Role of Phytomolecules on the Basic Biology of Aging

6

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Abstract

Aging is an inevitable process influenced by genetic, lifestyle, and environmental components which increases the primary risk of multiple age-related chronic diseases. The efficacy of any herbal medication depends on delivering adequate levels of plant extract from the therapeutically active phytomolecules. Phytomolecules such as flavonoids, phenolics, and hydrophilic molecules are predominant in vegetables, nuts, teas, wines, fruits, grains, olive oil, and chocolate. Polyphenols are secondary plant metabolites and are packed with potential health benefits of plant-rich dietary polyphenols as plant-rich antioxidant diets. In this chapter, we have focused on several recently identified phytochemicals having potent antiaging properties, i.e., silymarin, 18α-glycyrrhetinic acid, piceatannol, withanolide, and other polyphenols, on the lifespan of model organisms and summarize the current understanding of phytomolecules interaction with various signaling mechanism pathways of aging context relevant to human wellness. Natural phytochemicals are widely approved for antiaging properties that have less side effects compared to synthetic and that are easier to manage for human beings.

Keywords

Phytochemicals · Antiaging · Antioxidant

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Abbreviations

AD	Alzheimer's diseases
C. elegans	*Caenorhabditis elegans*
DR	Dietary restriction
PD	Parkinson's diseases
ROS	Reactive oxygen species

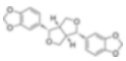
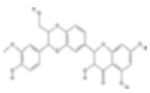
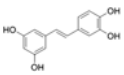
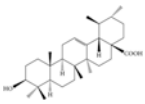
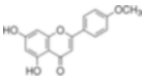
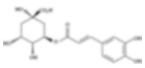
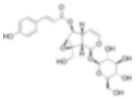
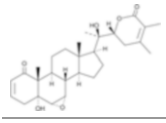
6.1 Introduction

Caenorhabditis elegans (*C. elegans*) is a free living model organism, with well-characterized genome, short life cycle, and small body size, and conserves 65% of the genes linked with human disease (Walker et al. 2000; Hill et al. 2000). *C. elegans* is a well-established model organism for the work on aging emerged in several fields, including genetics, neurobiology, and developmental biology (Luyten et al. 2016). Aging is a natural phenomenon that deteriorates the total physiology of an organism due to widespread systematic dysfunction of almost all organs, leading to enhanced exposure to environmental problems and increased risk of destruction and disease (Fulop et al. 2010). Free radicals are an atom, molecule, or compound generated by metabolic reaction in the physical structure. Reactive oxygen species (ROS) generated by normal metabolism directly regulate the aging process. Mitochondrial dysfunction is a hallmark of aging diseases and modification in mitochondrial dynamics related to a loss of mitochondrial fitness with unhealthy aging (Sebastián et al. 2017). Phytomolecules are secondary metabolites which have been used for decades in traditional system of medicine in the form of antioxidants, drugs, flavors, dyes, scents, insecticides, pheromones, and so forth by more than 80% of the world population (Ekor 2014). Polyphenols and other food phenolics are the subject of increasing scientific interest because of their potential beneficial effects on human wellness. Phytochemicals are present in various edibles, including fruit, veggies, grains, and nuts as well as in beverages including juice, tea, chocolate, and wine (Prakash et al. 2012). Various plant-based molecules have been reported for their properties to prevent chronic diseases like prevention of malignant neoplastic disease, diabetes, obesity, cardiovascular disease, as well as neurological dysfunctions (Zhang et al. 2015; Si and Liu 2014). Phytomolecules act as a significant part in the maintenance of age-associated pathologies via a positive feedback mechanism. This chapter discusses the applications of several new phytomolecules with different pharmacological properties (Table 6.1).

