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The Effect Of Ellagic Acid On Anti-Aging

Jinchan Sun

School of Food and Pharmacy, Zhejiang Ocean University, Zhoushan, China
Corresponding author: 3398625057@zjou.edu.cn

Abstract:

Aging includes a variety of phenotypes, which are determined by a variety of complex mechanisms, with cell aging and mitochondrial dysfunction as the main influencing factors. Ellagic acid is a natural compound with strong biological activity, which can delay aging by resisting oxidation, eliminating inflammation, repairing mitochondrial in the body, inhibit oxidative stress, and eliminate cell aging caused by oxidation, the elimination of mitochondrial dysfunction and other molecular pathways. Its ability to resist oxidation is mainly reflected in the strong free radical scavenging ability of ellagic acid, which can reduce the level of high-level ROS is mainly reflected in ellagic acid's potential to reduce the level of inflammation-related factors, participate in the regulation of inflammatory signaling pathways, and thus reduce the level of inflammation in the body; the repair of mitochondrial dysfunction is mainly reflected in the potential of ellagic acid with regards to participate in the activation of mitochondrial autophagy, improve mitochondrial quality, enhance respiratory capacity, and delay cell aging. This article delves into the origins and metabolic routes of ellagic acid, exploring the intricate biological mechanisms underlying its anti-aging properties, and analyzes the related application value and research fields of ellagic acid.

Keywords: Ellagic acid; Urolithin; Anti-aging; Biological pathway.

1. Introduction

Aging represents an unavoidable biological growth, embodying the gradual decline or diminution of functions across individual, organ, cell and molecular levels [1]. There are many reasons for aging, the most important ones are cell aging and impaired mitochondrial function [2]. For thousands of years, human exploration of life has never stopped. Whether in the past or now, people have been committed to finding ways to fight aging. With the rapid development of science and technology, more and more substances that have an effect on aging in nature have been discovered. As a natural polyphenolic compound, ellagic acid has gradually attracted attention for its significant anti-aging effect. Studies have shown that it and its derivatives have strong biological activity, and can delay aging by resisting oxidation, eliminating inflammation and repairing mitochondrial dysfunction and other molecular pathways [3-5]. At present, people are not fully exploring ellagic acid, not only the study of its related mechanisms in vivo is lacking, but also the related research fields are still limited. Starting from the related mechanisms of aging, according to the important influencing factors such as mitochondrial dysfunction, oxidation and inflammatory reaction in the aging process, through collecting relevant research evidence, this paper elaborates in detail the anti-aging effect of ellagic acid through various ways, and analyzes the relevant application value and research field of ellagic acid. It provides a new idea and direction for exploring the biological pathway of anti-aging effect of ellagic acid, drug preparation and expanding related fields.

2. Mechanisms of Senescence and Aging

The natural progression of aging involves degenerative changes, in particular the continuous accumulation of senescent cells [2]. It has many significant characteristics, including gene sequence instability, telomere shortening and depletion, loss of protein homeostasis, imbalance of nutrient sensing mechanism, modifications in intercellular signaling patterns, cellular senescence, reduction in stem cell populations, epigenetic shifts, and mitochondrial malfunction [1]. With the advancement of age, senescent cells accumulate, paralleled by mitochondrial malfunction. This malfunction promotes aging due to heightened levels of reactive oxygen species and disrupted energetic processes. Aged cells are able to regulate their surrounding microenvironment through a secretory profile that is associated with senescence, commonly designated as the SASP. This phenotype elicits a prolonged, yet subdued inflammatory response, ultimately contributing to inflammation. At the same time, it can also promote cancer recurrence and chemotherapy resistance. The dysfunction of mitochondria and the senescence of cells are two intimately interconnected hallmarks of aging, yet the crucial genes that orchestrate the linkage between these two processes remain obscure and unidentified [2].

2.1 Cellular Senescence and its Molecular Pathways

Cell aging is defined as irreversible cell cycle arrest, which is associated with a series of phenotypes including sustained accumulation of DNA damage, telomere shortening, increased secretion of metabolic programming and aging-related secretory phenotypes, and increased aging-related β-Gal activity [6]. These phenotypes are present at various stages of aging, and there is a certain correlation between each phenotype.

