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Age-Related Changes in Proportions of Urolithins A, B, and 0

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Abstract

Nowadays, aging is the actual theme above the world. Scientists are working on to prevent aging. In this article, we discuss how Urolithin effects on human body and aging process.

Urolithin A (UA) is a natural compound produced by gut bacteria from ingested ellagitannins (ETs) and ellagic acid (EA), complex polyphenols abundant in foods such as pomegranate, berries, and nuts.

Mitochondria play a crucial role in cellular function and are particularly important in aging and decrepit cells by the function of mitophagy. During this process pathological mitochondria are killed, that controls the quality of mitochondrias and proteins.

Mitochondrial dysfunction can trigger cellular responses associated with inflammation and cellular senescence.

Urolithins (microbial metabolites) found in various tissues after ellagitannin consumption, has been demonstrated to possess antioxidant and anti-inflammatory effects.

Introduction

Traditionally, Georgia_has been at the forefront of aging [Lezhava, 2011]. Nowadays, unfortunately, the reason of that fundamental process is still unknown. An aging theory was created, which combines the both basic approach_1.aging is a programmed process; 2. Aging is a stochastic process. [Tkemaladze, 2022; Chichinadze et al., a2012; Chichinadze et al., b2012].

Also, there has been a cross-effect test of a new pharmacological group - senolytics - dasatinib and quercetin was conducted on humans in Georgia [Jaba T, 2022]. Beside senolytics, there has been being worldwide studies about senomorphics which includes urolithins. There are trillions of microorganisms in the human intestine. They can react to the intestinal microenvironment by metabolizing food or producing small molecular compounds to affect the host's digestive ability and resist the risk of infection and autoimmune diseases. Many studies have revealed that intestinal flora and its metabolites play an important role in human physiology and the development of diseases. [Lu et al., 2022]

Urolithin A (UA) is a natural compound produced by gut bacteria from ingested ellagitannins (ETs) and ellagic acid (EA), complex polyphenols abundant in foods such as pomegranate, berries, and nuts. UA was discovered 40 years ago, but only recently has its impact on aging and disease been explored. Several preclinical studies show how UA protects against aging and age-related conditions affecting muscle, brain, joints, and other organs. [D'Amico et al., 2021 Impact of the Natural Compound Urolithin A on Health, Disease, and Aging. Trends in molecular medicine, 27(7), 687–699. Urolithins are primarily known for their role in gut health and their interaction with the microbiota. A role of the microbiome in human aging is important: the microbiome directly impacts aging through the gastrointestinal system. Probiotics and prebiotics may be effective alternatives, considering the relationship between the microbiome and healthy aging.[Boyajian et al.,2021].

There are several studies about urolithin the benefit of Urolithin A to improve muscle performance. [Singh et al., 2022] Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. Cell reports. Medicine, 3(5), 100633. Oral urolithin A treatment caused prominent anti-cancer and anti-inflammatory action in various in vivo studies, including models of pancreatic cancer, and models of obesity. The main molecular mechanisms of these effects might be the modulation of aryl hydrocarbon receptors, which antagonism may lead to decreasing of chronic inflammation. Other primary targets of urolithin A might be the processes of protein phosphorylation (for instance, it decreases the phosphorylation of protein kinase B) and p53 stabilization. Anti-inflammatory effects of urolithin A can be reached in physiologically relevant concentrations. This might be of vital importance for preventing immune suppression associated with chronic inflammation in cancer.[Rogovskii et al.,2022]. The Therapeutic Potential of Urolithin A for Cancer Treatment and Prevention.

Urolithins (microbial metabolites) found in various tissues after ellagitannin consumption, has been demonstrated to possess antioxidant and anti-inflammatory effects. The current research mainly focused on the ameliorative effect of Uro B on intestinal immunity function and exploring the potential mechanisms of its protective role in aging. The D-gal-induced accelerated aging model in vivo demonstrated that Uro B could elevate the activities of superoxide dismutase, catalase, glutathione peroxidase, and total anti-oxidation capability, decrease malondialdehyde content, regulate the levels of inflammatory cytokines (IL-6, TNF-α, IFN-γ, IL-4, and IL-1β) in the small intestine, and reshape the composition of gut microbiota and decrease the intestinal barrier injury in aging mice. Therefore, these findings indicated that Uro B effectively weakened the injury to the small intestine and ameliorated intestinal immunity function through the downregulation of the HMGB1-TLR4-NF-κB pathway in aging mice. Uro B could be considered a healthcare product to prevent diseases associated with an aging immune system.[Chen et.,al2021]

