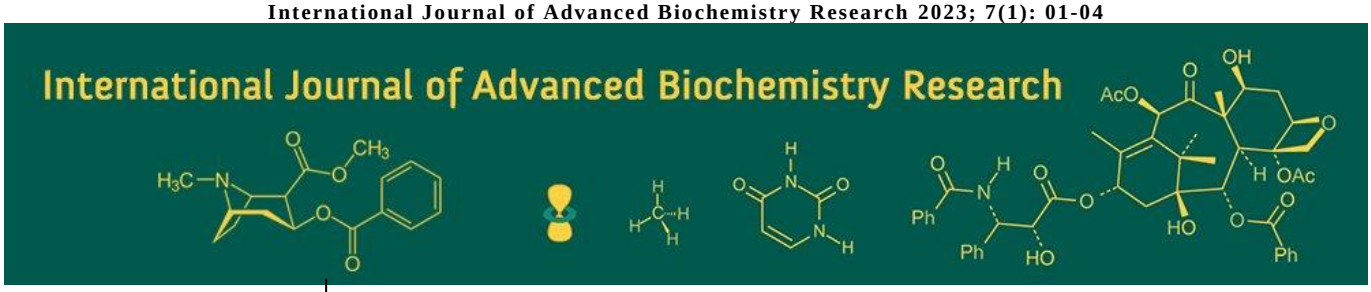

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Cellular senescence, mTOR signaling pathway and polyphenol

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Abstract
Cellular senescence is an important part of the aging process and forms the basis of age-related diseases. In our study, we discussed the relationship between the mammalian target of the rapamycin (mTOR) signaling pathway and the polyphenols that affect this pathway and cellular senescence. For this, we determined the keywords 'mTOR' or 'polyphenol' or 'cellular aging'. We searched these keywords in scientific databases such as Scopus, Institute for Scientific Information-Web of Science, Google Scholar, Science Direct and PubMed. According to the search results, we evaluated 35 studies especially in the last ten years.
In conclusion, the importance of the mTORC1 signaling pathway in cellular senescence likely derives from its extraordinary ability to control a wide variety of important cellular processes. Polyphenols can modulate the mTOR signaling pathway. The anti-aging property of polyphenols is due to their important role in modulating major signaling pathways that affect the longevity of organisms, such as the mTOR signaling pathway. In this context, consumption of foods rich in natural polyphenols can prevent or delay the aging process and age-related diseases.

Keywords: Cellular senescence, mTOR signaling pathway, polyphenol

Introduction
Cellular senescence is defined as a stable cell cycle arrest caused by damage or stress applied to proliferating cells [1]. Accumulation of senescent cells reduces the regenerative potential of tissues, promoting tissue dysfunction and tumor development in a non-autonomous cell [2, 3]. This accumulation has proven to be a physiologically important driver of age-related functional decline, morbidity, and mortality [4]. Senescent cells produce multiple proinflammatory chemokines and cytokines, collectively termed senescence-associated secretory phenotype (SASP), which inhibit autocrine response and aging and regulate immune surveillance of senescent cells [5].
The mammalian target of rapamycin (mTOR) is a protected serine–threonine protein kinase that senses and integrates various intracellular and extracellular signals, such as cell growth factors and different nutrients, to cellular and organismal responses [6]. mTOR is present as a catalytic subunit in at least two protein complexes. It belongs to the family of phosphatidylinositol-3 kinases (PI3K) related kinases [7]. The first proof that mTOR is a lifespan regulator come from studies with the fruit fly Drosophila melanogaster [8] and the nematode C. elegans [9]. mTOR was subsequently associated with a role in controlling the survival of the yeast strain S. cerevisiae. Inhibition of mTOR by rapamycin doubled the survival time (lifespan) of non-dividing cells in this simple organism [10].
Polyphenols constitute a significant class of intricate and pervasive plant metabolites in the human diet [11]. Dietary polyphenols have been shown to be beneficial in the prevention and treatment of a number of pathological diseases [12]. This is because different polyphenols have different sugar units and acylated sugars at various positions on their backbones. Polyphenols have been produced as food or medicine, which have positive effects on health due to their strong biological functions, absence of side effects and widespread availability [13]. Polyphenols are the most plentiful native biochemicals found in vegetables, fruits seeds and spices, as well as red wine, coffee and cocoa. Many useful effects of polyphenols have been shown, including antioxidant and free radical scavenging activity, anti-inflammatory and anti-tumor properties and anti-thrombotic and anti-microbial activity [14].

Natural polyphenols have a variety of positive health impacts, including slowing the senescence process. Polyphenols are able to prevent or postpone the establishment of senescence by influencing the molecular pathways of senescence, which helps to avoid or treat aging and age-related illness [15].

In this study, the mTOR signaling pathway and the relationship of polyphenols affecting this pathway with cellular senescence were evaluated. For this, the keywords 'mTOR' or 'polyphenol' or 'cellular senescence' were determined. These keywords were searched in scientific databases such as Scopus, Institute for Scientific Information-Web of Science, Google Scholar, Science Direct and PubMed. According to the search results, 35 studies were evaluated, especially in the last ten years.

Cellular senescence and mTOR

Interest in the mTOR signaling pathway as a regulator of cellular senescence and lifespan was strengthened by the finding that rapamycin prolongs the lifespan of genetically heterogeneous cells [16]. Miller *et al*. administered rapamycin, an mTOR kinase inhibitor, to mice at a dose three times higher than that used in their previous study. They found that genetically heterogeneous mice increased life expectancy by 23% in males and 26% in females [17]. Wu *et al*. analyzed senescence parameters in mice using the mTOR hypomorphic mouse model. In these animals, they found an approximately 20% increase in median survival with decreased mTORC1 and mTORC2 activity [18]. In the study by Selman *et al*., they found that deletion of the mTORC1 substrate S6K1 also prolongs lifespan. However, it has been reported to occur only in females and not in male mice [19]. Altogether, these findings suggest an evolutionarily conserved role for mTOR as a longevity regulator. The lifespan prolonging effects of mTOR inhibitors are associated with mTORC1 inhibition, whereas inhibition of mTORC2 can even be detrimental because mTORC2 controls insulin-mediated suppression of hepatic gluconeogenesis [20].

