       | ![Structure of Sevelamer](image) | Used to treat hyperphosphatemia in patients with chronic kidney disease | 16.0% increase in mean lifespan and regulating cellular and organismic phosphate levels [327] |
| CAS          | Chemicals | Structure         | Clinical application | Anti-aging activity and proposed anti-aging mechanism |
|--------------|-----------|-------------------|----------------------|-----------------------------------------------------|
| 79902-63-9   | Simvastatin | ![Simvastatin Structure](image) | Hypolipidemic         | 25.0% increase in mean lifespan and decreasing specific protein prenylation [328] |
| 871700-17-3  | Trametinib | ![Trametinib Structure](image) | Anti-cancer           | 12.0% increase in mean lifespan and inhibiting Ras-Erk-ETS signaling [329] |
| 58880-19-6   | Trichostatin A | ![Trichostatin A Structure](image) | Antifungal antibiotic | 27.0% increase in mean lifespan and changing the level of histone acetylation, influencing the expression of hsp22 gene [330] |
| 57-27-2      | Morphine  | ![Morphine Structure](image) | Treatment of acute pain and chronic pain | 22.0% increase in mean lifespan and needs further research [331] |

With anti-aging activities in *Caenorhabditis elegans*
| CAS    | Chemicals  | Structure | Clinical application                      | Anti-aging activity and proposed anti-aging mechanism |
|--------|------------|-----------|-------------------------------------------|-------------------------------------------------------|
| 14028-44-5 | Amoxapine | [Structure image](#) | Antidepressant | 33.0% increase in mean lifespan and antioxidant [176] |
| 298-57-7   | Cinnarizine | [Structure image](#) | Treatment of vertigo, motion sickness, and vomiting | 15.0% increase in mean lifespan and antioxidant [176] |
| 59865-13-3 | Cyclosporin A | [Structure image](#) | Immunosuppressants | 18.0% increase in mean lifespan and antioxidant [176] |
| 427-51-0   | Cyproterone acetate | [Structure image](#) | Antiandrogen and progestogen | 23.0% increase in mean lifespan and antioxidant [176] |
| 17230-88-5 | Danazol    | [Structure image](#) | Treatment of endometriosis | 13.0% increase in mean lifespan and antioxidant [176] |
| CAS           | Chemicals                  | Structure | Clinical application          | Anti-aging activity and proposed anti-aging mechanism |
|--------------|---------------------------|-----------|-------------------------------|------------------------------------------------------|
| 127-33-3     | Demeclocycline hydrochloride | ![Structure](structure1.png) | Antibiotic                     | 16.0% increase in mean lifespan and antioxidant [176] |
| 564-25-0     | Doxycycline                | ![Structure](structure2.png) | Antibiotic                     | 18.0% increase in mean lifespan and antioxidant [176] |
| 10592-13-9   | Doxycycline hydrochloride  | ![Structure](structure3.png) | Antibiotic                     | 18.0% increase in mean lifespan and antioxidant [176] |
| 119431-25-3  | Eliprodil                 | ![Structure](structure4.png) | NMDA antagonist, treatment of acute ischemic stroke | 16.0% increase in mean lifespan and antioxidant [176] |
| 23256-50-0   | Guanabenz acetate         | ![Structure](structure5.png) | Antihypertensive               | 12.0% increase in mean lifespan and antioxidant [176] |
| CAS      | Chemicals                        | Structure | Clinical application | Anti-aging activity and proposed anti-aging mechanism |
|----------|----------------------------------|-----------|----------------------|-------------------------------------------------------|
| 29110-48-3 | Guanfacine hydrochloride        | ![Guanfacine structure](image) | Treatment of hyperactivity | 15.0% increase in mean lifespan and antioxidant [176] |
| 27833-64-3 | Loxapine succinate              | ![Loxapine structure](image) | Antipsychotic         | 43.0% increase in mean lifespan and antioxidant [176] |
| 57149-08-3 | Naftopidil dihydrochloride      | ![Naftopidil structure](image) | Antihypertensive      | 14.0% increase in mean lifespan and antioxidant [176] |
| 54527-84-3 | Nicardipine hydrochloride       | ![Nicardipine structure](image) | Used to treat high blood pressure and angina           | 23.0% increase in mean lifespan and antioxidant [176] |
| CAS    | Chemicals          | Structure | Clinical application                                                                 | Anti-aging activity and proposed anti-aging mechanism |
|--------|-------------------|-----------|--------------------------------------------------------------------------------------|-----------------------------------------------------|
| 39562-70-4 | Nitrendipine    | ![Structure](image) | Used in the treatment of primary (essential) hypertension to decrease blood pressure and can reduce the cardiotoxicity of cocaine | 25.0% increase in mean lifespan and antioxidant [176] |
| 894-71-3  | Nortriptyline hydrochloride | ![Structure](image) | Tricyclic antidepressant                                                             | 21.0% increase in mean lifespan and antioxidant [176] |
| 60607-34-3 | Oxatomide        | ![Structure](image) | Anti-allergic                                                                         | 25.0% increase in mean lifespan and antioxidant [176] |
| 130-61-0  | Thioridazine hydrochloride | ![Structure](image) | Antipsychotic                                                                         | 31.0% increase in mean lifespan and antioxidant [176] |