When cells exhibit aging-related phenotypes, they are more prone to a loss of DBS repair that endangers genomic stability. The termini of linear chromosomes, known as telomeres, consist of a shelterin protein complex that safeguards them, along with the repetitive DNA sequence TTAGGG, which aids in preserving genomic stability. Telomere loss and shortening lead to increased cell aging and tissue aging [7]. Moreover, senescent cells exert their influence through a paracrine signaling process, involving SASP, and thereby contribute to the aging process [1].

2.2 Oxidative Stress and DNA Damage in Aging

Under aging and stress conditions, nerve cells typically exhibit increased oxidative phosphorylation (OXPHOS) [8], which is due to increased astrocyte glycolysis by neurons in response to their increased demand for lactic acid. Furthermore, augmented OXPHOS gives rise to an overproduction of superoxide radicals and hydrogen peroxide molecules. When the output of reactive oxygen species outstrips the neutralization capabilities of the body's antioxidant safeguards, oxidative stress ensues. Elevated levels of these reactive oxygen species, commonly known as ROS, can initiate the aging process due to oxidative stress [9].

Persistent DNA damage stands as a pivotal factor among the leading contributors to the aging process. Although the underlying molecular mechanism is still unclear, the changes in some functional factors induced by DNA damage have been found to accelerate aging. Firstly, DNA damage will cause ataxia-telangiectasia mutation (ATM), which will activate the extracellular shuttle and down-regulation of LARP7, inhibit the activity of SIRT1 deacetylase, enhance acetylation and improve the transcription activity of p53 and NF-κB (p65), and accelerate cell aging [10]. The accumulation of DNA damage will initiate a signal cascade reaction to avoid the replication of the damaged genome by inducing apoptosis or aging [11]. This also reflects the important value of apoptosis and aging in maintaining the health of the body.

2.3 Inflammation and SASP

Persistent low-grade systemic inflammation has a profound impact on individual health. It not only quietly accelerates the pace of aging, but also acts as a „driving force“ behind a variety of age-related diseases. Persistent inflammation exhibits a tight correlation with the gradual decline of various physiological functions, specifically the weakening of immune system functionality, the compromised cellular repair capacity, and the disrupted metabolic function. Maintaining regular work and rest, balanced diet, moderate exercise, all help to reduce the level of inflammation, in order to achieve the purpose of delaying aging.

When cells age, they secrete a series of aging-associated secretory phenotype (SASP) factors, which will continue to induce low-level systemic inflammation, which provides a new direction for delaying aging [12]. Recent new findings on the relationship between inflammation and aging show that inflammation driven by kB and neuroendocrine effects received by GnRH may be regulated by the hypothalamus to regulate systemic aging [13].

3. Ellagic Acid

3.1 Structural Composition and Distinguishing Features of Ellagic Acid

The molecular formula of ellagic acid (EA) is $C_{14}H_6O_8$, accompanied by a molar mass measurement of 302.194g/mol. Its chemical structure (Fig. 1) has an aromatic ring, which is strongly associated with its biological activity, including antioxidant activity. Unadulterated EA assumes the hue of a golden needle-like crystal, boasting a melting point exceeding 360°C, insoluble in ether, soluble in alkali and pyridine, and slightly soluble in water and alcohol.

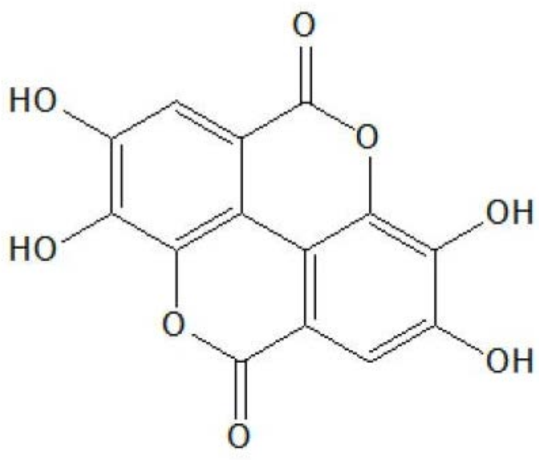

Fig. 1 Molecular structure of ellagic acid [14].

