Review Article **Open Access**

Apigenin as a bioactive compound for longevity: Targets and mechanisms in senescent cells

Kamon Chaiyasit[1,2], Kadesanee Likitkriengkri[3], Kanokpong Muangsri[1], Varit Srisukthaveerat[1]

[1]Integrative Nutrition and Herbal Medicine Association, Bangkok, Thailand, [2]Esperance Integrative Cancer Center, Bumrungrad International Hospital, Bangkok, Thailand, [3]Senizen Wellness, Bangkok, Thailand

***Corresponding author:** Kamon Chaiyasit, Integrative Nutrition and Herbal Medicine Association, 325 Yothatikan Khu Khot Road, Thanya Buri, Pathum Thani, Bangkok 12120, Thailand

Submission Date: February 3rd, 2025; **Acceptance Date**: February 28th, 2026; **Publication Date:** March 3rd, 2026.

Please cite this article as: Chaiyasit K., Likitkriengkri K., Muangsri K., Srisukthaveerat V. Apigenin as a bioactive compound for longevity: Targets and mechanisms in senescent cells. *Bioactive Compounds in Health and Disease*. 2026; 9(3): 131-147. DOI: https://doi.org/10.31989/bchd.v9i3.1929

ABSTRACT

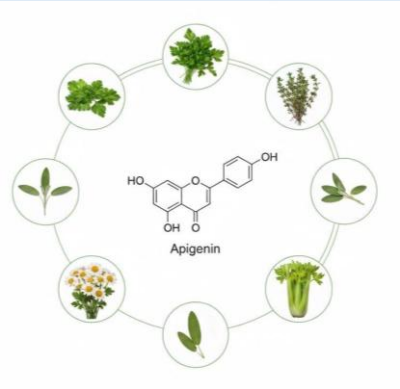
Bioactive compounds have emerged as a focal point in contemporary health and biomedical research due to their potential in disease prevention, health promotion, and longevity enhancement. With the global rise of the longevity movement, attention has increasingly shifted toward understanding how functional foods and bioactive compounds influence molecular mechanisms associated with aging. This review focuses on apigenin, a naturally occurring flavonoid found in many fruits, vegetables, and herbs. Although apigenin exhibits poor bioavailability due to limited solubility and rapid metabolism, it has been shown to exert multiple effects due to its longevity and cellular health.

In terms of cellular senescence, apigenin exhibits senomorphic activity, modulating the senescent cell phenotype rather than directly inducing their death. Specifically, it suppresses the senescence-associated secretory phenotype (SASP) by inhibiting key inflammatory signaling pathways such as NF-κB and p38-MAPK, thereby reducing chronic inflammation and tissue degeneration. However, evidence for its senolytic activity remains inconclusive, as current findings have not shown direct senolytic effects in senescent cell models.

Interestingly, studies in other cellular systems show that apigenin can modulate molecular pathways associated with apoptosis, including the regulation of Bcl-2 family proteins and caspase activation, which may indirectly support cellular renewal processes. Given these findings, apigenin stands out as a promising candidate for further development as a functional ingredient in longevity-focused nutrition. Its potential role as a bioactive modulator of senescent cell behavior highlights new opportunities for future research in nutraceuticals and functional food innovation aimed at promoting healthy aging.

Novelty of the study: This review highlights apigenin as a longevity-oriented functional food bioactive that targets senescent cells through senomorphic mechanisms and NAD^+ modulation via CD38 inhibition, distinguishing it from previously reported conventional senolytic compounds.

Keywords: apigenin, NAD^+ metabolism, CD38 inhibitor, cellular senescence, Senescence-associated secretory phenotype (SASP)



Graphical Abstract: Apigenin as a bioactive compound for longevity: Targets and mechanisms in senescent cells.

INTRODUCTION

Longevity has become one of the most popular trends in modern health and wellness, drawing increasing public attention worldwide. This growing interest has expanded scientific research beyond medical treatment to explore the mechanisms of aging and cellular degeneration at both the cellular and molecular levels. In addition to medical interventions, the field of wellness and preventive health now focuses heavily on understanding how nutrition and lifestyle can modulate aging processes. Consequently, there has been a surge of nutraceutical and functional food products developed under the concept of promoting longevity [1]. One of the earliest bioactive compounds to inspire an idea of the longevity movement in the nutraceutical field was resveratrol, a polyphenolic compound first recognized as a key component of red wine. Beyond red wine, resveratrol is also found in other plants such as mulberry, Japanese knotweed, and peanuts [2-4]. Mechanistically, resveratrol has been shown to activate the expression of key longevity-related genes, including sirtuin-1 (*SIRT1*), forkhead box O1 (*FoxO1*), AMP-activated protein kinase (*AMPK*), and nicotinamide phosphoribosyltransferase (*NAMPT*) [4-5]. These pathways resemble those induced by caloric restriction or fasting, resulting in improved metabolic profiles and protective effects against non-communicable diseases (NCDs). As research progressed, studies at the molecular level revealed that cellular aging involves multiple interconnected mechanisms that extend beyond metabolic regulation and mitochondrial function. New insights highlighted the roles of autophagy [6] and senescent cells [7] in the aging process, driving further exploration of drugs and bioactive compounds capable of modulating these pathways. This shift has opened a new frontier in longevity science, where functional nutrition and molecular biology converge to uncover the secrets of healthy aging.

The senescent cell theory describes senescent cells as aged cells that permanently cease division but evade apoptosis, unlike normal aging cells. Instead, they remain metabolically active and secrete inflammatory factors known as the senescence-associated secretory phenotype (SASP), which disrupts tissue homeostasis, damages neighboring cells, and interferes with normal metabolic processes. The accumulation of these cells increases with age and contributes to cellular dysfunction and the development of age-related diseases. Consequently, research interest in senolytic agents compounds that selectively eliminate senescent cells has grown rapidly. Among the most studied bioactive flavonoids**,** quercetin and fisetin have shown potential to reduce senescent cell burden and to exhibit senolytic activity through mechanisms such as apoptosis induction and SASP suppression [8].

Among the various flavonoids that have attracted increasing attention as bioactive compounds, apigenin has emerged as a particularly promising molecule. Several studies have reported its pharmacological activities, including anti-cancer properties, sleep-promoting effects, and the ability to reduce advanced glycation end-products (AGEs) [9]. More recently, there has been growing interest in apigenin's role in longevity research, as emerging evidence suggests that it influences multiple anti-aging mechanisms at the cellular level. These findings have sparked a surge of scientific interest in exploring its function as a natural compound with geroprotective potential.