| CAS        | Chemicals     | Structure | Clinical application                                                                 | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|------------|---------------|-----------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 2068-78-2  | Vincristine sulfate | ![](image) | Anti-cancer                                                                          | 12.0% increase in mean lifespan and antioxidant [176]                                                                |
| 97-59-6    | Allantoin     | ![](image) | Used to treat gastric ulcer, duodenal bulb ulcer, chronic gastritis                    | 21.9% increase in mean lifespan and caloric restriction mimetics [332]                                                 |
| 169590-42-5| Celecoxib     | ![](image) | COX-2 selective nonsteroidal anti-inflammatory drug (NSAID) It is used to treat the pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain | 19.0% increase in mean lifespan and inhibiting insulin-like signaling [333]                                            |
| 99-66-1    | Valproic acid | ![](image) | Used to treat epilepsy and bipolar disorder and to prevent migraine headaches          | 35.0% increase in mean lifespan and regulating IIS pathway [334]                                                       |
| 103-90-2   | Acetaminophen | ![](image) | Used to treat pain and fever                                                          | 49.0% increase in mean lifespan and regulating CBP-1 [224]                                                            |
| CAS     | Chemicals   | Structure | Clinical application                                                                 | Anti-aging activity and proposed anti-aging mechanism |
|---------|-------------|-----------|--------------------------------------------------------------------------------------|-------------------------------------------------------|
| 69-52-3 | Ampicillin  | ![Ampicillin Structure](image) | Antibiotic                                                                           | 34.0% increase in mean lifespan and antimicrobial [284] |
| 41859-67-0 | Bezafibrate | ![Bezafibrate Structure](image) | Treatment of hypertriglyceridemia                                                     | 13.0% increase in mean lifespan and regulating NHR-49/PPARalpha-dependent manner [335] |
| 637-07-0 | Clofibrate  | ![Clofibrate Structure](image) | Lipid-lowering agent used for controlling the high cholesterol and triacylglyceride level in the blood | 16.0% increase in mean lifespan and regulating NHR-49/PPARalpha-dependent manner [335] |
| 49562-28-9 | Fenofibrate | ![Fenofibrate Structure](image) | Used to reduce cholesterol levels in people at risk of cardiovascular disease         | 19.0% increase in mean lifespan and regulating NHR-49/PPARalpha-dependent manner [335] |
| 127-48-0 | Trimethadione | ![Trimethadione Structure](image) | Anticonvulsant                                                                        | 47.0% increase in mean lifespan and regulating neuromuscular activity [336] |
| 42971-09-5 | Vinpocetine | ![Vinpocetine Structure](image) | Treatment of cerebrovascular disorders and age-related memory impairment              | 15.0% increase in mean lifespan and regulating PDE1 [176] |
| CAS     | Chemicals  | Structure | Clinical application                                      | Anti-aging activity and proposed anti-aging mechanism                                      |
|---------|------------|-----------|----------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 59-30-3 | Folic acid | ![Folic acid structure](image) | Used to treat anemia caused by folic acid deficiency       | 27.0% increase in mean lifespan and antioxidant, regulating SIR-2.1, SKN-1, and DAF-16 [337] |
| 77-67-8 | Ethosuximide | ![Ethosuximide structure](image) | Used to treat absence seizures                             | 17.0% increase in mean lifespan and disrupting sensory function, regulating DAF-16 [336, 338, 339] |
| 50264-69-2 | Lonidamine | ![Lonidamine structure](image) | Anti-cancer                                                | 8.0% increase in mean lifespan and promoting longevity in a pmk-1-sensitive manner by increasing formation of ROS [340] |
| 50-55-5 | Reserpine  | ![Reserpine structure](image) | Antipsychotic, and antihypertensive                        | 31.0% increase in mean lifespan and antioxidant, modulating acetylcholine release [341, 342] |
| 13292-46-1 | Rifampicin  | ![Rifampicin structure](image) | Antibiotic                                                 | 56.0% increase in mean lifespan and reducing advanced glycation end products and activating DAF-16 [343] |
| CAS     | Chemicals       | Structure | Clinical application | Anti-aging activity and proposed anti-aging mechanism |
|---------|-----------------|-----------|----------------------|-----------------------------------------------------|
| 6998-60-3 | Rifamycin SV   | ![Rifamycin SV Structure](image) | Antibiotic | 21.0% increase in mean lifespan and reducing advanced glycation end products and activating DAF-16 [343] |
| 723-46-6  | Sulfa-methoxazole | ![Sulfa-methoxazole Structure](image) | Antibiotic | 34.0% increase in mean lifespan and increasing lipid peroxidation oxidative stress [344] |
| 56-75-7   | Chloramphenicol | ![Chloramphenicol Structure](image) | Antibiotic | 16.0% increase in mean lifespan and needs further research [345] |

