Application of Flavonoids in Anti-Aging and Neuroprotection

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Abstract. Aging, as a biological process that every human experience, is always at the forefront of research in the past decades, aiming at improving the life quality of later years and slowing down the aging process. Flavonoids, a diverse group of compounds with clear and typical polypheonic structure that is largely found in plant-based foods and beverages, have emerged as promising candidates in this anti-aging research. This paper begins by elaborating aging, highlighting its multifaceted nature, its link to age-related health challenges, and the critical importance of addressing it for extended longevity. Meanwhile, flavonoid's structural diversity, dietary sources, and potential in promoting health have been emphasized. The core of the essay delves into the applicational effects of flavonoids in anti-aging. Exploring flavonoid's antioxidative properties, detailing how they act as safeguards against oxidative stress, protecting cellular integrity and countering age-related ailments. For their anti-inflammatory mechanisms, the paper uncovers how flavonoids have the ability to inhibit the regulatory of certain enzymes and transcription factors that is involved in inflammation, other mechanisms include the antioxidant capability and so on, these mechanisms contribute to flavonoid's anti-inflammatory property. Additionally, the paper investigates flavonoid's neuroprotective attributes, offering potential in preserving cognitive function during aging meanwhile to some extent preventing neuroinflammations and neurodegenerative disorders including Alzheimer's disease which have a clear association with aging. In sum, this essay comprehensively explores flavonoid's three main anti-aging properties, antioxidative, anti-inflammatory, and neuroprotective effect, offering a summarize of how flavonoids could potentially prevent the process of aging.

Keywords: Anti-Aging, flavonoids, antioxidation, anti-inflammation, neuroprotection.

1. Introduction

Aging, being a complex biological process that all human beings undergo, presents humanity with a range of physiological transformations and associated health concerns. As the understanding of aging deepens, humanity endeavor to uncover interventions that can enhance the quality of life during those later years of individual's lifespan. One possible routine of the exploration against aging that was gaining significant attention is a diverse group of compounds that abundantly exists in various dietary foods and beverages, called flavonoids. These compounds have captured a considerable amount of interest because of their potential role in mitigating the diverse challenges that come along with aging. Their intricate molecular structures encompass a multitude of biochemical properties such as antioxidative and anti-inflammatory. Meanwhile, given the profound impact of aging on both individuals and societies at large, the research in regards on anti-aging presents great significance, especially considering that the global population of aging continues to rise, addressing age-related health issues has become increasingly urgent. This paper serves as a fundamental summarize for anti-aging strategies, introducing the potential competence of flavonoids in addressing the aging challenges. In the upcoming sections, this paper will present a comprehensive exploration of flavonoids' antioxidative properties, anti-inflammatory mechanisms, and neuroprotective effects.

2. Aging and Its Implications

Aging, an intricate and inevitable biological process that every living organism undergoes, could be encapsulate in short as the accumulation of changes over time. As a multifaceted and complex phenomenon, aging embodies a substantial number of interconnected changes that manifest on the molecular, cellular, and organic levels. These biological changes can be caused by various factors, including disease, genetic defects, environment, development, and the natural innate aging process. Meanwhile, these changes occuring in cells and tissues cumulates and builds up detrimental effects on human body which will gradually impair cells and tissues from functioning and are either associated or responsible to the developing susceptibility to disease (including cardiovascular diseases, neurodegenerative disorders, metabolic dysregulation, and cancers) and death that is associated with the advancement of age [1]. In other words, aging encompasses a multitude of physiological changes that progressively manifest across various organ systems, ultimately culminating in diminished functional capacity and increased vulnerability to a variety of age-associated disorders.