1 The role of mitochondria in cell senescence

Mitochondria play a crucial role in cellular function and are particularly important in aging and decrepit cells. The mitochondria participate in critical central metabolic pathways, and they are fully integrated into the intracellular signalling networks that regulate diverse cellular functions. It is not surprising then that mitochondrial defects or dysregulation have emerged as having key roles in aging.[Annesley et al.,2019] mitochondrial dysfunction has emerged as a key factor in a myriad of diseases, including neurodegenerative and metabolic disorders.[Nunnari et al.,2012]

1.1 Energy Production

Mitochondria are often referred to as the “powerhouses” of the cell because they generate the majority of a cell's energy in the form of adenosine triphosphate (ATP) through a process called oxidative phosphorylation.[Panconesi et al.,2022]The mitochondrial electron transport chain utilizes a series of electron

transfer reactions to generate cellular ATP through oxidative phosphorylation.[Nolfi-Donegan, 2020] However, as cells age, mitochondrial function can decline. Decreased energy production can lead to reduced cellular metabolism and overall decreased vitality.

1.2 Reactive Oxygen Species (ROS) Production

Reactive oxygen species (ROS) are thought to play a dual role in plant biology.[Mittler et al., 2017] Mitochondria are also a significant source of reactive oxygen species (ROS) within the cell. ROS are chemically reactive molecules that can cause damage to cellular components, including DNA, proteins, and lipids. Aging and dysfunctional mitochondria can produce higher levels of ROS, leading to oxidative stress, which contributes to cellular damage and aging. [Brieger et al., 2012]

1.3 DNA Damage Accumulation

Mitochondria have their own small circular DNA called mitochondrial DNA (mtDNA). Over time, mutations can accumulate in the mtDNA due to oxidative stress and other factors. The accumulation of mtDNA mutations can impair mitochondrial function, leading to further declines in energy production and overall cellular health.[Quan et al., 2020]

1.5 Inflammation and Senescence

Mitochondrial dysfunction can trigger cellular responses associated with inflammation and cellular senescence. Inflammation can be initiated by the release of mitochondrial DNA or ROS, activating inflammatory pathways and contributing to the chronic low-grade inflammation seen in aging tissues. Senescence refers to a state of irreversible cell cycle arrest, and dysfunctional mitochondria can promote cellular senescence. The accumulation of senescent cells is a major cause of age-related inflammation and predisposes to a variety of age-related diseases.[Wang et al.,2022]

Overall, the declining function of mitochondria in aging and decrepit cells can have profound effects on cellular energy production, oxidative stress, DNA damage, quality control mechanisms, inflammation, and senescence. These processes contribute to cellular aging and the overall decline in tissue and organ function observed with age. General perceptions and experimental evidence pinpoint that the decline of physical function often initiates by cell senescence and organ aging.[Zhu et al.,2021]

recent investigations with rodent and cellular models of inflammation further showed that Uro-A protects against the inflammation-induced intestinal barrier damage through the activation of the aryl hydrocarbon receptor (AhR)-nuclear factor erythroid 2-related factor 2 (Nrf2)- dependent pathways, amelioration of cytokines biosynthesis (such as TNF-α and IL-6), and modulation of the tight junction proteins expression.[García-Villalba R et al.,2022]

2 The proliferation of mitochondria

Mitochondria replicate through three methods: fission, budding externally, and budding internally. Mitochondrial fission is a highly regulated process that, when disrupted, can alter metabolism, proliferation, and apoptosis. Fission enables both biogenesis of new mitochondria and clearance of dysfunctional mitochondria through mitophagy [Kleele et al., 2021]

Mitochondria also possess their own protein synthesis system of a prokaryotic type, including ribosomes, tRNAs, and aminoacyl-tRNA synthetases. Mitochondrial ribosomes are tolerant to the matrix and can translate mRNA

of any origin. Experimental evidence supports the action of the mitochondrially localized transcription factors on mitochondrial transcription, energy yield and apoptosis, [Psarra et al., 2008]

3 Causes of mitochondrial dysfunction

3.1 The role of mtDNA mutations as a driving force in senescence

One of the key characteristics of mtDNA is its proximity to the sites of reactive oxygen species (ROS) production during oxidative phosphorylation. ROS are natural byproducts of energy production, but can also cause damage to cellular components, including mtDNA. The proximity of mtDNA to ROS production makes it more susceptible to oxidative damage compared to nuclear DNA. [Bratic et al., 2013]

