Dietary peptides in aging: Evidence and prospects

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ABSTRACT

With improvements in healthcare and lifestyle, the proportion of the aging population is rising steadily across the world. Many physiological functions are altered during aging and resemble those occurring in disease conditions involving metabolic and mitochondrial disturbances. Thus, there is an urge to better develop dietary or medicinal interventions targeting the mechanisms underlying aging and aging-related diseases. Many reports indicate that in geroscience, dietary interventions such as bioactive peptides to slow aging are a matter of 'when' rather than 'if'. Leading targets for peptides include the metabolic-mitochondrial pathway accompanied by improved nutrient sensing. Modulation of these pathways diminish aging biomarkers in various model organisms and confers protection against a growing list of age-related pathophysiologies. Food derived bioactive peptides are characterized modulators of these pathways, while some verified in vivo and even clinically approved, and numerous others are under development. This brief review focuses on the latest scientific advances in understanding the anti-aging ability of bioactive peptides as well as delineates the possible future directions in this process.

1. Introduction

Aging, an inevitable part of life is defined as a progressive and global decline of physiological functions, leading to an augmented vulnerability to disease and a decline in healthspan, finally culminating in death [1]. Life expectancy has risen strikingly over the last century due to significant improvements in nutrition, and health care, consequently, the aging population is continuously exposed
to diseases such as hypertension, chronic coronary disease and diabetes [2–4]. The idea of mitigation of aging has excited curiosity throughout the history of humankind [5]. Presently, the field of aging research has moved from the legends of fountain of youth to a fast-expanding area of research subjected to scientific scrutiny based on the growing knowledge of molecular bases of aging [5–7]. The idea of mitigation of aging was first observed in 1939, indicating that restraint of caloric intake in mice and rats increases lifespan [8]. This initial discovery ~80 years ago indicated the plasticity of the aging process and formed the central concept that attenuation of aging and increase in healthspan was possible through a change of nutritional strategies [9]. Around 13 years after the initial aging discovery [8], in the year 1952, aging was related to natural selection and reproduction [10–12]. The next achievement in the area of aging research in the late 1980s focused on the identification of the genetic basis of aging in the nematode Caenorhabditis elegans [13]. The last 30 years have marked tremendous progress in the aging research including identification of insulin-like signaling pathway [14], mammalian target of rapamycin (mTOR) pathway [15], sirtuins [16], the mitochondrial model of aging [17], and, inflam-aging [18].

Further, significant evidence now indicates that nutrition has the most critical influences on human aging. The spectrum of aging and nutrition crossovers can be summarized that overeating and the resultant obesity shortens lifespan while optimum eating increases life expectancy [19]. Numerous claims have been made for the merits of different bioactives and diets for lifespan extension and mitigation of aging biomarkers. Intricate nutrient-sensing pathways fine-tune the metabolic responses to supplementation of dietary peptides in a highly conserved manner [20]. Hence, the intake of dietary peptides has shown to affect the onset of insulin resistance, mTOR, and other age-related biomarkers. Based on this framework, limited but critical evidence has arisen in the field of peptide and aging regarding the mitigation of aging biomarkers, the mechanisms to re-establish homeostasis, the interconnection between peptide structure, and compensatory responses, and the possibilities to extend lifespan. In this brief review, we have also attempted to discuss the anti-aging effects of dietary peptides in view of molecular hallmarks and mechanisms of aging. We argue that this area of research marks an inflection point, not only in nutrition research but also for aging research with unique biomedical implications.

2. Dietary peptides and aging biomarkers

The past three decades of aging research has transitioned from identifying aging phenotypes to investigating the cellular pathways that underlie these phenotypes. It is also vital to mention that the field of gerontological research has moved its exclusive focus from the lifespan and healthspan effects of dietary restriction, towards the idea that optimal eating and functional foods are associated with increased life expectancy and a reduction in aging biomarkers. Exciting parallel developments are also emerging in the field of nutrition, such as intermittent fasting, diets that mimic fasting, and time-restricted feeding. Further, multiple claims have been made for the competitive merits of different diets relative to one another [21]. However, it is an enormously complicated and vast topic, so we aim to solely focus on dietary bioactive peptides. Dietary proteins contain hundreds of encrypted sequences of amino acids, known as bioactive peptides, which can affect biological processes or substrates [22]. Bioactive peptides are defined as peptide sequences within a protein, usually 2 to 20 amino acids, that exert a beneficial effect on human health beyond their known nutritional value [23]. These peptides impact a large spectrum of human health and exhibit myriad of pharmacological activities including cardioprotective, antimicrobial, antioxidant, and mineral binding properties, all collectively improving healthspan [20,24,25]. Owing to their ability to attenuate the underlying basis of aging, the use of bioactive peptides has gained attention as nutraceuticals and functional foods [26,27]. The anti-aging mechanisms of dietary peptides have also revealed an intricate network of interacting cell signaling pathways and higher-order molecular processes. As research interest has grown in the field of bioactive peptides, we will focus on the healthspan and possible lifespan improvement by bioactive peptides and discuss their interactions with pathways that regulate aging. From the recently published literature, we discussed important aging-related pathways and processes by which dietary peptides modulate them (Table 1).