Furthermore, the process of aging presents a substantial challenge due to its sophisticated interaction with age-associated health issues. Foremost among these concerns are cardiovascular diseases, typified by conditions such as atherosclerosis and hypertension. These prominent age-related afflictions progressively increase in prevalence as individuals age, significantly raising rates of the morbidity of these diseases and mortality [2]. Equally noteworthy are neurodegenerative disorders, including well-known conditions like Alzheimer's and Parkinson's diseases, also have a higher morbidity with the advancement of age. These conditions distinctly underscore the far-reaching impact of aging on the complexities of neurological function, resulting in the decline of cognitive abilities, motor functions, and overall quality of life [3]. Additionally, metabolic irregularities further compound age-related challenges. Consider the case of type 2 diabetes, one of the most common disorders seen in elders nowadays globally, takes advantage of the disruptions caused by aging-related metabolic imbalances to deteriorate susceptibility to insulin resistance and glucose intolerance [4, 5]. There is no doubt that aging’s profound consequences extend beyond medical aspects, exerting substantial socioeconomic pressures as the aging population develops. It is also imperative to note that these health challenges not only burden those affected, but also pose significant hurdles for healthcare systems and societal structures on a global scale.

In conclusion, aging embodies a multifaceted and intricate biological process, its aftermath extends far beyond the confines of individual physiological decline. As populations continue to age, the importance of understanding the complexities of aging and formulating effective strategies to mitigate its negative consequences is heightened.

3. Introduction to Flavonoids

Flavonoids, a group of natural plant secondary metabolites, are vastly prevalent in a variety of plant-based sources [6]. These compounds own elaborate molecular polyphenolic structures, forming distinct subgroups, including flavones, isoflavones, anthocyanidins, flavanones, flavanols, and chalcones [7]. Each of these subclasses have its own distinctive biochemical properties and structure, which in turn bestow them with diverse biological activities.

Nowadays, flavonoids are an essential component of human’s daily life considering not only their rich content in human’s daily diets but also their significant beneficial effects on man’s health [6]. More specifically, flavonoids have multiple properties that provide significant impact to human’s health and development, according to research, they exhibit potent anti-carcinogenic, anti-oxidative, anti-inflammatory, and anti-mutagenic competences meanwhile possessing the capability of cellular enzyme function modulating [6, 8, 9]. With these meaningful properties that flavonoids hold, flavonoids became a vital part of various diseases prevention, such as a variety of cardiovascular diseases. These compounds even showcased some potential in resisting against the process of aging. In terms of aging, these properties underscore flavonoid’s ability to impact multiple influential biological factor that is associated with age-related diseases and aging itself, for instance: oxidative stress, inflammation, and cellular senescence [9]. The reduction of the formation of free radicals provides flavonoids with powerful antioxidative efficacy, they could also scavenge free radicals, which could effectively regulate oxidative stress—a central contributor to cellular damage associated with aging. Additionally, flavonoids possess the capacity to restrain regulatory enzymes as well as transcription factors that is vital for regulating the mediators that is involved in inflammation, thus mitigating inflammation [10]. Whereas inflammation is particularly relevant to aging since it accelerates the aging process and contributes to age-related ailments. Moreover, flavonoids have great potential to counteract cellular senescence, a phenomenon implicated in aging progression and are highly-associated with the development of certain diseases that is deeply related to aging. By restarining certain senescence-related secretion phenotypes (SASPs), eliminating senescent cells, and sustaining metabolic homeostasis, flavonoids could successfully counteract with cellular senescence [9].

In short, flavonoid’s diverse subclasses and multifunctional properties underscore their ability to influence essential aging components such as oxidative stress, inflammation, and cellular senescence. Meanwhile, flavonoids, rich in plants and usual diets, also provide an abundant number of benefits to human health and are widely applied in multiple areas.

4. Application Effects of Flavonoids in Anti-Aging

In present days, flavonoids have been considered as a promising dietary molecule that owns the potential of preventing aging and a series of aging associated disease. These extraordinary potential of flavonoids in combating the varied aspects of aging rests on their intricate biochemical properties. Emerging research has revealed that these polyphenolic compounds possess diverse mechanisms that collectively orchestrate their profound effects on the aging process.