Over time, accumulated damage to mtDNA can lead to the accumulation of mtDNA mutations. These mutations can disrupt the normal functioning of mitochondria, leading to a decline in energy production and increased production of ROS. This creates a vicious cycle where mitochondrial dysfunction and oxidative stress contribute to further mtDNA damage and mutations. The impact of somatic mtDNA mutations rapidly increases with age, so their importance is expected to grow as human life expectancy increases.[Khrapko et al., 2014]

The accumulation of mtDNA mutations has been associated with various age-related diseases and conditions, including neurodegenerative disorders, cardiovascular diseases, and age-related decline in tissues such as skeletal muscle. These mutations can affect the efficiency of energy production, impair cellular functions, and contribute to the senescence process.[Belcaro et al.,2018]

Furthermore, the limited repair mechanisms for mtDNA compared to nuclear DNA contribute to the persistence of mtDNA mutations. Mitochondria have a less robust DNA repair system, making it more challenging to correct DNA damage and mutations. As a result, damaged mtDNA can persist and accumulate over time.

The exact contribution of mtDNA mutations to senescence and age-related diseases is still an active area of research, and the precise mechanisms linking mtDNA mutations to senescence are not fully understood. [Yan et al.,2019]

3.2 The role for mitochondrial reactive oxygen species (ROS) in senescence

Mitochondrial ROS have been implicated in the process of cellular senescence, which is a state of irreversible cell cycle arrest associated with aging and age-related diseases.

3.2.1 ROS production

Mitochondria are a major source of cellular ROS production as a byproduct of oxidative phosphorylation. During this process, electrons leak from the electron transport chain, leading to the generation of ROS, primarily superoxide anion (O2-) and hydrogen peroxide (H2O2).

3.2.2. DNA damage

Mitochondrial ROS can cause oxidative damage to nuclear and mitochondrial DNA. This DNA damage can lead to the activation of DNA damage response pathways, such as the ATM and ATR pathways, triggering cellular senescence. During aging, damaged mitochondria that produce less ATP and more reactive oxygen species (ROS) accumulate.[Stefanatos et al.,2018] efects or mutations of mtDNA result in a range of diseases. Damaged mtDNA could be eliminated by mitophagy, and all paternal mtDNA are degraded by endonuclease G or mitophagy during fertilization.[Yan et al.,2019]

3.2.3 Telomere dysfunction

Aging organisms accumulate senescent cells that are thought to contribute to body dysfunction. Telomere shortening and damage are recognized causes of cellular senescence and aging. Several human conditions associated with normal ageing are precipitated by accelerated telomere dysfunction.[Rossiello et al., 2022]

3.2.4 Activation of signalling pathways

Mitochondrial ROS can activate various signalling pathways involved in senescence, including the p38 MAPK and p53 pathways. These pathways promote cell cycle arrest and the senescent phenotype.

3.2.5 Senescence-associated secretory phenotype (SASP)

Mitochondrial ROS can contribute to the induction of the SASP, which involves the secretion of various pro-inflammatory cytokines, chemokines, growth factors, and proteases. The SASP can reinforce senescence and influence neighbouring cells, contributing to tissue dysfunction and inflammation.

3.2.6 Epigenetic alterations

Mitochondrial ROS can induce epigenetic modifications, such as DNA methylation and histone modifications, which can influence gene expression patterns and contribute to the establishment and maintenance of the senescent state.

3.2.7 Mitochondrial dysfunction

Increased ROS production and oxidative damage can lead to mitochondrial dysfunction, impairing energy production and cellular homeostasis. Mitochondrial dysfunction itself can contribute to the induction of senescence.

While mitochondrial ROS can contribute to senescence, the relationship is complex and can vary depending on the cell type, context, and overall cellular redox balance. The impact of mitochondrial ROS on senescence is influenced by a delicate balance between ROS production, antioxidant defence systems, and cellular repair mechanisms.

3.3 Mitochondrial function and longevity

The link between mitochondrial function and longevity is an area of active research, and our understanding of this connection is still evolving. Several studies and observations highlight the importance of healthy mitochondrial function for longevity.

3.3.1 Energy production

Healthy mitochondrial function and efficient energy production are associated with optimal cellular and tissue function. Insufficient energy production can impact overall health and accelerate the aging process.