2.1. Metabolic function

Metabolic function is a vital factor involved in the aging pathology. Aging comes with a host of metabolic changes, including modulation of metabolic function, a decline in insulin sensitivity and alterations in cardiac function [28]. Initially, two metabolic stimulating peptides, LPVP and IAVPGEVA, were isolated after digesting soy glucinin with trypsin and pepsin with the ability to exhibit hypocholesterolemic activity [29]. The activity was determined via in vitro binding of conjugated bile acids with glucinin hydrolysate, indicating possible in vivo activity as well. Likewise, IAVPGEVA, IAVPTGVA, and LPVP, three peptides from soy glucinin (500 μmol/L), improved metabolic function by activation of the sterol-responsive element binding protein 2 (SREBP-2) pathway, and the low-density lipoprotein (LDL)-uptake in liver cells [30]. Treatments of liver cells with LTFFPSAED up-regulate the LDLR-SREBP2 pathway, leading to an improved cellular capability to uptake LDL [31]. Interestingly, these peptides also increase the phosphorylation of β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) on Ser 872 via the AMPK pathway upregulation suggesting their impact on glucose metabolism [32]. A recent study has shown that a peptic hydrolysate of hemp seed protein shows similar activity on HMG-CoA and mimics a statin-like mechanism inhibition of LDLR protein levels in HepG2 cells [33]. This ability to modulate metabolic enzymes HMG-CoA in vitro assay extends to peptides derived from amaranth protein hydrolysate [34] and Chia [35]. This indicates the dual pharmacological impact of the bioactive peptides to modulate glucose and cholesterol metabolism leading to possible improvement in metabolic function [32,36,37]. Further, a recent clinical study has shown that consumption of lupin protein or casein (30g/day) for 4 weeks can lead to a 12.7% reduction in plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) level in patients [38]. It indicates the ability of bioactive peptides to mimic the FDA approved LDL lowering drugs alicoumab (Praluent) and evolocumab (Repatha) [39]. Further, three egg white ovotransferrin peptides (IRW, IQW, and LKP) were identified as cardioprotective peptides [40,41]. Mechanistically, IRW was able to attenuate the impaired insulin signaling pathway and GLUT4 translocation indicating the beneficial effect towards metabolic syndrome prevention [42]. Likewise, multifunctional peptides from egg yolk protein hydrolysate, YINQMPQKSR, YIN-QMPQKSR4, VTGRFAGHPAAQ, and YIEAVNKVSRAEQ exhibited anti-diabetic activity towards α-glucosidase inhibition in vitro [43]. Further evidence of modulation of metabolism, especially cholesterol comes from peptides derived from cooked cowpea (in vitro) [44], royal jelly (in vivo) [45] among many others (in vivo) [46]. Further, yogurt, milk, soy, whey, and chickpea derived peptides lower blood pressure, body fat and improves metabolism in vivo [47–50].
Table 1