With anti-aging activities in other aging models:

| CAS    | Chemicals       | Structure | Clinical application | Anti-aging activity and proposed anti-aging mechanism |
|--------|-----------------|-----------|----------------------|-----------------------------------------------------|
| 53-06-5 | Cortisone       | ![Cortisone Structure](image) | Used to reduce inflammation and attendant pain and swelling at the site of the injury | In Asplanchna brightwelli: 21.0% increase in mean lifespan and stabilizing lysosomal membranes, or altering resource allocation by the rotifers [346] |
| 35891-70-4 | Myriocin   | ![Myriocin Structure](image) | Antibiotic ISP-1 and thermozymocidin | In S. cerevisiae: activating the Snf1/AMPK pathway, down-regulating the protein kinase A (PKA) and target of rapamycin complex 1 (TORC1) pathways [347] |
Table 4 Synthetic compounds with anti-aging activities

| CAS         | Chemicals               | Structure | Anti-aging activity and proposed anti-aging mechanism |
|-------------|-------------------------|-----------|------------------------------------------------------|
| With anti-aging activities in two aging models |                         |           |                                                      |
| 51-28-5     | 2,4-Dinitrophenol       | ![2,4-Dinitrophenol](image) | In mice: 7.0% increase in mean lifespan; enhancing tissue respiratory rates, improving serological glucose, triglyceride and insulin levels, decreasing reactive oxygen species levels and tissue DNA and protein oxidation, as well as reduced body weight [348] In D. melanogaster: 20.0% increase in mean lifespan; increasing the rate of oxygen consumption by isolated mitochondria and tissue homogenates, decreasing the activity of alcohol dehydrogenase [349] |
| With anti-aging activities in mice       |                         |           |                                                      |
| 91-53-2     | Ethoxyquin              | ![Ethoxyquin](image) | In C3H mice: 18.0% increase in mean lifespan in male, 20.0% in female and antioxidant [350] |
| 1001645-58-4 | SRT1720               | ![SRT1720](image) | In mice: 9.0% increase in mean lifespan and inhibiting proinflammatory gene expression [351] |
| With anti-aging activities in Drosophila melanogaster |                         |           |                                                      |
| 307297-39-8 | Epitalon                | ![Epitalon](image) | 17.0% increase in mean lifespan and antioxidant [352] |
| 34592-47-7  | Thiazolidine carboxylic acid | ![Thiazolidine carboxylic acid](image) | 31.0% increase in mean lifespan and antioxidant [353] |
| 133550-30-8 | AG-490                  | ![AG-490](image) | 18.0% increase in mean lifespan and activating ERK1/2 signaling [354] |
| 4431-00-9  | Aurintricarboxylic acid | ![Aurintricarboxylic acid](image) | 15.0% increase in mean lifespan and regulating p66ShcA [355] |
| CAS          | Chemicals                | Structure | Anti-aging activity and proposed anti-aging mechanism                                      |
|--------------|--------------------------|-----------|------------------------------------------------------------------------------------------|
| 91742-10-8   | HA-1004 (dihydrochloride)| ![Structure](image1) | 18.0% increase in mean lifespan and inhibiting protein kinase [354]                      |
| 103745-39-7  | HA-1077 (Fasudil)        | ![Structure](image2) | 15.0% increase in mean lifespan and inhibiting protein kinase [354]                      |
| 5108-96-3    | Pyrrolidine dithiocarbamate | ![Structure](image3) | 16.0% increase in mean lifespan and inhibiting NF-κB [356]                               |
| 75529-73-6   | Amperozide hydrochloride  | ![Structure](image4) | 38.0% increase in mean lifespan and antioxidatant [176]                                 |
| 193611-72-2  | BRL 15572                | ![Structure](image5) | 10.0% increase in mean lifespan and antioxidatant [176]                                 |
| 433695-36-4  | BRL 50481                | ![Structure](image6) | 18.0% increase in mean lifespan and antioxidatant [176]                                 |
| 145915-58-8  | DAPH (4,5-dianilinophthalimide) | ![Structure](image7) | 15.0% increase in mean lifespan and antioxidatant [176]                                 |
Table 4 continued