3.3.2 Oxidative stress

High levels of ROS can cause damage to cellular components, including DNA, proteins, and lipids. Reducing oxidative stress and maintaining antioxidant defence mechanisms can contribute to healthy aging and longevity. Living in an oxygenated environment has required the evolution of effective cellular strategies to detect and detoxify metabolites of molecular oxygen, known as reactive oxygen species. Here we review evidence that the appropriate and inappropriate production of oxidants, together with the ability of organisms to respond to oxidative stress, is intricately connected to aging and life span.[Finkel et al.,2000]

3.3.3 Apoptosis and autophagy

Mitochondria also plays a crucial role in programmed cell death (apoptosis) and autophagy, mechanisms that help eliminate damaged and dysfunctional cells. This is important for maintaining the health of tissues and organs. Apoptosis is considered a vital component of various processes including normal cell turnover[Elmore S et al.,2007] Autophagy is a homeostatic process by which damaged or dysfunctional cellular components are removed through the formation of autophagosomes, which sequester the cellular components and then fuse with lysosomes6. Autophagy enables cells to recover from stress, such as oxidative and endoplasmic reticulum stress, and energy depletion. Urolithin A attenuates auditory cell senescence by activating mitophagy-Impairing autophagy through the knockdown of autophagy-related genes induces premature senescence in human fibroblasts.[Cho SI et al., 2022]

3.3.4 Mitochondrial DNA

mtDNA is more susceptible to mutations and damage compared to nuclear DNA. The accumulation of mtDNA mutations can reduce mitochondrial function efficiency and contribute to aging and age-related diseases.mtDNA is packed by many proteins to form a nucleoid that uniformly distributes within the mitochondrial matrix, which is essential for mitochondrial functions.[Yan et al.,2019]

3.3.5 Metabolic health

Mitochondrial function is closely linked to metabolic health. Dysfunctional mitochondria can lead to metabolic imbalances, such as impaired glucose and lipid metabolism, which are associated with age-related diseases like diabetes and cardiovascular disorders. Maintaining healthy mitochondrial function can help support overall metabolic health and longevity. Oxidative stress (OS) plays a substantial role in inflammatory and neurodegenerative diseases, causing cellular damage and mitochondrial dysfunction. [Belcaro et al.,2018]

3.3.6 Hormesis and adaptive responses

Mitochondrial function can be influenced by hormesis, a phenomenon where exposure to mild stressors can induce adaptive responses that enhance cellular defence mechanisms. Hormetic responses can improve mitochondrial function and promote longevity.

4 Clearance of abnormal mitochondria from the cell

The removal of abnormal or dysfunctional mitochondria from cells is a process known as a quality control. Cells have evolved various mechanisms to eliminate damaged or excessive mitochondria to maintain overall mitochondrial health.

4.1 Mitophagy

One of the types of clearance is mitophagy, which is a selective form of autophagy specifically targeted at mitochondria..the damaged mitochondria are sequestered and engulfed by specialized structures called autophagosomes, which are formed by the process of autophagy. Autophagosomes encapsulate the damaged mitochondria and deliver them to lysosomes, where they undergo degradation and recycling. Mitophagy helps to maintain a healthy population of functional mitochondria by removing those that are damaged, dysfunctional, or have exceeded their lifespan. The process of mitophagy is regulated by specific proteins, such as PINK1 (PTEN-induced kinase 1) and Parkin, which mark damaged mitochondria for degradation. Urolithin A (Mitopure) is a known mitophagy activator. [Singh et al.,2022]

Mitophagy and Quality Control

How mitophagy controls the quality of mitochondria?

Mitochondria are essential organelles that execute and coordinate various metabolic processes in the cell. Mitochondrial dysfunction severely affects cell fitness and contributes to disease. Mitophagy is an autophagic response that specifically targets damaged, and hence potentially cytotoxic, mitochondria.[Bravo-San Pedro et al., 2017] It is an essential mechanism for maintaining mitochondrial quality control and preventing the accumulation of damaged mitochondria. However, in aging cells, the efficiency of mitophagy may decline, resulting in the accumulation of dysfunctional mitochondria. [Eldeeb et al.,2022]

As a result, the cell has evolved mechanisms to coordinate protein and organellar quality control, such as the turnover of proteins via mitochondria-associated degradation, the ubiquitin-proteasome system, and mitoproteases, as well as the elimination of mitochondria through mitophagy. [Ng et al., 2021]

4.2 Ubiquitin-Proteasome System

The ubiquitin-proteasome system (UPS) is another mechanism involved in eliminating abnormal or misfolded proteins, including those within mitochondria. The ubiquitin-proteasome system (UPS) plays an important role in the cellular processes of protein quality control and homeostasis.[Park et al.,2020] In the context of mitochondrial quality control, the UPS can target proteins that are mislocalized or misfolded within mitochondria for degradation. This process helps to prevent the accumulation of damaged proteins that may compromise mitochondrial function