EA falls within the classification of naturally occurring polyphenols, which are abundantly present in diverse soft fruits, nuts, and various other plant tissues. It is a gallic acid dimeric derivative and a polyphenol dilactone. This substance can not only exist in free form, but also exist in nature in the form of ellagic tannin (ETs), glycoside (EAM) and other condensation forms. At present, there are about 17 kinds of EA compounds in nature, distributed in the families of Myricariaceae, Rosaceae, Fagaceae, Poaceae and Myricariaceae. EA compounds are a kind of chemical components widely distributed in nature.

3.2 The Derivative of Ellagic Acid

The phytochemicals, including anthocyanins, equol, and protocatechuic acid, can carry out biological functions through direct absorption in the intestine. A link exists between EA and its beneficial effects on health. Nevertheless, EA, being a polar macromolecule that adheres to Lipinski's five rules, poses significant challenges in achieving direct absorption. Moreover, due to glycine co-localization, direct absorption of EA by the intestine is challenging. EA must first undergo conversion by intestinal flora into bioactive substances before it can be absorbed and subsequently distributed to various tissues for functional execution. The intestinal flora is responsible for metabolizing EA into Uro. An abundance of experimental evidence demonstrates that Uro serves as the active moiety of EA within the biological system, exerting significant effects in regulating antioxidant, anti-inflammatory, and anti-aging mechanisms [5].

EA first undergoes lactone ring removal in the colon environment and is transformed into Uro-M5.Subsequently, through a series of reactions, the compound undergoes multiple hydroxyl group losses, evolving into various tetrahydroxyurolithin derivatives. These are then metabolized further, losing another hydroxyl group to form trihydroxyurolithin analogues. Subsequently, dihydroxylation reactions lead to dihydroxyurolithin species. Finally, further metabolic transformations eliminate a hydroxyl group, yielding monohydroxyuro-1, also known as Uro-B. Fig. 2 clearly illustrates the pathway of Uro-A metabolism within the living organism.

Urolithin, as a metabolite of EA, is easily absorbed and utilized by intestinal tract. Meanwhile, it has been consistently observed in different human intervention experiments that EA can produce Uro after added intake, and EA can be converted into Uro after incubation by human fecal microbial community [15,16]. This can show that EA is converted into Uro after metabolism by intestinal microorganisms. After ingestion of foods abundant in ETs, they undergo initial hydrolysis into EA within the gastric cavity and intestinal tract. Subsequently, they travel to the farthest segment of the mammalian colon, where colonic intestinal flora convert them into dibenzopyran 6-1 derivatives, i.e. uro, which are more easily absorbed and have a much higher bioavailability and bioactivity than EA. This is commonly linked to a decrease in the likelihood of developing disease, and subsequently, these metabolic byproducts undergo absorption and distribution to diverse tissues throughout the body.

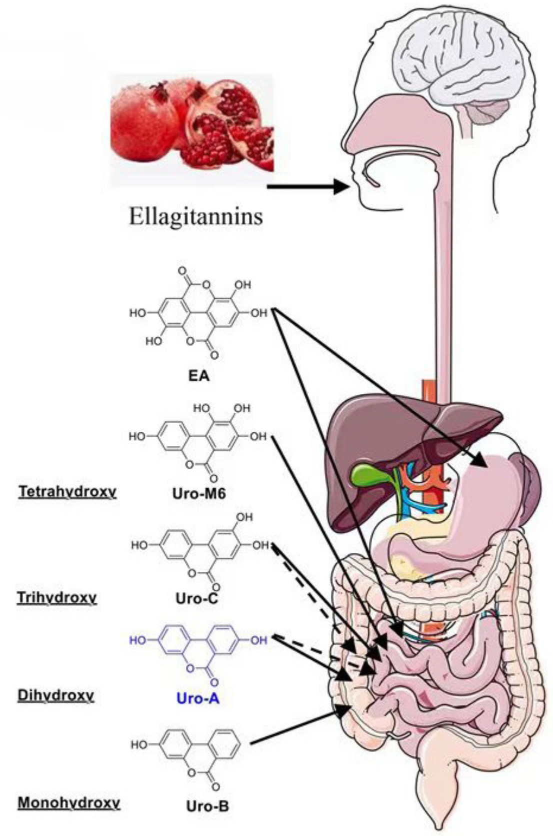

Fig. 2 The biochemical route of urolixin A in

humans (dashed lines indicate possible) [5].