4.1. Antioxidation Properties of Flavonoids

At the very center of flavonoids' anti-aging capabilities lies their identity as free radical scavengers. Nowadays, a prominent benefitial impact in forstalling the damages casued by reactive oxygen species and various other free radicals that exists inside human has been proven to be demonstrated by the consumption of dietary flavonoids. These compounds excel in intercepting and neutralizing reactive oxygen species (ROS), which eventually will defuse oxidative stress that leads to cellular damage, a hallmark of aging [11]. Oxidative stress is, in short, a physiological imbalance that is related to the overproduction of reactive oxygen species, it generally happens when the reactive oxygen species is redundantly produced and it overwhelms the body's ability to neutralize and eliminate them. This may lead to various severe consequences such as cellular damage. And cellular damage is closely related to a substantial amount of health-related concerns like cancer, neurodegenerative disorders, CVD, diabetes, and aging. Many significant cellular components like biological molecules, proteins, and DNA molecules could also be harmed by oxidative stress [6]. In general, the excessive amount of reactive oxygen species will eveutally cause oxidative stress, and can possibly lead to damage at the cellular and molecular levels. Furthermore, the process of aging is commonly related to this damage which will cause the growth or occurrence of other age associated diseases. Meanwhile, antioxidants are essential compounds that take a significant role in safeguarding cells from the damages caused of oxidative stress. These compounds could avoid and prevent the oxidative effect caused by ROS, thus protecting the cells, and it is vital to note that oxidative stress is primarily attributed to the imbalance between ROS and antioxidants. Fortunately, flavonoids with its free radical and ROS scavenger’s identity, have been considered a powerful antioxidant, and have great potential to be contructed into medications that is specifically targeted to prevent oxidative stresses [6].

The fundamental antioxidation mechanism of flavonoids is related to their reaciton with free radicals. Free radicals actually take part by oxidizing flavonoids, in which would result the redicals to become less reactive, thus increasing its stablility. In other words, reactive oxygen species are stabilized by flavonoids via the process when flavonoids react with the reactive compound of the radical [6]. During this oxidation process, flavonoid’s hydroxyl group is highly reactive, and its high reactivity will make those free radicals inactivates. It is worth noting that certain flavonoids possess the capability to directly scavenge superoxide, while some other types of flavonoids can effectively counter peroxynitrite, a radical that is extremely reactive oxygen-derived [6, 8]. Moreover, Studies have shown that there are multiple flavonoids including rutin, myricetin and quercetrin contributes to inhibit the production of superoxide radicals [6]. It is also noted by past research that while flavonoids scavenge radicals, they can inhibit the oxidation of LDL in in vitro studies. Furthermore, it is noted that the inhibition of oxidation of LDL could successfully protect its particles, hence it is notionally predicted that these flavonoids might have preventive abilities on atherosclerosis, an aging-associated cardiovascular disease [6]. Other than atherosclerosis, flavonoid have also been found to some extent prevent other various aging related diseases such as diabetes, hepatotoxicity, and inflammation, even aging itself. This is mainly attributed to flavonoid's ability to effectively prevent lipid peroxidation, which is responsible for those diseases [6].

Overall, antioxidant action mechanisms can involve in three main aspects: the inhibition of ROS formation, achieved through either enzyme suppression or chelation of trace elements that contributes to the formation of free radicals, the scavenging of ROS, and the upregulation or safeguarding of the defense systems related to antioxidant [12]. The intricate and sophisticated interaction between flavonoids and oxidative stress modulation bears substantial implications for aging. As previously mentioned, cumulative oxidative stress detrimentally impacts cellular components, including biological molecules, proteins, and DNA molecules, culminating in the manifestation of various age-related degenerative conditions and diseases. The use of flavonoids as antioxidants can effectively block the reactive oxygen species from delievring oxidative damage to those DNA in animal models [6, 13]. Flavonoids' capacity to scavenge reactive oxygen species and prevent oxidative stress not only protects cellular components, but also contributes to extended cellular lifespan, effectively mitigating the molecular basis of aging and to some extent preventing various aging related disease.