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5 Urolithin's role in the clearance of abnormal or dysfunctional mitochondria from cells

Urolithins are a group of bioactive compounds that are produced in the gut through the metabolism of dietary ellagitannins by the gut microbiota. While urolithins have been primarily studied for their potential health benefits, including their role as antioxidants and anti-inflammatory agents, emerging research suggests they may also play a role in mitochondrial quality control and the removal of abnormal mitochondria from cells. Urolithin has been demonstrated to possess antioxidant and anti-inflammatory effects.[Chen et.,al2021] [Fonseca et al., 2021]

Urolithin A attenuates auditory cell senescence by activating mitophagy.Urolithin A (UA) induces mitophagy in various mammalian cells. This study was aimed at investigating the effect of the mitophagy activator, UA, on premature senescent auditory cells. There are some researches about The formation of mitophagosomes and mitophagolysosomes was restored upon UA pre-treatment of H2O2-induced senescent cells. The knockdown of mitophagy-related genes (*Parkin* and *Bnip3*) resulted in annulment of UA-induced anti-senescent activity. UA significantly increased the ATP content, mitochondrial DNA (mtDNA) integrity, and mitochondrial membrane potential in senescent HEI-OC1 cells. These findings indicate that UA counteracted mitophagy decline and prevented premature senescence in auditory cells. [Cho SI et al., 2022]

6 Age-related decrease urolithine producing

Microbial composition and activity can change with age, which can potentially affect the production of urolithins. Aging is associated with a decline in mitochondrial function and reduced exercise capacity.[Liu et al., 2022]

The production of urolithins depends on the metabolism of ellagitannins by specific gut bacteria, such as certain strains of the genus Gordonibacter and Akkermansia. Age-related changes in the gut microbiota, including alterations in the abundance and diversity of microbial species, have been reported. These changes could potentially impact the production of urolithins.

Additionally, factors such as dietary habits and lifestyle choices, which can also change with age, may influence the availability of ellagitannins in the diet. Ellagitannins are found in foods such as pomegranates, berries, and nuts. Variations in dietary intake could affect the substrate availability for urolithin production by gut bacteria.

Understanding the factors that affect urolithin production and their implications for health, particularly in the context of aging, is an area of ongoing scientific investigation.

7 Metabolism of ellagic acid is determined by aging

ETs are one of the main groups of hydrolyzable tannins. Urolithins are bioactive compounds that are derived from ellagitannins, which are naturally occurring polyphenolic compounds found in certain fruits and nuts. To date, 13 urolithins and their corresponding conjugated metabolites (glucuronides, sulfates, etc.) have been described and, depending on the urolithin, detected in different human fluids and tissues (urine, blood, feces, breastmilk, prostate, colon, and breast tissues). The bioavailability of ETs and EA is very low. They undergo extensive metabolism by the gut microbiota to produce 6H-dibenzo[b,d]pyran-6-one derivatives, known as Uros. The gut microbiota can transform EA into Uros by lactone-ring cleavage, decarboxylation, and dehydroxylation reactions, starting with pentahydroxy-Uro (Uro-M5) and following to tetrahydroxy-Uros (Uro-D, Uro-E, and Uro-M6) and trihydroxy-Uros (Uro-C and Uro-M7) to finalize in dihydroxy-Uros (Uro-A and isoUro-A) and monohydroxy-Uro (Uro-B), which is generally detected when isoUro-A is also produced. The pathway of Uros formation and the place in the intestinal tract where they are produced were elucidated using a gastrointestinal simulation model (TWIN–SHIME) with fecal samples from two individuals with distinct urolithin metabotypes (UMs). Differences in the Uro profile were observed between UMs and along the large intestine, showing predominant Uro production in the distal colon region.[García-Villalba R et al., 2022]

To investigate whether oral administration of urolithin A improved the 6-minute walk distance, muscle endurance in hand and leg muscles, and biomarkers associated with mitochondrial and cellular health.[Liu et al., 2022]This paper reviews the origin of urolithins, the urolithin producing microorganisms and the effects of urolithins on regulating intestinal diseases. This review will provide a theoretical basis for the regulation of urolithins in the homeostasis of intestinal flora and a reference for the scientific utilization of urolithins and foods rich in ETs and EA. [Lu et al., 2022].