This review presents the role of apigenin in targeting senescent cells through both senomorphic and senolytic mechanisms. The manuscript is based on a comprehensive literature search conducted using major databases, including PubMed, ScienceDirect, Scopus, and Google Scholar, with relevant studies systematically synthesized to provide a focused perspective on these mechanisms. In addition, the article discusses apigenin as a bioactive compound with translational potential for development into functional foods and nutraceuticals. It addresses its natural plant sources, strategies for standardization and quantification, molecular structure, absorption characteristics, bioavailability, and its broader effects on longevity-related pathways. These include antioxidant and anti-inflammatory activities, as well as the modulation of proteins and molecular targets associated with longevity and overall health. By framing apigenin within the context of longevity science, this review aims to provide a conceptual and translational foundation for future research and product development in the field of longevity-oriented functional foods and nutraceutical innovation.

Apigenin structure in food: Apigenin (C15H10O5) is a compound belonging to the flavonoid group widely found in various edible plants. In many countries, it has been recognized for its potential use in functional foods and nutraceuticals for promoting health and preventing disease. From a chemical perspective, apigenin is classified as a flavone, which is a subclass of polyphenols. Numerous flavones have been identified to date, and most compounds in this group share a characteristic C6–C3–C6 backbone, consisting of two aromatic rings connected by a heterocyclic ring containing an oxygen atom. The differentiation among flavones primarily depends on the specific chemical substituents attached to this base structure.

In the case of apigenin, its molecular framework comprises two aromatic rings (referred to as ring 1 and ring 2) connected by a heterocyclic ring. The molecule contains hydroxyl groups positioned at C-5 and C-7 on ring 1 and at C-4' on ring 2, giving it the systematic chemical name 4',5,7-trihydroxyflavone [10]. This unique structural arrangement contributes to apigenin's strong antioxidant properties, which are characteristic of many flavones. The conjugated ring system and hydroxyl substituents enable apigenin to effectively scavenge

reactive oxygen species (ROS) and stabilize free radicals, making it a compound of significant biochemical and pharmacological interest.

In natural foods, apigenin rarely exists as a single isolated compound; rather, it is typically found in combination with a variety of phytochemicals that work synergistically to enhance biological activity and exert diverse health effects through multiple mechanisms. Among these, other flavonoids, such as quercetin, are commonly found alongside apigenin, and both compounds have been extensively studied for their pharmacological properties, particularly their roles in disease prevention and cellular longevity mechanisms. In foods, apigenin most often occurs in the form of glycosylated derivatives, including apigenin-6-C-glucoside (isovitexin), apigenin-7-O-glucoside, apigenin 6-C-glucoside 8-C-arabinoside (schaftoside), apigenin-8-C-glucoside (vitexin), apigenin 7-O-neohesperidoside (rhoifolin), and apiin [11]. Each of these derivatives exhibits different levels of stability and bioavailability, and further research is still needed to fully understand their respective biological activities and absorption profiles. While parsley is often cited as a major dietary source of apigenin, studies have identified a wide range of other food sources rich in this compound that have been investigated for their health-promoting potential and suitability for extraction as functional food ingredients. These include celery (*Apium graveolens*), artichoke (*Cynara scolymus*), and oregano (*Origanum vulgare*), among others [12]. As shown in Figure 1, rutabaga (*Brassica napus*) contains a higher reported apigenin content compared to other plant species listed in the table. Parsley represents the next prominent source with relatively high apigenin levels. Notably, apigenin is found in several commonly consumed edible vegetables, as illustrated in Figure 1. These data provide a practical foundation for selecting high-yield plant sources for extraction and standardization of apigenin, which may subsequently be developed as a functional ingredient for use in functional food formulations.

Common Name	Scientific Name	Apigenin (mg/kg)	Picture
Rutabaga	*Brassica napus* var. *napobrassica*	3850	
Kumquat	*Fortunella crassifolia*	218.7	
Peppermint	*Mentha × piperita* L.	539	
Rosemary	*Rosmarinus officinalis* L.	55	

Oregano	*Origanum vulgare*	257	
Chinese celery	*Apium graveolens* var. *secalinum*	240	
Guava	*Psidium guajava*	579	
Bilimbi fruit	*Averrhoa bilimbi*	458	
Mulberry leaf	*Morus alba*	547	
Parsley	*Petroselinum crispum*	2154.6	
Celery	*Apium graveolens*	338	
Chinese cabbage	*Brassica rapa* subsp. *pekinensis*	187	
French peas	*Pisum sativum*	176	
Bell pepper	*Capsicum annuum*	272	

Garlic	*Allium sativum*	217	
Snake gourd	*Trichosanthes cucumerina*	42.4	
Kadok	*Piper sarmentosum*	34.5	
Wolfberry leaves	*Lycium barbarum*	547	
Daun turi	*Sesbania grandiflora*	39.5	

Figure 1: Plant Sources and Reported Apigenin Content [12,16]

Apigenin Bioavailability Profile: Due to its chemical structure, apigenin exhibits poor oral absorption, with a reported bioavailability of approximately 0.708% in animal studies using rats. This limited bioavailability is thought to result from its instability and extensive first pass intestinal metabolism. Apigenin has very low solubility in aqueous solutions but dissolves well in polar organic solvents such as dimethyl sulfoxide (DMSO) and moderately in ethanol. Its poor water solubility represents a major limitation for oral absorption [13]. In nature, apigenin exists in both glycoside and aglycone forms, with the glycoside form predominant in plants, where it commonly occurs bounded to sugar molecules. This glycosylation enhances stability under natural conditions; however, once ingested, apigenin glycosides must undergo enzymatic hydrolysis to release free apigenin, a process that may require microbial activity in the gut. Conversely, the aglycone form of apigenin can be directly absorbed without enzymatic cleavage but is less stable and poorly soluble in water, which limits its bioavailability. A pharmacokinetic study conducted by Kyung Hee University in South Korea compared apigenin and apigenin-7-O-glucuronide in rats and found that the glycosylated form showed higher absorption, with a greater Cmax value than the aglycone form [14]. In a human study investigating dietary sources of apigenin, ingestion of parsley containing apigenin-7-O-glucoside resulted in the detection of apigenin-4'-glucuronide in plasma after four hours, whereas consumption of parsley leaf powder mixed with yogurt led to a peak concentration (Cmax) after six hours. These findings indicate that the form and matrix of apigenin ingestion significantly influence its absorption. Nevertheless, naturally occurring apigenin shows inherently low

gastrointestinal absorption and multiple bioavailability limitations [15]. To overcome these challenges, recent research has focused on developing improved delivery systems using pharmaceutical formulation techniques such as liposomes and nanoparticles to enhance apigenin's absorption and stability under physiological conditions.