4. Anti-Aging Effect of Ellagic Acid

Lately, EA has garnered escalating attention from the scientific community for its potential in combating aging, prompting a surge in investigations exploring its underlying mechanism, which has gradually been exposed. At present, it is clear that EA can fight aging by improving mitochondrial function mechanism, eliminating oxidation and inflammatory reaction. In addition, it may also act on other organs such as skeletal muscle and skin.

4.1 Acts on Mitochondrial Function Mechanisms to Combat Aging

Cellular aging frequently correlates with the malfunctioning of mitochondria and the deficiency of autophagic processes. Studies have shown that urolithin generated by the metabolism of EA can effectively improve mitochondrial health, restore it to normal level to fight against age-related organ dysfunction [5]. Mitochondrial autophagy can improve the quality of mitochondria in cells and improve mitochondrial respiratory capacity [17]. Urolithin, a metabolite of EA, can activate mitochondrial autophagy through multiple pathways, including Pink1-Parkin-dependent mitochondrial autophagy pathway and other mitochondrial protein-activated mitochondrial autophagy pathway that is not dependent on Pink1-Parkin (Fig. 3) [18]. UA stabilizes the kinase PINK1, activating its mitochondrial autophagy mediated by parkin. Parkin ubiquitinated mitochondrial proteins, accumulated after phosphorylation by PINK1, binding to LC3 as an adapter protein docking site. At the same time, UA increased the level of BNIP3, activating the mitochondrial autophagy pathway that is not dependent on parkin. In both pathways, LC3 promotes mitochondrial phagosome membrane, and decomposes mitochondria after fusion with lysosomes.

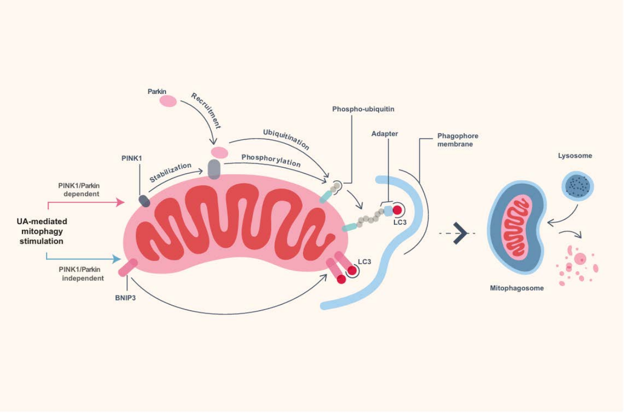

Fig. 3 Mitochondrial autophagy pathway activated by urolithin, a metabolite of EA [18].

4.2 The Antioxidant Effect of Ellagic Acid and the Key Link in the Antioxidant Process

At present, ellagic acid's antioxidant capabilities have garnered significant attention in various research efforts. Pomegranate rich in EA is an important research object. The experimental results of the clearance ability of EA extracted from pomegranate skin to DPPH, hydroxyl radical and superoxide anion show that EA has a certain clearance ability to DPPH free radical and superoxide anion, and with the increase of sample concentration, the clearance rate gradually increases, that is, the antioxidant activity is improved [19]. Not only EA has strong antioxidant activity, but also UA, the metabolite of EA, also has strong antioxidant activity, which can effectively remove a variety of free radicals. Therefore, when using EA to remove free radicals, its clearance rate maintains its high level even after metabolism [20].