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Source</th>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPVP, IAVPGVEA, IAVPTGCA</td>
<td>Soy</td>
<td>Hypcholesterolemic</td>
<td>[29] [30]</td>
</tr>
<tr>
<td>LTPGCAED</td>
<td>Soy</td>
<td>Hypcholesterolemic</td>
<td>[31]</td>
</tr>
<tr>
<td>Multiple (90 Sequences)</td>
<td>Soy</td>
<td>Hypcholesterolemic in patients</td>
<td>[38]</td>
</tr>
<tr>
<td>Lupin peptides</td>
<td>Egg yolk</td>
<td>Antidiabetic activity</td>
<td>[43]</td>
</tr>
<tr>
<td>YINQMPQKSRE, YINQMPQKSREA, VTGRCAGHPAAQ, and YIEAVNKVSPRAGQF</td>
<td>Fermented quinoa</td>
<td>Antioxidant activity</td>
<td>[58]</td>
</tr>
<tr>
<td>IVLQVQEG, TLRFPEN, VGFGL, FTLIN, and LENSDDKYY</td>
<td>Bovine whey peptides</td>
<td>Antioxidant activity</td>
<td>[59]</td>
</tr>
<tr>
<td>ALPM, GDLE, VGIN and AVEGPK</td>
<td>Lentil</td>
<td>Antioxidant activity</td>
<td>[61]</td>
</tr>
<tr>
<td>LLSTQGQPSFLSGF, NSSLTPLIRLYL, TLEPNVSFLPVLHL</td>
<td>Rapseppedase</td>
<td>SOD induction</td>
<td>[62]</td>
</tr>
<tr>
<td>LY, RALP and GHS</td>
<td>Loach peptides</td>
<td>Antioxidant activity</td>
<td>[65]</td>
</tr>
<tr>
<td>AP, VAP AKK and GY</td>
<td>Silk peptides</td>
<td>Hypoglycemic activity</td>
<td>[78-79]</td>
</tr>
<tr>
<td>KVEPOQDPEW, BABF, EMDEAQDPEW</td>
<td>Abalone</td>
<td>mTOR activation</td>
<td>[83-84]</td>
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<td>LVVWVPWQGR</td>
<td>Chlorella pyenoidose</td>
<td>AMPK activation</td>
<td>[89]</td>
</tr>
<tr>
<td>Soy β-conglycinin and other soy peptides</td>
<td>Soy</td>
<td>AMPK activation</td>
<td>[90,91]</td>
</tr>
<tr>
<td>Lunasin</td>
<td>Soy</td>
<td>H4K16 Deacetylation</td>
<td>[98]</td>
</tr>
<tr>
<td>Cottonseed meal protein hydrolysate</td>
<td>Cottonseed meal protein hydrolysate</td>
<td>AMPK/SIRT1 Activation</td>
<td>[108]</td>
</tr>
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</table>

2.2. Mitochondrial dysfunction

The free radical theory of aging theorized that the surplus production of free radical molecules arising from mitochondrial metabolic processes, such as respiration, represents a key factor that drives aging [51,52]. Hence, the modulation of free radical damage by dietary peptides presents itself as a logical approach to mitigate aging biomarkers and phenotype. In recent years, multiple studies have reported peptides derived from food sources, such as SAGNPN, GLAGA, AEEEYPDL, WYYY, PSLPA and SNAAC displayed potent antioxidant activity in vitro [53–56]. Another, recently identified peptide NVPVVEY from Sardinelle protein hydrolysates exhibited antioxidant activity in vitro [57]. Likewise, 5 antioxidant peptides IVLQVQEG, TLRFPEN, VGFGL, FTLIN, and LENSDDKYY derived from fermented quinoa exhibited ability to scavenge free radicals while maintaining non-toxic effects in keratinocytes [58]. Bovine whey peptides such as ALPM, GDLE, VGIN and AVEGPK inhibited free radical formation in muscle cells [59]. Similarly, peptide RGPLVNPDPKPFL derived from tomatoes exhibited potent antioxidant activity in vitro, probably due to the presence of Gln, Val, and Pro [60]. Likewise, lentil peptides derived via Savinase, LLSTQGQPSFLSGF, NSSLTPLIRLYL, TLEPNVSFLPVLHL showed compelling antioxidant activities in vitro [61]. However, the in vitro activity of such peptides is sometimes lost after simulated gastrointestinal digestion as they are cleaved by pepsin into the smaller peptides, indicating lower bioavailability [55]. This indicates that in vivo bioavailability of peptides is a prerequisite for peptide success. In a recent study, rapseppedase-protein-derived peptides LY, RALP and GHS exhibited ROS inhibition as evidenced by surge in SOD activity in vivo in hypertensive rats [62,63]. SOD2 is a key mitochondrial enzymatic antioxidant associated with life span and surplus of this enzyme is vital for protecting animals from premature death [64]. Similarly, loach peptides prepared by papain digestion also increased SOD, catalase (CAT) and glutathione peroxidase (GSH-Px) activity in vivo [65]. Likewise, in vivo supplementation of elastin peptide increased mRNA production of ENOS, indicating modulation of mitochondrial function possibly via PGC1α in transgenic mice and hypertensive rats [66,67]. This evidence from multiple food sources in both cells and in vivo models is promising to indicate the ability of peptides to improve mitochondrial function towards mitigation of aging markers. Despite being an encouraging signpost, majority of in vitro results and the limited choice of animal models studies certainly plague complete warrant of transfer from bench to bedside.