When apigenin is administered orally, it must first be hydrolyzed by digestive or gut microbiome-derived enzymes to release free apigenin before absorption can occur. However, apigenin undergoes extensive first-pass metabolism [16]. During hepatic metabolism, apigenin is processed through both phase I and phase II pathways. In phase I metabolism, apigenin is primarily metabolized by cytochrome P450 (CYP) enzymes, specifically CYP1A2 and CYP1B1 [16-17]. Additionally, apigenin is known to act as a potent inhibitor of CYP1A2 and CYP2C9, indicating that co-administration with drugs metabolized by these enzymes should be approached with caution, as it may alter plasma drug concentrations [17]. Beyond CYP-mediated metabolism, apigenin can also be metabolized by flavin-containing monooxygenase (FMO) and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzymes [15]. In phase II metabolism, apigenin primarily undergoes conjugation reactions such as glucuronidation and sulfation, and is excreted mainly through urine, with smaller amounts eliminated via feces. Interestingly, in plant cells or bacterial systems, apigenin can be converted into luteolin as part of its metabolic process, demonstrating the close structural similarity between these two flavonoid molecules. This structural resemblance contributes to certain shared pharmacological activities, while slight variations in hydroxyl group positioning may result in distinct biological effects between the two compounds [18-19].

The Role of the Bioactive Compound Apigenin in Promoting Longevity: The study of longevity and healthy aging has gained increasing attention as people strive to maintain good health, prevent disease, and achieve a long life with an improved quality of living. In the past, the term longevity was mainly associated with the aging population who sought to maintain wellness and extend their lifespan through self-care. However, in the modern era, the concept of longevity has evolved into a broader social phenomenon that encompasses people of all ages, as health awareness and proactive self-care have become integral parts of daily life. Therefore, the term longevity is no longer limited to older adults [20-21]. Research in the field of longevity now emphasizes not only the extension of lifespan but also the improvement of health span—the period of life spent in good health, free from serious disease or disability. Consequently, studies on longevity aim to understand and extend both lifespan and health span by exploring biological mechanisms underlying aging at the cellular, genetic, and clinical levels. This has led to the development of multiple aging-related theories, including those involving oxidative stress, telomere length, gut microbiome, and various biomolecular markers such as SIRT1, AMPK, and NAD. It is evident that research in longevity science remains dynamic and evolving, with growing interest in identifying molecules that can slow down the cellular aging process while enhancing overall health. Early studies focused on pharmacological molecules such as metformin and rapamycin, which have shown potential to extend cellular lifespan and mitigate aging-related decline. More recently, attention has shifted to naturally occurring bioactive compounds, including resveratrol, curcumin, and anthocyanins, which are being actively explored for their roles in promoting longevity and healthy aging [22].

Apigenin is recognized as a bioactive compound classified within the phytochemical group derived from various fruits and vegetables, many of which have been reported to provide significant health benefits, including parsley, celery, mango, and chamomile [12,23].

Regarding its effects on longevity and disease prevention, apigenin exhibits strong antioxidant activity, functioning as a free radical scavenger—one of the key factors contributing to aging—by reducing DNA damage. Studies have shown that apigenin decreases levels of reactive oxygen species (ROS) and malondialdehyde (MDA), markers of oxidative stress [15,24-26]. Furthermore, chronic low-grade inflammation has been identified as a crucial mechanism leading to cellular degeneration and the onset of various chronic diseases, such as diabetes, cardiovascular diseases, and cancer. The concept of "inflammaging" has been introduced to describe the inflammation-driven aging process, which also contributes to age-related conditions such as sarcopenia in the elderly [27-28]. Apigenin has been reported to reduce inflammation both in vitro and in vivo through mechanisms that involve downregulating inflammatory cytokines such as TNF-α, IL-6, interleukin-1 receptor-associated kinase 4 (IRAK4), and IL-18. It also modulates key enzymes related to the inflammatory process, including COX-2, iNOS, and MCP-1 [15,26]. In addition, apigenin has been shown to attenuate inflammation by activating the AMPK signaling pathway, which is well recognized for its role in reducing cellular aging processes and promoting metabolic balance [15,29].

In recent years, NAD has gained significant attention in the fields of longevity and wellness, leading to the development of numerous NAD-based products in the functional food and nutraceutical markets. Increasing scientific interest has focused on the role of NAD in the aging process, revealing its critical functions in regulating cellular metabolism, mitochondrial activity, DNA repair, and SIRT1 function. It has been well established that NAD levels decline with age, partly due to the increased expression of the CD38 protein, which cleaves NAD and thereby reduces its cellular availability. This decline in NAD results in decreased metabolic efficiency and impaired cellular energy utilization, contributing to cellular aging [30]. Interestingly, apigenin has been pharmacologically shown to inhibit CD38, thereby indirectly increasing intracellular NAD levels [31]. This elevation in NAD enhances glucose and lipid metabolism, reduces metabolic dysfunction, and mitigates cellular degeneration. For example, studies have demonstrated that apigenin, by inhibiting CD38, increases NAD levels, alleviates mitochondrial oxidative stress, and reduces renal injury, tubulointerstitial fibrosis, and tubular cell damage in diabetic rat models [30,32]. Another key reason apigenin has attracted attention in the longevity field and has been developed into dietary supplements is its reported effect on promoting sleep quality, an essential component of health and a cornerstone of lifestyle medicine. The proposed mechanisms underlying apigenin's sleep-promoting effects include reducing oxidative stress, increasing acetylcholinesterase activity, and enhancing glutathione levels, thereby decreasing oxidative stress in the brain and improving sleep quality. Additionally, apigenin has been found to elevate brain-derived neurotrophic factor (BDNF) and serotonin levels, inducing a sense of calmness and relaxation that facilitates better sleep. Experimental studies in animal models further suggest that apigenin exerts sleep-promoting effects by modulating GABAergic activity, supporting its role in enhancing overall sleep quality [31,33].

In addition to studies focusing on metabolic regulation and the modulation of longevity markers, increasing attention has been directed toward eliminating senescent cells, which are aged cells that arise as part of the natural aging process and can induce neighboring cells to undergo similar aging changes. This cellular senescence contributes to the overall aging of tissues and the decline of organ function, ultimately leading to the development of various diseases. For instance, senescence in immune cells can impair the body's ability to regulate abnormal cell proliferation and

reduce resistance to infections. Therefore, identifying bioactive compounds with senolytic activity has become a key challenge and an area of great interest in the fields of functional food and longevity research. Among such compounds, apigenin has been recognized as a promising bioactive molecule with potential senolytic properties, which will be further discussed in the following section.