4.2.1 The Antioxidant Mechanism of Ellagic Acid

EA is a plant polyphenolic substance with rich redox properties. The antioxidant potential of EA exhibits a direct relationship with the extent of hydroxylation [21]. As EA undergoes progressive dehydrogenation, the antioxidative abilities of its derivative products steadily diminish. Several aspects of its antioxidant activity include scavenging free radicals, overcoming oxidative stress caused by high levels of ROS, and inhibiting lipid peroxidation [1]. Among them, the ability to scavenge free radicals is the most representative of its antioxidant activity. EA has multiple phenolic hydroxyl structures, which can act as hydrogen donors and react with free radicals, thereby neutralizing the activity of free radicals and preventing damage to cells and tissues. In this process, EA itself is oxidized and transformed into relatively stable products, which can effectively block the chain reaction of free radicals.

4.2.2 Activation of Nrf2 Pathway and Antioxidant Defense Nrf2

Nrf2 is a key transcription factor, whose regulatory influence is paramount in maintaining the redox balance within cells [3]. The mechanism of oxidative stress was introduced above. Free radicals, particularly reactive oxygen species (ROS), initiate oxidative stress in organisms, thereby necessitating intricate and diverse antioxidant defense mechanisms to counterbalance the deleterious effects [1]. In these mechanisms, the enzymatic system plays a crucial role, and superoxide dismutase (SOD) and catalase (CAT) are the best enzymatic antioxidants. They protect cells from oxidative damage by catalyzing reactions that effectively neutralize harmful reactive oxygen species (ROS) and other oxidative intermediates. Fresh research indicates that EA possesses the capacity to activate antioxidant response elements by bolstering the activity of Nrf2, a transcription factor involved in redox homeostasis. After the supplementation of ellagic acid in mice, a significant boost was observed in the mRNA expression levels, as well as the activities of SOD and CAT enzymes in the intestinal tissue. This suggests that ellagic acid can bolster the mice's antioxidant mechanisms and mitigate the harmful effects of oxidative stress via the Nrf2/HO-1 signaling route [3].

4.3 Anti-Inflammatory Effects of Ellagic Acid

There are various related signaling pathways in the occurrence and progression of inflammation. Inflammatory signaling cascades are intricate networks involving multiple enzymatic cascades and signaling mediators. Key among these are MAPK cascades, cytokine-triggered networks, and phosphoinositide-regulated kinases. These components regulate cellular responses and orchestrate the inflammatory process. Alongside these canonical pathways, an alternative inflammatory mechanism, particularly the Hippo pathway, plays a significant role.This alternative mechanism is intricately associated with a diverse set of inflammatory modulators, including transcription factors like FoxO1/3, cytokines such as TNF-α, enzymes like COX-2, and other key players like HIF-1α, AP-1, JAK, and STAT proteins [22].

EA has strong anti-inflammatory effects, and certain research has highlighted the potential utility of EA in addressing a wide range of chronic inflammatory disorders, suggesting its beneficial role in therapeutic applications. In the inflammatory process, stellate cells occupy a pivotal role, and it has been demonstrated that EA can effectively quell their activation [23]. However, at present, the specific mechanism of EA's anti-inflammatory effect is not clear. It has been proposed that EA may show certain anti-inflammatory effect when fighting various diseases associated with TLR signaling pathway [4]. An alternative study demonstrated that EA exhibits the ability to reduce the proinflammatory biomarker interleukin-6 (IL-6) and modulate the anti-inflammatory agent interleukin-10 (IL-10), effectively mitigating the impact of lipopolysaccharide-induced inflammation in mice [24]. In addition, some studies have observed that EA exerts anti-inflammatory effects by regulating NF-kB activation pathway [13].

4.4 Other Ways to Combat Aging

EA metabolites have been shown to have a positive effect on enhancing healthy lifespan and muscle indicators in skeletal muscle function, Research has shown that it can enhance muscle function, improve muscle structure, and increase activity in mice by inhibiting protein degradation [25]. Uro-A exerts profound anti-aging impacts on the fibroblasts of aging skin, not only bolstering the synthesis of type I collagen but also meticulously modulating the expression levels of metalloproteinase-1 related to type I collagen. Taking 50μM concentration of Uro-A as an example, it can arrest the cell cycle at the G2/M transition, thereby attaining noteworthy anti-aging benefits [26].