Although it is now widely accepted that mTOR inhibition prolongs lifespan, the exact mechanism by which this occurs is still unknown. Inhibiting mTORC1 alone may not stop senescence, but may stop age-related diseases [21]. However, many researchers have demonstrated a direct correlation between the effects of mTOR inhibitors on longevity and the slowing of senescence. The normal aging process is characterized by progressive loss of physiological integrity, resulting in decreased functionality, increased vulnerability to death, and shortened lifespan [22]. Cellular senescence telomere wear, epigenetic alterations, genomic instability, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, stem cell depletion, and altered intercellular communication are some of the conserved features of senescence that have been suggested recently [22,23]. Some of these signs of aging are known to be regulated by the mTOR signaling pathway [6].

mTOR and polyphenols

Recent research has shown that polyphenols can modulate the mTOR signaling pathway [24]. It has also been reported that the anticancer activity of mammary carcinogenesis modulation of turmeric containing curcumin, a polyphenol, is mainly due to its activity on the mTOR signaling pathway and other signaling pathways [25]. Another polyphenol isoliquiritigenin treatment has been reported to have a significant inhibitory effect on the proliferation of MKN28 cells of gastric cancer. Akt phosphorylation levels are significantly reduced following treatment with isoliquiritigenin. These findings indicate that isoliquiritigenin can affect apoptosis and autophagy in MKN28 cells by suppressing the signaling pathway to phosphoinositide 3 kinase/Akt/mTOR [26]. Apigenin is a promising polyphenol in the prevention of skin cancer. UVB has cancerous effects on the skin. Apigenin is able to reverse the proliferative effects shown after UVB administration, which is mediated by increased mTOR signaling and resulted in keratinocyte proliferation and progression of cancer keratinocyte proliferation and progression of cancer. This result demonstrates the important role of mTOR inhibition in UVB protection by apigenin [27]. Quercetin is a flavonoid that is very capable of stopping the proliferation of colon cancer cells. Quercetin has antiproliferative effects by reducing mTOR signaling [28]. Calycopterin is a polyphenol that has been tested in hepatoblastoma cancer cells. It was determined that calicopterin increased the expression of mitochondrial apoptotic proteins and decreased caspase 3 and 9 levels by inhibiting the PI3K/Akt/mTOR signaling pathway [29]. Herbacetin is also a polyphenol with similar effects on apoptosis by inhibiting the PI3K/Akt/mTOR signaling pathway [30]. Phloroglucinol is a polyphenol tested on HT-29 colon cancer cells. The results have shown that this agent has the ability of adversely regulating insulin growth factor-1 (IGF-1) signaling. Inhibition of IGF-1 is resulted in the inactivation of downstream signaling cascades like PI3K/Akt/mTOR [31].

Cellular senescence and polyphenols

Cellular senescence is an important mechanism that directly guides the aging of the organism. Natural anti-aging polyphenols have great potential for use in the prevention and treatment of the visible manifestations of premature and chronological aging and its age-related disorders [15]. Zia *et al*. reported that curcumin is a polyphenol with anti-aging, anti-cancer, anti-microbial, anti-inflammatory and antioxidant properties. Additionally, they reported that its anti-aging property is due to the important role of curcumin in modulating major signaling pathways that affect the longevity of organisms, such as the mTOR signaling pathway [32]. Aging causes multiple changes in biological processes, including energy metabolism and nutrient sensing, reducing cell proliferation and causing cellular senescence. Resveratrol, which is among the polyphenolic phytochemicals, reduces the negative effects of the aging process thanks to its multiple biological activities. On the other hand, resveratrol is not an approved drug and may not be approved in the future; however, it can be used as an important functional food and food supplement. Foods with high levels of resveratrol can prevent age-related diseases [33].

Autophagy decreases during aging. Various pharmacological compounds, including natural polyphenols, have been proposed to induce autophagy. Polyphenols have the ability to modulate the expression of pro- and anti-apoptotic factors, neutralize free radical species, affect mitochondrial functions, chelate redox-active transition metal ions, and inhibit protein aggregation. Moreover, polyphenols have advantages over chemical autophagy

inducers due to their inherent biocompatibility and safety. In this context, polyphenols can be considered as a potential therapeutic tool for healthy aging as part of a diet or as separate compounds (supplements) [34]. Foods rich in polyphenols protect against age-related diseases such as atherosclerosis, cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension and Alzheimer's disease. Resveratrol and pterostilbene, polyphenols found in grapes and blueberries, have beneficial effects as anti-aging compounds by modulating hallmarks of aging, including oxidative damage, inflammation, telomere wear and cellular senescence [35].

Conclusion

In conclusion, the importance of mTORC1 signaling pathway in cellular senescence is likely due to its extraordinary ability to control a wide variety of important cellular processes. Polyphenols can modulate the mTOR signaling pathway. In addition, cellular senescence is an important part of the aging process and forms the basis of age-related diseases. The anti-aging property of polyphenols is due to their important role in modulating major signaling pathways that affect the longevity of organisms, such as the mTOR signaling pathway. In this context, consumption of foods rich in natural polyphenols can prevent or delay the aging process and age-related diseases.

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