Senolytic and Senomorphic Properties of Apigenin: One of the most important and intriguing hallmarks of aging in the field of longevity science is cellular senescence. In 1891, scientist Weissman proposed that cells have a limited capacity for division and proliferation. Later, in the 1990s, Greider reported that the telomeres of human fibroblasts progressively shorten with each division, leading to the discovery and growing understanding of senescent cells. In 2019, it was reported that dasatinib and quercetin could selectively eliminate senescent cells [34], sparking significant scientific interest in identifying potential senolytic molecules. The process of cellular senescence is complex and involves multiple pathways, including DNA damage, oxidative stress, inflammation, telomere shortening, and oncogenic signaling [35]. Notably, apigenin has been shown to possess pharmacological properties relevant to these processes, including antioxidant, anti-DNA-damage, anti-inflammatory, and anticancer effects [15], suggesting its potential to modulate senescence-related mechanisms. When cells are exposed to such stressors, they undergo cell cycle arrest and express specific senescence markers such as increased β-galactosidase activity, elevated levels of p53 and p16INK4a, and chromatin alterations that maintain their non-proliferative state. Senescent cells also secrete various inflammatory mediators, collectively known as the senescence-associated secretory phenotype (SASP), which includes IL-1, IL-6, IL-8, chemokines, MCP-1, growth factors, and matrix metalloproteinases (MMPs). The production of these factors is often linked to oxidative stress, as excessive reactive oxygen species (ROS) can cause mitochondrial dysfunction, DNA damage, lipid peroxidation, and protein dysfunction, thereby induce inflammation and promoting SASP gene expression [34-35]. The accumulation of senescent cells in tissues such as blood vessels, skin, adipose tissue, and muscles contributes to the aging process and functional decline of these organs. In muscle tissue, this accumulation can lead to sarcopenia, while in blood vessels it can cause arterial stiffness, endothelial dysfunction, and cardiovascular diseases. Moreover, SASP-induced genomic instability in neighboring cells can promote oncogene expression and suppress immune surveillance, potentially facilitating cancer development. Given the central role of senescent cells in aging and organ degeneration, there is growing scientific interest in identifying compounds that can inhibit or eliminate senescent cells to slow aging, prevent age-related diseases, and promote cellular longevity. Therefore, the following discussion will focus on the potential roles of apigenin in senolytic and senomorphic activities.

Apigenin has been studied to better understand its mechanisms related to various senotherapeutic activities, particularly its effects on senescent cells at the molecular level. Previous research has already established that apigenin possesses anti-inflammatory properties, and subsequent studies have demonstrated that it exhibits senomorphic activity, meaning that apigenin acts on senescent cells without directly inducing their death but rather by suppressing the secretion of SASP (senescence-associated secretory phenotype) factors. In its senomorphic role, apigenin regulates the expression of SASP components in senescent cells, as experiments have shown that apigenin reduces the expression of IL-1α, IL-1β, IL-6, and (C-X-C motif chemokine ligand) CXCL [36]. These molecules are inflammatory cytokines [37] secreted by senescent cells,

which negatively affect neighboring cells, leading to functional impairment and inflammation [38], a process contributing to cellular aging and the development of age-related diseases. Studies have also reported that apigenin exhibits senomorphic effects on fibroblasts by inhibiting NF-κB p65 activity through targeting IRAK1/lκBα signaling, thereby suppressing SASP-mediated inflammation and preventing fibroblast dysfunction. As shown in Figure 2, apigenin reduces various inflammatory cytokines, reflecting its senomorphic properties. Additionally, apigenin has been shown to inhibit IL-1α signaling via IRAK1, p38 MAPK, and NF-κB in breast cancer cells, reducing SASP secretion and limiting the inflammatory response in surrounding tissues. Another study reported that apigenin interferes with the interaction between ATM/p38 and HSPA8 (heat shock protein 70 subfamily), thereby preventing senescent cells from transmitting signals that promote SASP production, thus reducing chronic inflammation at the tissue level [36]. Normally, HSPA8 functions as a chaperone protein that assists in proper protein folding and degradation, playing a critical role in the cellular autophagy process [39-40]. Another proposed mechanism for apigenin's senomorphic activity involves its inhibition of phospholipase A2 (PLA2) by direct binding to peroxiredoxin 6 (PRDX6), thereby maintaining mitochondrial homeostasis and controlling inflammation, ultimately leading to reduced SASP production through an additional pathway.

The senolytic activity of apigenin, similar to other senolytic agents, is thought to target mitochondria to induce apoptosis in senescent cells [34], thereby reducing the population of aged or "zombie" cells. Senescent cells typically resist apoptosis due to the overexpression of anti-apoptotic proteins from the Bcl-2 family and the activation of survival signaling pathways such as PI3K/AKT, p53/p21, ephrin, and HSP90 [41-43]. Therefore, bioactive compounds with senolytic activity often target these molecular pathways. The most well-known example is quercetin, which acts on the PI3K/AKT pathway, followed by fisetin, another dietary supplement compound found in tea and strawberries, which also targets the same pathway [44]. However, the effectiveness of senolytic activity varies across cell types [45]. Although existing research does not clearly indicate a strong senolytic effect of apigenin compared to its well-established senomorphic activity [46], several studies have reported that apigenin influences proteins and signaling pathways associated with apoptosis in cancer cells [47], which are relevant to senolytic mechanisms that eliminate senescent cells via anti-apoptotic pathways. While these studies were not specifically conducted on senescent cells, apigenin has been shown to regulate the apoptosis pathway by downregulating Bcl-2 expression, leading to cell apoptosis, and increasing caspase-3 levels, a key protein in the apoptosis cascade [48-50]. Additionally, apigenin has been found to inhibit PI3K/AKT signaling by blocking Akt activity, thereby suppressing survival signals and promoting apoptosis. It also stabilizes p53, which regulates cell cycle control and promotes the expression of pro-apoptotic proteins. The molecular mechanisms underlying the potential senolytic properties of apigenin are illustrated in Figure 2. Although these findings are primarily derived from studies in cancer and other cell models rather than senescent cells, they demonstrate that apigenin modulates molecular pathways involved in senolytic mechanisms. Therefore, a promising direction for future development is to combine apigenin with other bioactive compounds to enhance its anti-senescent effects through complementary senolytic and senomorphic activities. For example, combining apigenin with quercetin or fisetin could yield synergistic effects that

integrate senolytic and senomorphic actions, representing a potential strategy for developing functional foods and dietary supplements aimed at promoting longevity and combating cellular senescence.