| CAS          | Chemicals                  | Structure | Anti-aging activity and proposed anti-aging mechanism |
|--------------|----------------------------|-----------|------------------------------------------------------|
| 53177-12-1   | EUK-8                      | ![](image1) | 54.0% increase in mean lifespan and antioxidant [357] |
| 81065-76-1   | EUK-134                    | ![](image2) | 54.0% increase in mean lifespan and antioxidant [357] |
| 98299-40-2   | Hexahydro-siladiphenidol   | ![](image3) | 15.0% increase in mean lifespan and antioxidatant [176] |
| 142273-20-9  | Kenpaullone                | ![](image4) | 27.0% increase in mean lifespan and antioxidatant [176] |
| 83846-83-7   | Ketanserin tartrate        | ![](image5) | 13.0% increase in mean lifespan and antioxidatant [176] |
| 13614-98-7   | Minocycline hydrochloride  | ![](image6) | 43.0% increase in mean lifespan and antioxidatant [176] |
| CAS       | Chemicals                              | Structure                                      | Anti-aging activity and proposed anti-aging mechanism                  |
|-----------|----------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------|
| 66104-23-2| Pergolide methanesulfonate             | ![Structure](image)                            | 37.0% increase in mean lifespan and antioxidatant [176]               |
| 497-27-8  | 4-Phenyl-3-Furoxan-carbonitrile        | ![Structure](image)                            | 30.0% increase in mean lifespan and antioxidatant [176]               |
| 58-33-3   | Promethazine hydrochloride             | ![Structure](image)                            | 32.0% increase in mean lifespan and antioxidatant [176]               |
| 7681-67-6 | Propionyl-promazine hydrochloride      | ![Structure](image)                            | 20.0% increase in mean lifespan and antioxidatant [176]               |
| 78416-81-6| Trequinsin hydrochloride               | ![Structure](image)                            | 27.0% increase in mean lifespan and antioxidatant [176]               |
14, 9, and 109 natural products with anti-aging activity reported only in mice or rat, fruit fly, and *C. elegans*, respectively, while 14 compounds present anti-aging activities in other aging models, such as mammalian cells and *S. cerevisiae*. Among the 109 compounds with anti-aging activity in *C. elegans*, 18 with antioxidative activity, five regulating IIS pathway, four regulating AMPK, four regulating mTOR signaling, 10 regulating SIR-2.1, six regulating SKN-1/Nrf2 pathway, seven regulating JNK-1, 16 with unknown mechanisms, and about half of 109 compounds revealed to regulate multiple signaling pathways.