2.3. Insulin-like signaling (ILS) pathway

The aging-associated genes identified in the C. elegans encode components of the insulin and insulin-like growth factor intracellular signaling pathway [14]. Individually, IGF-1 and FOXO factors induce reduced oxidative stress, apoptosis, proinflammatory signaling, and endothelial dysfunction and extend lifespan. A dietary peptide Pyropia yezoensis (PYP15) exerts cytoprotective effects against dexamethasone-induced myotube atrophy via the upregulation of the p-IGF-IR, p-IRS-1, FoxO1 and FoxO3a protein expression levels in C2C12 myotubes [68]. Also, casein glycomacropeptide-derived peptide IPPKKNQDKTE reduces high glucose-induced insulin resistance and accompanying reduced oxidative stress [69]. Similarly, peptide rich casein hydrolysates improved insulin resistance of C57BL/6J mice fed with high-fat diet [70]. Recently, a peptide from bitter melon proteins was identified with ability to bind to IR and stimulated IR kinase activity towards improved glucose uptake in cells and glucose clearance in mice [71]. Similar bioactive peptides from beans and hemp inhibited adipocyte lipid accumulation and increased glucose uptake both in cells and in mice [72–77]. Di and tri-peptides (AP, VAP and AKK; GY), identified from the silk peptide ESK6, significantly stimulated basal and insulin-mediated glucose uptake by 3T3-L1 fibroblasts in a dose-dependent manner [78,79]. Another bioactive peptide, RGPLVNPDPKPFL, derived from common bean stimulated the insulin secretion towards overall improvement in glucose function [80]. Likewise, soybean peptide aglycin restored insulin signaling transduction by maintaining IR and IRS1 expression at both the mRNA and protein levels, as well as elevating the expression of p-IR, p-IRS1, p-Akt and membrane GLUT4 protein [81].

2.4. mTOR pathway

Initially identified from rapamycin research, the target of rapamycin (TOR) proteins are shown to inhibit the growth of cells and act as an immune modulator [15,82]. As the evidence for mTOR as a conserved nutrient sensor made it an attractive candidate to mitigate aging phenotypes, the use of dietary peptides as mTOR modulators certainly stand a strong change for anti-aging activity across species. A small evidence indicates that dietary peptides have impact on this critical node. A novel peptide, KVEPOQDPEW, isolated from abalone (Haliotis discus hannai) exerts its pharmacological effect by modulating mTOR signaling [83]. Likewise, other abalone by-product peptides (BABB, EMDEAQDPEW) modulate oxidative damage and related MAPKs via through suppression the mTOR pathway [84]. Both of these peptides attenuate hyperproliferation and modulate mTOR node of cancer cells. Similar results are also exhibited by Anthopleura anjunae oligopeptide indicating modulation of P38/AKT/mTOR Signaling Pathway [85]. Further, PYP15 peptide (Pyropia yezoensis) treatment attenuates dysfunctional Akt-mTORC1 signaling Pathway in C2C12 myotubes.
towards improvement in cellular homeostasis [68]. Likewise, another bioactive peptide derived from Porphyra yezoensis exhibited a dose-dependent decrease in mTOR in the MCF-7 cells [86].

2.5. AMPK pathway

Disturbances in the maintenance of energy metabolism provoke diseases and jeopardize healthy aging. AMPK is an energy sensor that maintains cellular energy homeostasis and is activated during dietary restriction [87]. Therefore, the fine-tuning of AMPK activity by dietary peptides could contribute to the mitigation of aging. Mushroom derived peptides from Auricularia polytricha exerts hepatoprotective activity via up-regulated expression of genes controlling free fatty acid oxidation, such as AMPK and PPARα genes [88]. Similarly, another bioactive peptide LLVVWPWTQR obtained from Chlorella pyenoidose lower hyperlipidemia via modulation of AMPK signaling [89]. Further, in spontaneously diabetic Goto-Kakizaki rats, the consumption of soya peptides specifically increases GLUT4 translocation and AMPK activity [90]. The pepsin and pancreatin derived soy peptides enhance glucose uptake in cells via the activation of the AMPK enzyme [91]. As the AMPK signaling controls the aging process via an integrated cellular signaling network, these findings of the ability of bioactive peptides extend our knowledge and warrant their use for mitigation of aging biomarkers via AMPK activation.