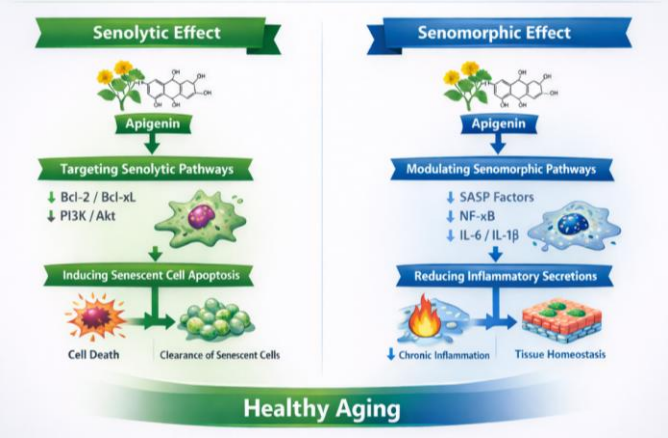


Figure 2: Mechanism of Apigenin in Senescence Cells

The development of apigenin as a bioactive compound for longevity applications is both promising and challenging, requiring advancements in extraction methods to produce stable apigenin formulations and pharmaceutical techniques to improve its bioavailability in dietary supplement preparations. Recent efforts have focused on incorporating apigenin into liposomes to enhance absorption, and further studies investigating its stability in various food matrices could enable its use as a functional food ingredient [51]. Another approach involves encapsulation techniques to improve apigenin stability, such as using chitosan-based encapsulation, which enhances resistance to acidic conditions, oxygen exposure under normal atmospheric environments, and degradation over time, thereby supporting better absorption and prolonged stability [52]. In the context of longevity research, future studies should determine the optimal apigenin dosage and identify appropriate biomarkers to evaluate its effects following consumption. Additionally, it is crucial to assess potential interactions between apigenin and other drugs, particularly when used for sleep improvement or other therapeutic purposes, as data on apigenin–drug interactions remain limited. Comprehensive studies addressing these aspects are necessary to ensure the safe and effective development of apigenin as a bioactive compound for promoting longevity and overall health.

Future direction: The advancement of research on apigenin and other bioactive compounds with senolytic and

senomorphic properties represents an important opportunity to elevate the role of functional foods and nutraceuticals within the longevity framework. Notably, current evidence suggests that apigenin exhibits more prominent and well-characterized senomorphic activity than direct senolytic effects, highlighting a relative gap in studies specifically investigating its capacity to selectively eliminate senescent cells. To date, much of the mechanistic research has focused on apoptosis induction in cancer cells rather than targeted senolysis in senescent cells, underscoring the need for further investigation in this area. In the context of nutraceutical and functional food development, apigenin exhibits an additional distinctive advantage: beyond modulating senescence-associated pathways, it has been reported to inhibit CD38, thereby promoting intracellular NAD^+ elevation. This dual action—senomorphic regulation combined with NAD^+ modulation—positions apigenin as a uniquely promising bioactive compound for longevity-oriented functional food innovation. However, a major limitation remains the lack of validated, reliable human biomarkers for assessing senolytic and senomorphic activity in clinical settings. The translation of these compounds

toward health claims requires robust biomarker development to objectively measure their biological impact in humans. While efforts have been made to design more comprehensive longevity-oriented studies—such as investigations of combined extracts from Ganoderma lucidum, ginseng, and several anti-aging ingredients evaluating effects on senescent cell targets [53] similar to apigenin, telomere length, telomerase activity, and mitochondrial membrane stability—the field still lacks standardized, clinically applicable biomarkers that can reliably support health claim substantiation. In addition, several plant-derived bioactive compounds have been reported to modulate SASP by reducing the secretion of pro-inflammatory cytokines such as IL-6 and IL-1. Curcumin, a well-established functional food ingredient with long-standing use and continued development in anti-inflammatory formulations, demonstrates specific regulatory effects on inflammatory cytokine molecules and associated signaling pathways involved in the inflammatory cascade.[54] Similarly, Resveratrol commonly utilized in functional foods for their antioxidant and longevity-supporting properties have been shown to suppress key SASP-related cytokines, including IL-1, IL-6, and TNF-α. These findings indicate a growing body of evidence supporting the use of bioactive compounds in functional foods that target inflammatory mediators associated with SASP.[55] If future studies more clearly delineate their capacity to suppress SASP production from senescent cells, thereby exerting senomorphic effects, this would further strengthen the positioning of functional foods within the longevity framework. Such an approach enhances the conceptual and translational relevance of functional foods as modulators of senescence-related inflammatory pathways, similar to the proposed role of apigenin.

Regarding apigenin, its potential as a longevity-oriented functional food ingredient is supported by evidence of anti-inflammatory activity and modulation of senomorphic and senolytic pathways. Accumulating evidence further suggests that apigenin may exert additional metabolic benefits, including glucose-lowering effects, improvement of insulin sensitivity, and hepatoprotective activity, thereby expanding its relevance beyond cellular senescence and positioning it as a promising candidate for targeting metabolic dysfunction and chronic low-grade inflammation associated with aging [16]. Future development should focus on standardizing apigenin content in botanical extracts, evaluating absorption, metabolism, and bioavailability, and optimizing formulation strategies to enhance functional efficacy. Additionally, targeted clinical investigations are warranted to explore system-specific applications, including the effects of apigenin on neuroinflammation, its potential role in stress reduction and cortisol regulation in humans, and its cardioprotective properties mediated through anti-inflammatory mechanisms. Determining effective dosing ranges for each intended health claim will be essential for regulatory approval and product positioning. Continued dose-finding studies in human populations will be critical to establish clinically effective and safe intake levels capable of supporting systemic resilience, slowing functional decline across organ systems, and potentially contributing to the prevention of non-communicable diseases. Such evidence-based translational development may ultimately facilitate the integration of apigenin into functional food and nutraceutical strategies to promote healthspan and extend healthy longevity in humans.

Equally important are comprehensive safety evaluations, including the assessment of potential herb–drug interactions and the identification of possible adverse effects associated with apigenin use. These data are critical for ensuring consumer safety and for supporting the responsible development of plant-derived bioactive compounds as functional foods and nutraceuticals targeting longevity-related pathways.

Conclusion: Apigenin is an interesting bioactive compound with multiple reported health benefits (sleep, cardiovascular, cancer) and can be found in various edible plants such as chamomile, celery, and oregano. However, there are concerns regarding the stability and bioavailability of apigenin extracts, as absorption remains limited and often requires encapsulation or advanced delivery techniques to improve systemic availability. In the context of longevity, apigenin has been discussed for its potential roles in disease prevention, sleep improvement, and modulation of telomere function and NAD^+ levels. Notably, apigenin exhibits senomorphic activity by regulating senescent cells and suppressing excessive SASP production, which contributes to chronic inflammation and tissue aging. However, there is still no clear evidence supporting its direct senolytic activity, as current studies have not demonstrated selective elimination of senescent cells. Although certain molecular markers associated with senolytic pathways have been reported in other cellular models, these findings have not yet been confirmed specifically in senescent cell systems. Therefore, future development of apigenin for longevity applications may involve combination strategies with other bioactive compounds possessing validated senolytic properties to enhance overall anti-senescent efficacy. From a functional food development perspective, apigenin shows considerable promise for future longevity-oriented applications. However, successful translation will require careful consideration of several factors, including selecting plant sources with high apigenin yields, optimizing extraction and standardization processes, and stabilization into consumer-ready formulations. Addressing bioavailability limitations remains critical, and the incorporation of advanced delivery systems—such as liposomal encapsulation or other nanoformulations, as discussed in this review—may significantly enhance its biological efficacy. Determining appropriate dosing ranges for specific indications will also be essential, particularly for longevity-related targets such as cardiovascular protection, anti-cancer potential, and metabolic disease modulation. Given its dual functional characteristics as a senomorphic regulator and CD38 inhibitor capable of modulating intracellular NAD^+ levels, apigenin represents a uniquely attractive candidate for the development of next-generation functional foods and nutraceuticals aimed at delaying functional decline and promoting healthy aging. Nevertheless, further mechanistic clarification, dose-optimization studies, and well-designed clinical investigations will be necessary to support its advancement in longevity science.