Table 4 continued

| CAS       | Chemicals                  | Structure                      | Anti-aging activity and proposed anti-aging mechanism                                                                 |
|-----------|----------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 274-85-1  | 1,2,4-Triazolo[1,5-a]pyridine | ![Structure](image1)          | 12.0% increase in mean lifespan and antioxidant [359]                                                                |
| 138090-06-9 | (R,R)-cis-Diethyl-tetrahydro-2,8-chrysenediol | ![Structure](image2)          | 7.0% increase in mean lifespan and increasing stress resistance [176]                                                |
| 2390-54-7  | Thioflavin T                | ![Structure](image3)          | 60.0% increase in mean lifespan and regulating HSF-1 and SKN-1 [360]                                                |
| 175698-05-2 | 3,3-Diethyl-2-pyrolidinone  | ![Structure](image4)          | 31.0% increase in mean lifespan and regulating neuromuscular activity [336]                                          |
| 631-64-1   | Dibromoacetic acid          | ![Structure](image5)          | 15.0% increase in mean lifespan and inducing protective stress response [225]                                        |
| 82-76-8    | *N*-Phenyl periacid(ANSA)  | ![Structure](image6)          | 22.7% increase in mean lifespan and increasing aging related pharyngeal pumping rate [63]                            |
| 51314-51-3 | Benzimidazole derivative M084| ![Structure](image7)          | 19.10% increase in mean lifespan; regulating IIS pathway, AMPK, SIR-2.1, SKN-1, mitochondrial electron transport chain, and mitochondrial unfolded protein response [361–364] |
| 111-17-1   | 3,3'-Thiodipropionic acid   | ![Structure](image8)          | 16.0% increase in mean lifespan and increasing lipid peroxides [365]                                                 |

With anti-aging activities in *Asplanchna brightwelli*
Among the 55 complex or extracts from natural products, 8, 14 and 29 of them were tested in mice, fruit fly and *C. elegans*, respectively. A majority of these extracts present antioxidative activity.

Among the 62 clinical medicine with anti-aging activity, three (rapamycin, metformin, caffeine) present anti-aging activities in three aging models, six (aspirin, berberine, huperzine A, minocycline, phenformin, and vitamin E) in two aging models, two (buformin and melatonin) in rats, four (ivabradine, acarbose, metoprolol, and nebivolol) in mice, 8 in *D. melanogaster*, 37 in *C. elegans*, cortisone in *Asplanchna brightwelli* and myriocin in *S. cerevisiae*, respectively. Interestingly, the anti-aging mechanisms of the most drugs are different from their clinical applications.

We also summarized 35 synthetic compounds with explicit anti-aging activity (Table 4). 2,4-Dinitrophenol presents anti-aging activities in mice and fruit fly, ethoxyquin and SRT1720 in mice. Seven and 24 compounds present anti-aging activity in fruit fly and *C. elegans*, respectively. 3,3′-Thiodipropionic acid with anti-aging activity in *Asplanchna brightwelli*. Twenty-one of the 35 compounds present antioxidative activity.

In total, there are 212 and 46 compounds present anti-aging activity in *C. elegans* and fruit fly, respectively, indicating *C. elegans* and fruit fly are the most popular aging models for anti-aging screening. Those compounds present anti-aging activity in both *C. elegans* and fruit fly are worth to be further investigated in mammalian models.

4 Prospects of Discovering Anti-aging Molecules from Natural Products

Many clinical medicines are derived from natural products. But in the past two decades, pharmaceutical companies have been enthusing the drug development strategy of high-throughput screening (HTS) and combinatorial synthesis of enormous synthetic libraries of small molecules. Natural products were largely neglected for unsuitable for HTS of targeted protein assay and difficult in compound isolation and synthesis. But the achievement of new lead discovery and new drug approval was disappointing [85]. Compared with synthetic compounds, natural products are secondary metabolite, evolutionarily optimized with biologically relevant chemical space and preferred ligand binding motif, are not only biologically active, but with a high degree of bioavailability, suitable for functional and phenotypic assays [86]. Recent innovation in techniques for structural elucidation, metabolomics for profiling and isolation, and metagenomics or gene manipulation for synthetic pathways has facilitated to explore the enormous biodiversity on earth, including plant, microorganism and marine organism [87]. Engineered production of natural products from uncultivated species could extremely expand the chemical space of natural products by synthetic biology [88]. Moreover, modern computer-assisted drug design could utilize natural-product-derived fragments to computationally infer the biomolecular targets and activities of natural products and fragment-based de novo design. As summarized in above, currently discovered agents with anti-aging activity, majority of them are natural products. Therefore, natural products are invaluable sources and provide great promise for developing anti-aging medicine.

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Compliance with Ethical Standards

Conflict of interest  The authors declare no conflict of interest.

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