4.2. Anti-Inflammatory Properties of Flavonoids

Other than antioxidation properties, flavonoids' anti-inflammatory properties emerge as another central aspect of their anti-aging ability. Inflammation is a complicated yet essential host defensive response that is typically designed to respond to microbial infections [10]. Various factors could trigger the process of inflammation and in usual circumstances, inflammation could be considered as a rapid and self-limiting process. However, there are some situations where prolonged inflammation occur that takes up an extra period of time, which will play a role in the advancement of various chronic or degenerative conditions [14]. Fortunately, flavonoids have been tested to have the ability to regulate the inflammatory responses. In a regular inflammatory process, flavonoids can act or function in multiple areas. The first way flavonoids could act is with it identify of antioxidants that scavenges reactive oxygen species and reduces the accumulation of free radical. As detailed mechanism is explained previously, it is vital to note that the cumulation of free radicals and ROS will lead to oxidative stress and eventually beneficial to the growth of inflammation. Hence flavonoids could also to some extent prevent inflammations considering it being antioxidants that could prevent oxidative stress from happening. The second way lies with flavonoid's ability to inhibit the functioning of regulatory enzymes like protein kinases and phosphodiesterase. Meanwhile flavonoids are also transcription factors that is associated with the regulation of mediators that is involved in the process of inflammatory. The final mechanism involves flavonoids acting as modulators of immune cell activity, enabling them to restrain various actions of immune cells, including signaling transduction, inhibiting the activation of cell, maturation, and the secretory processes [14]. Furthermore, flavonoids could also act through interacting with various enzyme systems. Studies have indicated that flavonoids possess the capability to impede the metabolism of arachidonic acid via enzymatic pathways. This attribute provides flavonoids the properties of anti-inflammatory and anti-thrombogenic. The release of arachidonic acids tends to be the initiation of a general inflammatory response considering that neutrophils which contains lipoxygenase would base on arachidonic acids to produce chemotactic compounds [6].

Additionally, the immune system and inflammatory cell's normal activity and function can be significantly affected by certain members of flavonoids. Several flavonoids, including luteolin, hesperidin, quercetin, and apigenin, have been found to exhibit anti-inflammatory and analgesic abilities. It is recognized that flavonoids could potentially influence the activity of enzyme systems that takes up a vital part in initiating the inflammatory pathways, particularly serine-threonine protein kinases and tyrosine. Flavonoids have a tendency of competitively bind to ATP on enzymes at catalytic sites, resulting in the inhibition of kinases. These enzymes participate in the mechanisms of transduction of signal and the activation of cells, which are integral to immune cell functions. Studies have also indicated that flavonoids possess the capability to suppress isoforms of inducible nitric oxide synthase, cyclooxygenase, and lipoxygenase from their expression. These isoforms are accountable for the generation of substantial amounts of nitric oxide, leukotrienes, proteinoids, and various other mediators involved in the process of inflammation, including cytokines, adhesion molecules, and chemokines. Furthermore, inhibitory effects on phosphodiesterases that play a role in cellular activation are also demonstrated by flavonoids. A significant portion of flavonoids' anti-inflammatory impact is directed towards modulating protein cytokine's biosynthesis, which facilitate the attachment of circulating leukocytes to injury sites. Meanwhile, specific flavonoids exhibit robust inhibition of prostaglandin's production, a class of potent proinflammatory signaling molecules [12]. Flavonoid's structure also holds a part in their anti-inflammatory activity. These compounds possess a flat ring-like structure with unsaturation at C2–C3, and the positioning of hydroxyl groups is vital in conferring this property. Notably, at the 3' and 4' positions of the B-ring situates hydroxyl groups that bear high importance, and their absence results in the loss of the compound's anti-inflammatory activity [15].