Abbreviations: AGEs, Advanced Glycation End-products; AMPK, AMP-Activated Protein Kinase; ATM, Ataxia Telangiectasia Mutated; Bcl-2, B-cell Lymphoma 2; BDNF, Brain-Derived Neurotrophic Factor; CD38, Cluster of Differentiation 38; COX-2, Cyclooxygenase-2; Cmax, Maximum Plasma Concentration; CYP, Cytochrome P450; CYP1A2, Cytochrome P450 1A2; CYP1B1, Cytochrome P450 1B1; CYP2C9, Cytochrome P450 2C9; CXCL, C-X-C Motif Chemokine Ligand; DNA, Deoxyribonucleic Acid; DMSO, Dimethyl Sulfoxide; FMO, Flavin-Containing Monooxygenase; FoxO1, Forkhead Box O1; GABA, Gamma-Aminobutyric Acid; HSPA8, Heat Shock Protein Family A (Hsp70) Member 8; IL, Interleukin; IL-1α Interleukin-1 Alpha; IL-1β Interleukin-1 Beta; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-18, Interleukin-18; iNOS, Inducible Nitric Oxide Synthase; IRAK1, Interleukin-1 Receptor-Associated Kinase 1; IRAK4, Interleukin-1 Receptor-Associated Kinase 4; MCP-1, Monocyte Chemoattractant Protein-1; MDA, Malondialdehyde; MMPs, Matrix Metalloproteinases; NAD, Nicotinamide Adenine Dinucleotide; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NAMPT, Nicotinamide Phosphoribosyltransferase; NCDs, Non-communicable Diseases; NF-κB, Nuclear Factor Kappa-light-chain-

enhancer of Activated B Cells; PI3K, Phosphoinositide 3-Kinase; PLA2, Phospholipase A2; PRDX6, Peroxiredoxin 6; ROS, Reactive Oxygen Species; SASP, Senescence-Associated Secretory Phenotype; SIRT1, Sirtuin 1; TNF-α, Tumor Necrosis Factor Alpha

Competing Interests: The authors have no financial interests or conflicts of interest.

Authors' Contributions: All authors contributed to this study.

Acknowledgment and Funding: The authors declare no acknowledgments or funding.

REFERENCES

1. Martinović A, Mantovani M, Trpchevska N, Novak E, Milev NB, Bode L, et al. Climbing the longevity pyramid: overview of evidence-driven healthcare prevention strategies for human longevity. *Front Aging*. 2024; 5:1495029. DOI: https://doi.org/10.3389/fragi.2024.1495029
2. Wang H, Chen X, Li J, Chen Z, Zhou A, Ye L. Oxyresveratrol from mulberry (Morus alba L.) ameliorates post-inflammatory hyperpigmentation in vitro by anti-melanogenesis, inhibiting melanosome transfer, and providing photoprotection. *Journal of Functional Foods*. 2024; 122:106557. DOI: https://doi.org/10.1016/j.jff.2024.106557
3. Feng L, Zhang T, Ye W, Qu D. Reveratrol and rutin alleviate dss-induced ulcerative colitis by affecting the polarization of intestinal epithelial t cells. *Journal of Functional Foods*. 2025; 129:106866. DOI: https://doi.org/10.1016/j.jff.2025.106866
4. Bejenaru LE, Biţă A, Belu I, Segneanu AE, Radu A, Dumitru A, et al. Resveratrol: a review on the biological activity and applications. *Applied Sciences*. 2024;14(11):4534. DOI: https://doi.org/10.3390/app14114534
5. Avital-Cohen N, Chapnik N, Froy O. Resveratrol induces myotube development by altering circadian metabolism via the SIRT1-AMPK-PP2A axis. *Cells*. 2024;13(12):1069. DOI: https://doi.org/10.3390/cells13121069
6. Gramatyka M. Time does matter: the cellular response to resveratrol varies depending on the exposure duration. *International Journal of Molecular Sciences*. 2025;26(12):5542. DOI: https://doi.org/10.3390/ijms26125542
7. Centonze M, Aloisio Caruso E, De Nunzio V, Cofano M, Saponara I, Pinto G, et al. The antiaging potential of dietary plant-based polyphenols: a review on their role in cellular senescence modulation. *Nutrients*. 2025; 17(10):1716. DOI: https://doi.org/10.3390/nu17101716
8. Tang H, Zhang X, Hu S, Song Y, Jin W, Zou J, et al. Natural products acting as senolytics and senomorphics alleviate cardiovascular diseases by targeting senescent cells. *Targets*. 2025;3(3):23. DOI: https://doi.org/10.3390/targets3030023
9. Perez-Gutierrez RM, Muñiz-Ramirez A, Garcia-Campoy AH, Mota-Flores JM. Polyphenols of leaves of Apium graveolens inhibit in vitro protein glycation and protect RINm5F cells against methylglyoxal-induced cytotoxicity. *Functional Foods in Health and Disease*. 2018;8(3):193-211. DOI: https://doi.org/10.31989/ffhd.v8i3.399
10. Liu S, Zheng X, Luo Z, Tang C, Hu Y, Peng Q, et al. The synthesis and bioactivity of apigenin derivatives. *Fitoterapia*. 2024; 179:106228. DOI: https://doi.org/10.1016/j.fitote.2024.106228
11. Raish M, Ahmad A, Shahid M, Jardan YAB, Ahad A, Kalam MA, et al. Effects of apigenin on pharmacokinetics of dasatinib and probable interaction mechanism. *Molecules*. 2023;28(4):1602. DOI: https://doi.org/10.3390/molecules28041602
12. Charrière K, Schneider V, Perrignon-Sommet M, Lizard G, Benani A, Jacquin-Piques A, et al. Exploring the role of apigenin in neuroinflammation: insights and implications. *Int J Mol Sci*. 2024; 25:5041. DOI: https://doi.org/10.3390/ijms25095041
13. Morakul B, Teeranachaideekul V, Limwikrant W, Junyaprasert VB. Dissolution and antioxidant potential of apigenin self nanoemulsifying drug delivery system (SNEDDS) for oral delivery. *Sci Rep*. 2024; 14:8851. DOI: https://doi.org/10.1038/s41598-024-59617-z
14. Seo SW, Choi SH, Hong JK, Kim KM, Kang SC, Yoon IS. Pharmacokinetics and extensive intestinal first-pass effects of apigenin and its active metabolite, apigenin-7-O-

glucuronide, in rats. *J Pharm Investig*. 2024; 54:467–481. DOI: https://doi.org/10.1007/s40005-024-00662-1