2.6. Epigenetic alterations

Studies on ‘aging epigenetics’ have revealed there are progressive changes to epigenetic information in both dividing and nondividing cells throughout life [92]. These changes involve modification in DNA methylation patterns, histones, and chromatin transformation. Some of the major aging-associated epigenetic markers include increased histone H4K16 acetylation, H4K20 trimethylation, or H3K4 trimethylation, as well as decreased H3K9 methylation or H3K27 trimethylation [93,94]. It is now well understood that the relationship between DNA methylation and aging is complex [95] but general understanding has associated hypermethylation with aging phenotype [96]. Such epigenetic modifications in histones and DNA methylation, accompanied by other epigenetic alterations constitute characteristic features of aging [97]. Thus, modulation of epigenetic alterations via dietary intervention can directly maintain telomere length, one of the hallmarks of aging. One of key evidence for the ability of bioactive peptides comes from soy peptide Lunasin [98]. The transcriptional activation of HMGCoAR via specific acetylation of histone H3 by P300/CBP-associated factor (PCAF) is an essential step in hepatic cholesterol biosynthesis [99]. Lunasin reduces the H3K14 acetylation by PCAF, thus lowering the HMGCoAR expression and reducing cholesterol biosynthesis towards clearance LDL-cholesterol from the bloodstream [98]. These epigenetic effects of lunasin are very similar to other soybean peptides such as IAVPGEVA, IAVPCTVA, and LPYP, indicating possible convergence of epigenetic mechanisms [100]. As epigenetic markers are altered in cells during physiological aging, and the revocable nature of epigenetics, a comprehensive identification and study of epigenetics modulating peptides is central to the science of gerontology.

2.7. Sirtuins

In 1999, SIRT1 was identified as a protein deacetylase that removes acetyl groups from histone proteins in cellular coenzyme nicotinamide adenine dinucleotide (NAD⁺) dependent manner [101,102]. Further, it was revealed that SIRT1 was the underlying protein in the lifespan expansion observed under dietary restriction in yeast [103]. Mice and humans express seven sirtuins of which SIRT1, SIRT2, SIRT3, SIRT6, and SIRT7 are bona fide protein deacetylases, whereas SIRT4 and SIRT5 do not exhibit deacetylase activity but remove other acyl groups from lysine residues in proteins [104,105]. Sirtuins control the response to calorie restriction and protect against age-associated diseases, thus increasing healthspan and—in some cases—lifespan [106]. Hence the ability of functional food or a peptide to induce sirtuins will be supporting the working model that sirtuins and improved NAD⁺ levels might mitigate the aging process [107]. Only one evidence from literature indicates that peptide-rich cottonseed meal protein hydrolysate activates the SIRT1 pathway in vivo [108]. This leaves a large research gap and an extraordinary important research opportunity for studying the impact of dietary peptides on NAD⁺ content and sirtuins, especially on SIRT1, SIRT3, and SIRT6.

2.8. Telomeres

Telomeres play a crucial role in cell fate and aging by adjusting the cellular response to stress and growth stimulation [109]. Hence, it will be interesting to observe if a dietary peptide can modulate telomere length in different organisms. While reviewing the literature, we identified a major research gap in the area of bioactive peptides and telomere studies. Peptides from Irisin, exert neuroprotection and modulate the life span [110]. Peptides with similar sequences and amino acids have been well studied in food sources, therefore we encourage the investigation of food-derived peptides towards telomere cytoprotection.

3. Perspectives and future directions

Peptides are remarkable biomolecules with a huge diversity of important pharmacological roles in vivo. In this section, we will not solely focus on the already given evidence but critically evaluate the evidence coming from literature followed by a discussion of future aspects. However, the first question arising is whether bioactive peptides are a food or a drug. The national regulatory system states if a product is taken as food for nutrition, it is designated as food while if used to mitigate a disease it is a drug. The latter category includes both natural health products and pharmaceuticals, possibly placing peptides in the health food or drug category. Therefore, peptides as a health food, for overall improvement in health status or as drug candidates, for specific disease mitigation are gaining strong attention. It is vital to mention that bioactive peptides such as LKPNM and VY have been commercialized and several peptides are undergoing clinical trials.