Generally, flavonoids exhibit anti-inflammatory properties through various mechanisms, including the restraint of regulatory enzymes and transcription factors that play crucial parts in regulating inflammation-related mediators. Additionally, flavonoids act as potent antioxidants, effectively scavenging free radicals and reducing their formation. As a result, flavonoids have a profound influence on a few immune cells and mechanisms that play pivotal roles in the process of inflammation [10]. Meanwhile, inflammation promotes the growth of various age-related diseases like cardiovascular diseases and neurodegenerative disorders. Flavonoids' ability to counteract inflammation diminishes the severity of these pathologies, potentially preventing the occurrence of these disease, and contributing to enhanced physiological resilience in aging individuals. With flavonoids' anti-inflammatory properties, these compounds have the potential to prevent aging from happening, meanwhile preserving vital bodily functions, and alleviating the burden of age-associated ailments.

4.3. Neuroprotective Effects of Flavonoids

The last properties that will be highlighted would be the neuroprotective capabilities of flavonoids. Flavonoid's neuroprotective effects mainly lie within the ability to counter a series of age associated cognitive decline, neurodegeneration disorders, and neuroinflammation. The term "neuroinflammation" typically describes a sophisticated immune response inside the central nervous system (CNS) as a reaction to a variety of internal or external stimuli. These triggers may encompass pathogens, toxins, and misfolded proteins, ultimately resulting in inflammatory cell infiltration, gliosis, neuronal loss, and other related processes within the brain tissue. Meanwhile, during the process of neuroinflammation, immune cells like microglia and astrocytes produces those pro-inflammatory mediators. These mediators would suppress neuronal differentiation while triggering apoptosis and necroptosis of neurons, which would eventually elevate the excitatory neurotransmitter's production and impedes monoamine neurotransmitter's transmission, culminating in neuronal degeneration [16]. Fortunately, according to recent research, natural dietary flavonoids demonstrate a lot of beneficial anti-neuroinflammatory effects. These effects encompass the downregulation of pro-inflammatory mediator expression, acceleration of anti-inflammatory cytokine secretion, inhibition of Astro cytosis, and the suppression of microglia activation and polarization. Generally, the inhibition of NLRP3 inflammasome activation, and the modulation of JAK/STAT, MAPKs, NF-κB, and apoptotic pathways is the primary mechanisms through which flavonoids combat neuroinflammation. Additionally, these flavonoids activate pathways such as BDNF/CREB, Nrf2, Wnt/β-Catenin, PI3k/Akt, AMPK, and facilitates the deacetylation of SIRT1-mediated HMGB1 [16].

Flavonoids also exhibit beneficial effects in terms of preventing the occurrence of age-related neurodegenerative diseases. Neurodegeneration usually occur in brain and spinal cord; it is generally marked by a gradual and progressive decline in neuronal cell numbers within those specific areas. It underlies the pathological manifestations of various neurodegenerative disorders, such as Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [17]. Flavonoids have been shown to engage with glial signaling pathways and various other cellular pathways, resulting in improved neuronal function, and influencing neuronal regeneration. For instance, flavonoids found in blueberries can activate the ERK pathway, which, in turn, boosts the activity of cAMP response element-binding protein (CREB). This activation of CREB will cause an up-regulation of BDNF within the hippocampus of rats. Such activation of the cAMP response element-binding protein induced by flavonoids holds significance in the control of synaptic plasticity and memory [15]. Meanwhile, the capacity of flavonoids being able to traverse the blood-brain barrier implies that flavonoids can indeed directly influence the brain [18] Moreover, cognitive decline that is related to aging has been consistently observed in both animal and human studies, even with the absence of pathological neurodegeneration. These cognitive changes tend to affect areas associated with the retention of newly learned information, such as executive function, working memory, and short-term memory. The general decreased risk of cognitive decline observed in individuals with higher consumption of fruits and vegetables is possibly connected to an increased intake of certain specific flavonoids [19]. Recent research exploring the connections between long-term dietary flavonoid consumption and subjective cognitive decline (SCD) in the United States has revealed that even after making various adjustments for age, total energy intake, major non-dietary factors, and specific dietary factors, an increased consumption of the total flavonoids was still linked to the reduced odds of experiencing subjective cognitive decline [20].