15. Chen P, Chen F, Guo Z, Lei J, Zhou B. Recent advancement in bioeffect, metabolism, stability, and delivery systems of apigenin, a natural flavonoid compound: challenges and perspectives. *Front Nutr*. 2023; 10:1221227. DOI: https://doi.org/10.3389/fnut.2023.1221227
16. Allemailem KS, Almatroudi A, Alharbi HOA, AlSuhaymi N, Alsugoor MH, Aldakheel FM, et al. Apigenin: a bioflavonoid with a promising role in disease prevention and treatment. *Biomedicines*. 2024; 12(6):1353. DOI: https://doi.org/10.3390/biomedicines12061353
17. Nagayoshi H, Murayama N, Kim V, Kim D, Takenaka S, Yamazaki H, et al. Oxidation of naringenin, apigenin, and genistein by human family 1 cytochrome P450 enzymes and comparison of interaction of apigenin with human P450 1B1.1 and Scutellaria P450 82D.1. *Chem Res Toxicol*. 2023;36(11):1778-1788. DOI: https://doi.org/10.1021/acs.chemrestox.3c00229
18. Wróblewska-Kurdyk A, Kordan B, Bocianowski J, Stec K, Gabryś B. Effects of apigenin and luteolin on Myzus persicae (hemiptera: aphididae) probing behavior. *International Journal of Molecular Sciences*. 2025;26(9):4452. DOI: https://doi.org/10.3390/ijms26094452
19. Mahwish, Imran M, Naeem H, Hussain M, Alsagaby SA, Al Abdulmonem W, et al. Antioxidative and anticancer potential of luteolin: a comprehensive approach against wide range of human malignancies. *Food Sci Nutr*. 2025;13(1):e4682. DOI: https://doi.org/10.1002/fsn3.4682
20. Morganti F. Longevity as a responsibility: constructing healthy aging by enacting within contexts over the entire lifespan. *Geriatrics.* 2024;9(4):93. DOI: https://doi.org/10.3390/geriatrics9040093
21. Falshaw N, Sagner M, Siow RC. The Longevity Med Summit: insight on healthspan from cell to society. *Front Aging*. 2024; 5:1417455. DOI: https://doi.org/10.3389/fragi.2024.1417455
22. Arshad Z, Shahid S, Hasnain A, Yaseen E, Rahimi M. Functional foods enriched with bioactive compounds: therapeutic potential and technological innovations. *Food Sci Nutr*. 2025;13(10):e71024. DOI: https://doi.org/10.1002/fsn3.71024
23. Vélez de la Rocha R, Sañudo Barajas JA, Chaidez-Quiroz C, Cárdenas Torres FI, Teran Cabanillas E, Vergara-Jiménez MJ. Phytochemicals, antioxidant activity and nutritional profile of pulp, peel and peel fiber of mango (Mangifera indica L.) cultivar Ataulfo. *Functional Foods in Health and Disease*. 2024;14(10):713-727. DOI: https://doi.org/10.31989/ffhd.v14i10.1449
24. Oyagbemi AA, Femi-Akinlosotu OM, Obasa AA, Ojo MS, Salami AT, Ajibade TO, et al. Apigenin mitigates oxidative stress, neuroinflammation, and cognitive impairment but enhances learning and memory in aluminum chloride-induced neurotoxicity in rats. *Alzheimers Dement*. 2025;21(5):e70223. DOI: https://doi.org/10.1002/alz.70223
25. Khonthun C, Khoothiam K, Chumphukam O, Thongboontho R, Oonlao P, Nuntaboon P, et al. Screening and characterization of antioxidant, anti-aging, and anti-microbial activity of herbal extract. *Functional Foods in Health and Disease.* 2023;13(2):52-68. DOI: http://www.doi.org/10.31989/ffhd.v13i2.1070
26. Gongpan P., Xu T., Zhang Y., Ji K., Kong L., Wang X., Chen H., Song Q., Sun Y., Geng C.A., Li J. Apigenin alleviates inflammation as a natural IRAK4 inhibitor. *Phytomedicine*. 2025;156519. DOI: https://doi.org/10.1016/j.phymed.2025.156519
27. Dugan B, Conway J, Duggal NA. Inflammaging as a target for healthy ageing. *Age Ageing*. 2023; 52(2): afac328. DOI: https://doi.org/10.1093/ageing/afac328
28. Yu F, Chen C, Liu W, Zhao Z, Fan Y, Li Z, et al. Longevity humans have youthful erythrocyte function and metabolic signatures. *Aging Cell*. 2025;24(5): e14482. DOI: https://doi.org/10.1111/acel.14482
29. Zhou M, Mao X, Zou LE, Yang Y, Zhao W, Yang Y, et al. Natural dietary flavonoid apigenin mitigates ulcerative colitis via modulating the AMPK/NF-kB/NLRP3 signaling axis. *J Agric Food Chem*. 2025;15405. DOI: https://doi.org/10.1021/acs.jafc.5c15405
30. Yusri K, Jose S, Vermeulen KS, Tan TCM, Sorrentino V. The role of NAD+ metabolism and its modulation of mitochondria in aging and disease. *npj Metab Health Dis*. 2025; 3:26. DOI: https://doi.org/10.1038/s44324-025-00067-0
31. Kramer D, Johnson AA. Apigenin: a natural molecule at the intersection of sleep and aging. *Front Nutr*. 2024; 11:1359176. DOI: https://doi.org/10.3389/fnut.2024.1359176