Following treatment with lyophilized black raspberries were reported in Barrett's esophagus patients. Similar concentrations were also obtained after 12 and 26 weeks of ingestion. Higher concentrations, but not significantly different, were observed after 90 days of strawberry (poly)phenol intake compared with 45 days, suggesting that the continuous intake of ETs could enhance either the abundance of some bacterial species or the capacity of certain species to increase Uro production. Several studies have reported the presence of Uro

conjugates in plasma and urine of men with localized prostate cancer after consuming a pomegranate fruit extract, a usual American diet, or standardized black raspberry products.[García-Villalba R et al., 2022]

8 The molecular mechanism of urolithin to get into the cell

Once urolithins are produced in the gut, they need to enter cells in order to exert their biological effects. The exact molecular mechanism of urolithin uptake into cells is not fully understood and may vary depending on the specific urolithin compound and cell type. Urolithin A (UA) is a natural compound produced by gut bacteria from ingested ellagitannins (ETs) and ellagic acid (EA), complex polyphenols abundant in foods such as pomegranate, berries, and nuts. [D'Amico et al.,2021]. [Tao et al., 2022] [Denk et al.,2022] [Liu et al., 2022] Certain membrane transporters may facilitate the entry of urolithins into cells. These transporters can recognize and transport specific molecules across the cell membrane.

Discussion

Differential individuals' capacity to metabolize ellagic acid derivatives into urolithins depends mainly on aging. In other words, the gut microbiota community involved in the catabolism of ellagitannins and ellagic acid seems to be developmentally regulated. UMs distribution as a function of aging consists of a progressive decrease of UM-A, concomitant to the increase of UM-B (and illustrated by the decrease of the UM-A/UM-B ratio in Fig. 2) up to 30–40 years of age, after which the UMs distribution remains approximately constant. In contrast to the correlation reported between diet and the equol-producer metabotype in early childhood,23 we did not find a clear association between diet, i.e., good or bad adherence to Mediterranean diet, and UMs distribution. Physical activity can affect the gut microbiota involved in polyphenol metabolism as described for isoflavones, as the percentage of equol and ODMA producers has been reported to be higher in individuals with higher physical activity. A slight association between UM-B and physical activity from childhood to adolescence is identified in scientific studys. [Cortés-Martín, A et al.,2018]

Conclusion

To sum up, everything above proves that the distribution of urolithin metabotypes in the population is determined as a function of age. The duration of life is limited, so there are some ways which can prolong the duration of human living in this article. The ways are:

1. Altitude therapy

2. Work out

3. Urolithin A (Maintaining the amount characteristic of a young person)

Here are 3 ways but maintaining the amount characteristic of a young person of urolithin A is the safest thing we prove below:

Due to the Life expectancy is limited by the number of heartbeats, considering that exercising accelerates heart beat, it partially reduces the life expectancy. Altitude method or exercise can extend one's life by killing abnormal mitochondria. Therefore, it is better to kill the pathological mitochondria without increasing the heart rate - to maintain the amount of Urolitin A that is characteristic of the young.

Targeting mitophagy to activate the recycling of faulty mitochondria during aging is a strategy to mitigate muscle decline. [Singh et al.,2022]

To study the effect of blood-letting puncture at "Well-points" of the twelve meridians on hippocampal mitophagy of hypobaric hypoxia-induced brain injury (HHIBI) rats, to explore its biological mechanisms underlying improvement of high altitude hypoxia-induced brain injury.[Huang et al.,

Altitude therapy, also known as altitude training or hypoxic training, is a method used by athletes and individuals seeking performance enhancement to improve their cardiovascular fitness and endurance. This type of training involves exposing the body to reduced oxygen levels typically found at higher altitudes.

Altitude can have various effects on the human body due to changes in atmospheric pressure and oxygen levels. As you ascend to higher altitudes, the air becomes thinner, resulting in reduced oxygen availability. This can lead to altitude-related health issues such as altitude sickness, acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). These conditions can cause symptoms like headache, dizziness, shortness of breath, nausea, and fatigue.

Extensive clinical experience with drugs in patients with pulmonary arterial hypertension suggests their potential for treatment of high altitude pulmonary hypertension. Small studies have demonstrated their efficacy in reducing pulmonary artery pressure in high altitude residents. [Sydykov et al.,2021]Barometric pressure falls with increasing altitude and consequently there is a reduction in the partial pressure of oxygen resulting in a hypoxic challenge to any individual ascending to altitude. [Imray et al.,2010]

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