Within all cognitive decline related diseases, AD accounts for 60-80% of all dementia cases and primarily affects older individuals, typically those aged 65 years or older. The pathogenesis of AD is closely linked to the buildup of amyloid-β (Aβ) aggregates and the hyperphosphorylation of tau proteins, which cause neurofibrillary tangles (NFTs) to form and impairs synaptic function. Globally, an estimated 35.6 million people are believed to be afflicted by AD, with approximately 4.6 million new cases emerging each year. Notably, the prevalence of AD escalates with age, doubling every 5 years from the age of 60 onwards [21]. Meanwhile, Quercetin, a flavonoid abundant in many plants and commonly present in the daily diet through fruits and vegetables, holds significant pharmacological effects and promising therapeutic potential. In a variety of models that is in vitro and in vivo, it exhibits beneficial properties in countering the underlying mechanisms of AD etiology. Quercetin safeguards neuronal cells by mitigating oxidative stress and neuroinflammation, as the mechanisms introduced previously, both oxidative stress as well as neuroinflammations take a vital role in terms of the formation of AD. Its anti-AD properties encompass inhibiting the aggregation of Aβ and phosphorylation of tau. The aggregation of Aβ represents a fundamental hallmark of AD. Quercetin intervenes in this process by disrupting the neurotoxic oligomeric Aβ species from forming. It also exhibits the capacity to destabilize preformed fibrillar Aβ, effectively reversing Aβ-induced neurotoxicity. Quercetin has also demonstrated its potential to reduce the phosphorylation of tau proteins and impede the NFTs from forming in a mouse model of Alzheimer's disease featuring triple transgenic characteristics. Furthermore, it contributes to the restoration of acetylcholine levels by inhibiting the hydrolysis of acetylcholine carried out by the AChE enzyme. AChE, or Acetylcholinesterase, is an enzyme responsible for breaking down acetylcholine in the brain. Inhibiting AChE leads to higher levels of acetylcholine, which can help improve the cognitive symptoms of AD. Nowadays, inhibiting AChE enzymes is also one of the most commonly used therapies to moderate AD. In laboratory-based studies conducted in vitro, it has been demonstrated that quercetin acts as a competitive inhibitor of both AChE and BChE. It is notable that Quercetin's inhibitory effect on these enzymes is concentration dependent [21].

In general, the preservation of cognitive function is a cornerstone in the pursuit of enhanced aging. Flavonoids' neuroprotective attributes encompass not only safeguarding neural tissue from oxidative stress but also counteracting neuroinflammatory processes that contribute to cognitive decline as well as neurodegeneration. By maintaining neuronal health and tempering neuroinflammation, countering age related cognitive declining disorders like AD, flavonoids actively promote cognitive vitality, contributing to prolonged cognitive function and an improved quality of life in aging individuals.

5. Conclusion

Flavonoids, a diverse group of natural compounds that is abundantly found in fruits, vegetables, and various plant-based foods, has been known for the substantial and significant health benefits that it offers. Recently, flavonoids emerged as multifaceted functional molecules with the potential to address the intricate challenges of aging. This writing has expounded upon the anti-inflammatory, antioxidative, and neuroprotective capabilities of flavonoids, explaining their potential in mitigating the diverse aspects of aging. Flavonoids act as preventions against oxidative stress, stimulate endogenous antioxidant defenses, prevent chronic inflammation, and safeguard cognitive function. Their natural sourcing, diverse health benefits, and cost-effectiveness render them appealing options for anti-aging interventions. However, interindividual variation in responses and the current limitations in clinical evidence pose significant hurdles to their widespread utilization. Despite these promising attributes, the road to discover flavonoids' full potential in anti-aging strategies requires further research as questions regarding bioavailability and individual variations persist. But still, flavonoid’s potential in enhancing the quality of aging is undeniable. Further investigation is needed and the imperative of enhancing the understanding of the complexities of aging.

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