As discussed above, nutrient sensing is dependent on the insulin, mTOR and AMPK pathway, and unique polymorphisms in these found in both pathological aging and centenarians around the world [111]. Available evidence strongly indicates that bioactive peptides can modulate these key pathways. As in mice, it has been hypothesized that selective pressures on the response to nutrient sensing (mTOR, AMPK, Sirtuins) may vary across different aging populations, that subsequently influence metabolism and aging. Multiple levels of studies i.e. from in vitro to in vivo have been conducted between the identification and the application of anti-aging peptides, particularly at cellular and animal scale. Our literature review indicates that success has been achieved on multiple fronts: i) it is now clear that multiple peptides can modulate metabolism in vivo, especially in obesity and CVD models; ii) physiology-based mechanisms have been identified for improvement of cardiac function, particularly through hypertension; iii) downstream modulation of AMPK/mTOR pathway and improvement in nutrient sensing; and, iv) indicative action of sirtuin and adjustment of histone acetylation, among others. Also, as originally noted in free radical theory of aging, recent work has also been shedding light on...
related pathways involved in the aging process, with the promise of dietary peptides to mitigate the oxidative homeostasis pathways [52]. It is essential to mention that the ability of bioactive to mitigate mitochondrial stress represents their strongest forces. Even though advancements have been achieved, yet, some improvements are certainly required. Due to the immense number of genetic factors involved, advances in the underlying signal transduction initiated by peptides are required further understanding; for example, the identification of the upstream or membrane level pathway activators. This helps elucidate the therapeutic signal pathways, and the consequent biological activity, which in turn improve the selection and identification of new peptides. Further, the choice of aging models must reflect the aging phenotypes as most animals receiving peptide therapeutics don’t reflect geriatric phenotypes. Hence, the results obtained even though very encouraging must be validated in other aging specific models.

Thirdly, to move dietary peptides from cellular models to humans, several hurdles need to be overcome. It is now clear from the cell and animal model systems that peptide interventions are beneficial for mitigating aging biomarkers. However, no evidence indicates that the results obtained in one type of rodent genetic environment can be replicated in another system such as mutant/rapidly aging models. In most studies, a few model systems have been assumed to be universally beneficial for pharmacological intervention, while quintessential basal in vivo systems have not been explored. Future studies in genetically diverse models such as yeast, worms, and flies hold promise for systematically explaining the genetic basis of aging mitigation by dietary peptides. The genetic diversity of model systems in validation of a pharmacological or nutraceutical is indispensable as the human population is also characterized by a large genetic heterogeneity that has a critical role in disease vulnerability and the response to drugs. This genetic heterogeneity is the foundation of precision or tailored medicine, which aims to pinpoint genetic factors of the disease and to help to customize both pharma and dietary to unique genetic/nutritional variants. It is rational to hypothesize that human physiology may react variably to peptides in contrast to rodents or cellular models due to divergent immune response. As diverse human populations across the world are aging, in the future, the field of nutrition/bioactives and geriatrics will have to interact closely to mitigate aging biomarkers.

Fourthly, the use of bioactive peptides has been criticized due to their susceptibility to digestive enzymes that could render them inactive before their pharmacological impact in vivo. However, most of our cited in vivo studies indicate their potent bioavailability and possible action of metabolites [112]. Some di-/tripeptides permeate through intestinal membranes in their intact forms via peptide transporter systems, while others are vulnerable to protease degradation [112]. Another set of evidence indicates that bioactive peptides might function locally through receptors on cell membranes [113]. The incorporation of metabolomics is expected to shed light on in vivo of the action of the bioactive peptides. Finally, there is an urgent need for translational research to understand the possible role of bioactive peptides on lifespan and healthspan extension. Once assumed to be impossible, it is now evident that changing the activity of several conserved genetic pathways such as mTOR, AMPK, and sirtuin can lead to lifespan and healthspan improvement effects, by targeting multiple pathways and effectively reducing endogenous oxidative stress. Besides, multiple peptides have been identified for modulation of nutrient-sensing pathways and target vital aging pathways such as mTOR, AMPK, and sirtuins. Yet, there is still a significant gap in knowledge about the structure-function relationship of bioactive peptides. Furthermore, most of pharmacologically active bioactive peptides obtained from food sources remain unexplored for their ability to extend lifespan. There is a prospective opportunity in exploring further as some of the peptides may have exhibited therapeutic effects by influencing the mTOR and AMPK, which play an important role in regulating lifespan.

Declaration of Competing Interest

There is no conflict of interest

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References