5. Health Effects and Potential Development Applications

As a natural antioxidant polyphenolic compound, EA has potential biological activity and medicinal value. This compound exerts diverse beneficial impacts on human well-being, particularly in terms of safeguarding against age-related ailments. Therefore, how to develop EA safely and effectively is of great significance.

5.1 Role of Ellagic Acid in the Prevention of Age-Related Diseases

EA's significant protective effects against age-related conditions stem primarily from its robust antioxidant capacity. This enables it to eliminate harmful free radicals circulating within the body, mitigating the harmful effects of oxidative stress on cellular health [1]. This antioxidant effect helps prevent aging and may prevent various diseases related to oxidative stress, such as cardiovascular diseases and cancers. In addition, EA also has anti-inflammatory effects, which can inhibit the occurrence and development of inflammatory reactions, thus reducing pain, swelling and tissue damage caused by inflammation [4]. This has important clinical significance for the treatment of inflammatory diseases. In addition, EA also improves nervous system function by regulating neurotransmitter levels and may reduce the symptoms of nervous system diseases [27]. Therefore, EA is expected to become a new drug treatment option for nervous system diseases.

5.2 Development and Application of Ellagic Acid

In addition to its role in the prevention of age-related diseases, EA also has anti-cancer, estrogen regulation, anti-obesity and other characteristics [5]. It may help reduce obesity and related complications, and examples of its salutary impacts include the prevention of cardiovascular conditions like atherosclerosis, as well as the amelioration of metabolic disorders such as hepatic steatosis, glucose intolerance, and adult-onset diabetes [4]. Based on extensive studies, EA demonstrates noteworthy prophylactic and curative potential against numerous malignancies, encompassing colorectal, mammary, and prostatic carcinomas, among others [5]. Given the numerous health benefits of EA, it has potential application value in the field of health care products and medicine. EA can be used as an antioxidant, anti-inflammatory agent or anticancer agent to develop new drugs or health care products. However, it should be noted that it may cause allergic reactions during application, and its side effects should be paid attention to during use.

6. Conclusion

This paper summarized the research progress of anti-aging effects of EA, including the source, metabolism, anti-aging effects, related mechanisms and application prospects of EA. Firstly, EA is naturally present in a wide array of berries and nuts, taking the shape of a condensed compound. Upon undergoing metabolic transformation by the intestinal flora, it transforms into urolithin, conferring numerous salutary benefits to human physiology. These benefits encompass antioxidative, anti-inflammatory, and anti-aging properties, among various other positive outcomes on bodily functions. EA can achieve the purpose of anti-aging by activating mitochondrial autophagy, improving mitochondrial levels and repairing their dysfunction. EA can also act on oxidation and inflammation, which are closely related to aging. The antioxidant effect of EA has been systematically verified by various experiments in vivo and in vitro. It achieves antioxidant effects through strong free radical scavenging ability. It has the ability to eliminate harmful radicals and oxygen species that are reactive in the body, thus reducing oxidative stress. Although the exact anti-inflammatory mechanism of EA remains unclear, it is well-established that ellagic acid has the capacity to lower the concentration of inflammatory factors and participate in the regulation of inflammatory pathways in the body, which is enough to show that it has certain anti-inflammatory effects. In addition, EA can also act on skeletal muscle and skin to fight aging. The investigation into the anti-aging mechanism of ellagic acid offers valuable insights into the aging process, establishing a scientific framework for the development of innovative anti-aging techniques. This, in turn, aims to enhance human quality of life and address health issues associated with aging.

The study of EA should not be limited to the field of health, but should be expanded to other fields. Its antioxidant and anti-aging properties can also be applied to the food industry as food preservatives and fresheners. In addition, it may be possible to link EA with the current hot research on cancer drugs, explore the value of EA in the field of medicine, and develop corresponding drugs or health care products. Although the research direction and application prospect of EA are very extensive, its development and application still face some problems, such as the extraction and purification of EA and other processing technologies are not perfect, and the research on the mechanism of bioactivity related to EA is not comprehensive enough, which needs further in-depth exploration and exploration.

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