32. Khaled M, Salama RAM, Aboughalia A, Tarek M, Fawzy NM. Apigenin ameliorates genitourinary dysfunction in a type 1 diabetic rat model via Drp1 modulation. *Sci Rep*. 2024; 14:5754.
DOI: https://doi.org/10.1038/s41598-024-56395-6
33. Conti F. Dietary protocols to promote and improve restful sleep: a narrative review. *Nutrition Reviews*. 2025; nuaf062.
DOI: https://doi.org/10.1093/nutrit/nuaf062
34. Sun Y, Li Q, Kirkland JL. Targeting senescent cells for a healthier longevity: the roadmap for an era of global aging. *Life Med.* 2022;1(2):103-119.
DOI: https://doi.org/10.1093/lifemedi/lnac030
35. Alum EU, Izah SC, Uti DE, Ugwu OPC, Betiang PA, Basajja M, et al. Targeting cellular senescence for healthy aging: advances in senolytics and senomorphics. *Drug Des Devel Ther*. 2025; 19:8489-8522.
DOI: https://doi.org/10.2147/DDDT.S543211
36. Zhang H, Xu Q, Jiang Z, Sun R, Wang Q, Liu S, et al. Targeting senescence with apigenin improves chemotherapeutic efficacy and ameliorates age-related conditions in mice. *Adv Sci (Weinh)*. 2025;12(20): e2412950.
DOI: https://doi.org/10.1002/advs.202412950
37. De Luca F, Camporeale V, Leccese G, Cuttano R, Troise D, Infante B, et al. From senescent cells to systemic inflammation: the role of inflammaging in age-related diseases and kidney dysfunction. *Cells*. 2025;14(22):1831.
DOI: https://doi.org/10.3390/cells14221831
38. Zhang F, Guo J, Yu S, Zheng Y, Duan M, Zhao L, et al. Cellular senescence and metabolic reprogramming: unraveling the intricate crosstalk in the immunosuppressive tumor microenvironment. *Cancer Commun*. 2024; 44:929-966.
DOI: https://doi.org/10.1002/cac2.12591
39. Guo S, Liang S, Hou Y, Yang Z. Effect of HSPA8 on the biological function of NPC cells and its mechanism. *Sci Rep*. 2025;16(1):2020.
DOI: https://doi.org/10.1038/s41598-025-31746-z
40. Wu E, He W, Wu C, Chen Z, Zhou S, Wu X, et al. HSPA8 acts as an amyloidase to suppress necroptosis by inhibiting and reversing functional amyloid formation. *Cell Res*. 2023; 33:851866.
DOI: https://doi.org/10.1038/s41422-023-00859-3
41. Kim JC, Kim NY, Kim Y, Baek DJ, Park TJ, Kang HY. Senolytic targeting of anti-apoptotic Bcl family increases cell death in UV-irradiated senescent melanocytes: search for senolytics. *Exp Dermatol*. 2025;34(1):e70037.
DOI: https://doi.org/10.1111/exd.70037
42. Stojanovic B, Jovanovic I, Dimitrijevic Stojanovic M, Stojanovic BS, Kovacevic V, et al. Oxidative stress-driven cellular senescence: mechanistic crosstalk and therapeutic horizons. *Antioxidants (Basel).* 2025;14(8):987.
DOI: https://doi.org/10.3390/antiox14080987
43. Della Vedova L, Baron G, Morazzoni P, Aldini G, Gado F. The potential of polyphenols in modulating the cellular senescence process: implications and mechanism of action. *Pharmaceuticals*. 2025;18(2):138.
DOI: https://doi.org/10.3390/ph18020138
44. El Sayed S, Saiyed D, Macri VI, Asamoah-Mensah A, Segars JH, Islam MS. Beneficial effects of fisetin, a senotherapeutic compound, in women's reproductive health and diseases: evidence from in vitro to clinical studies. *Nutrients.* 2026;18(3):393.
DOI: https://doi.org/10.3390/nu18030393
45. Gadecka A, Nowak N, Bulanda E, Janiszewska D, Dudkowska M, Sikora E, Bielak-Zmijewska A, et al. The senolytic cocktail, dasatinib and quercetin, impacts the chromatin structure of both young and senescent vascular smooth muscle cells. *Geroscience*. 2025;47(3):3907-3925.
DOI: https://doi.org/10.1007/s11357-024-01504-6
46. Stasiłowicz-Krzemień A, Rosiak N, Racaniello GF, Denora N, Cielecka-Piontek J. Effective and stable senomorphic apigenin delivery system obtained by supercritical carbon dioxide processing. *International Journal of Molecular Sciences*. 2025;26(17):8126.
DOI: https://doi.org/10.3390/ijms26178126
47. Kaewmanee M, Limpaiboon T, Ngernyuang N. Apigenin induces apoptosis and inhibits migration in human cholangiocarcinoma cells. *Toxics.* 2025;13(2):112.
DOI: https://doi.org/10.3390/toxics13020112
48. Bhosale PB, Jeong SH, Kim HH, Heo JD, Hwang KH, Moon YG, et al. Therapeutic potential and cancer cell death-inducing effects of apigenin nd its derivatives. *Int J Mol Sci*. 2025;26(20):10084.
DOI: https://doi.org/10.3390/ijms262010084
49. Aida R, Okano K, Nakata K, Hagiwara H. Apigenin-induced apoptosis in lung adenocarcinoma A549 cells: involvement in IFNA2, TNF, and SPON2 with different time points. *Anticancer Res*. 2025;45(7):2781-2790.
DOI: https://doi.org/10.21873/anticanres.17647

50. Liu C, Cai Y, Mou S. Apigenin inhibits liver cancer via mitochondrial apoptosis and Th1/Th2 balance regulation. *Cytotechnology*. 2025;77(6):195. DOI: https://doi.org/10.1007/s10616-025-00868-7
51. Dhara M, Vemula KD, Karim Z, Vadakkepushpakath AN, Shetty T, Munchinamane AP. Oral delivery of a GI-stable apigenin–cyclodextrin complex via pectin-coated nanoliposomes in situ gel: a DoE-optimized targeted colon cancer therapy by modulating gut drug sensitivity. *Gels*. 2025;11(11):873. DOI: https://doi.org/10.3390/gels11110873
52. Ang SS, Thoo YY, Siow LF. Apigenin encapsulated in spray-dried liposomes coated with chitosan: heat, pH, light, oxygen, salt and storage stability. *Int J Food Sci Tech*. 2024;59(6):37013710. DOI: https://doi.org/10.1111/ijfs.17112
53. Yuan L, Davis PF. Regetting-18 complex powder (R-18CP) – a formulation of components from food-medicine and its antiaging effects. *Funct Foods Health Dis*. 2025;15(7):369-379. DOI: https://doi.org/10.31989/ffhd.v15i7.1647
54. Cuero C. N., Colín-Ferreyra C., Hassan W. H., Peyruchaud O., Cerecero P., , Curcumin and amaranth as potential anti-inflammatory and protective agents in bone and joint diseases. *Funct Foods Health Dis.* 2024; 14(7): 487-502. DOI: https://doi.org/10.31989/ffhd.v14i7.1386
55. Rahmani AH, Alharbi HOA, Khan AA, Babiker AY, Rizvi MMA. Therapeutic potential of resveratrol, a polyphenol in the prevention of liver injury induced by diethylnitrosamine (DEN) through the regulation of inflammation and oxidative stress. *Funct Foods Health Dis*. 2024;14(12):898–920. DOI: https://doi.org/10.31989/ffhd.v14i12.1502