6.2 Antiaging Phytochemicals

Phytomolecules are plant-based secondary metabolites which have antioxidative and anti-inflammatory characteristics that promote better wellness and prevent diseases, such as malignant neoplastic disease, diabetes, cardiovascular disease, and

Table 6.1 List of phytomolecules with different pharmacological properties

Phytomolecules/ chemical structure	Source	Different properties	References
Sesamin 	Sesame oil	Antioxidant, anticancer, anti-inflammation, antiaging	Liu et al. (2014); Nakatani et al. (2018)
Silymarin 	*Silybum marianum*	Antioxidant, anti-inflammatory, diabetes, sepsis, osteoporosis, arthritis, hypercholesterolemia, cancer, viral infections, Alzheimer's, Parkinson's antiaging	Kumar et al. (2015); Liu (2016); Srivastava et al. (2017); Stolf et al. (2017)
Piceatannol 	Red wine, grapes, fruits	Antioxidant, anti-inflammatory, antiatherogenic, antiaging	Wang et al. (2002); Lyons et al. (2003); Ovesná et al. (2006); Shen et al. (2017)
Ursolic acid 	Basil, rosemary, etc.	Antioxidant, anti-inflammatory, antiaging activity	Liobikas et al. (2011); Kashyap et al. (2016); Bahrami and Bakhtiari (2016); Negi et al. (2016)
Acacetin 	*Premna integrifolia*	Antioxidant, anti-inflammatory, antidiabetic, antibacterial, antihyperglycemic, anti-obesity	Mali (2014); Asthana et al. (2016)
Chlorogenic acid 	Apple peels, green coffee beans	Antibacterial, antioxidant, anticarcinogenic, anti-obesity, antidiabetic, antiaging	Sato et al. (2011); Meng et al. (2013); Jeszka-Skowron et al. (2016); Zheng et al. (2017)
Specioside 	*Stereospermum suaveolens* "patala"	Analgesic, antidyspeptic, astringent, antiaging, liver stimulating, wound healing	Garg et al. (1994); Asthana et al. (2015)
Withanolide A 	*Withania somnifera*	Antioxidant, antistress, anti-inflammatory, antiaging	Kurapati et al. (2013); Baitharu et al. (2014); Akhoon et al. (2016)

neurodegenerative disorders, in animals (Zhang et al. 2015). In summation to the health-improving and disease-preventing effects, phytochemicals also have been demonstrated to delay the aging process and prolong life in several experimental animal studies using yeast, insects, flies, fishes, and rodents (Sadowska-Bartosz and

Bartosz 2014). The presence of phytochemicals is also capable of cutting down the side effects and enhances promoting lifespan. In this chapter, the longevity benefits and putative underlying mechanisms of phytochemicals help them to survive under environmental stresses and to protect them from microbial infections and environmental pollutants as are described briefly.

6.2.1 Sesamin

A polyphenolic compound sesamin is found in sesame seeds and extracted from sesame oil which contains significant amounts of lignins. It has antioxidant, anticancer, anti-inflammatory, and diverse pharmacological functions which are reported to exert a variety of health benefits such as modulation of lipid biosynthesis and alleviation of oxidative stress (Liu et al. 2014). Sesamin is also reported as an antiaging activity to promote lifespan in *C. elegans*. It has been reported that sesamin is more resistant to oxidative stress and extended the life of a *mev-1* mutant that produces abundant superoxide anions. Interestingly, sesamin can also extend the lifespan by overexpression of dietary restriction-related signaling pathways, in RNAi-treated worms which is a key regulator of autophagy (Nakatani et al. 2018).

6.2.2 Silymarin

Silymarin is a flavanone derivative extracted from the sources of the milk thistle *Silybum marianum*. Silymarin has been demonstrated to exert antioxidant and anti-inflammatory properties. It has also been reported for the treatment of various chronic disorders, such as hepatitis, gallstones, and cirrhosis. Apart from these properties, silymarin possess diabetes, sepsis, osteoporosis, arthritis, cancer, viral infections, and Alzheimer's diseases (AD) and Parkinson's diseases (PD) activity (Srivastava et al. 2017; Stolf et al. 2017). Silymarin was reported as an antiaging agent in the *C. elegans* model system. In addition to increased lifespan, silymarin also allows increased locomotion rate, increased stimulus response, and improved stress tolerance (Kumar et al. 2015; Liu 2016).

6.2.3 Piceatannol

Piceatannol, a resveratrol metabolite, is also present in many fruits and vegetables, as a natural stilbene. This is found even in some beverages like red wine (Lyons et al. 2003; Wang et al. 2002). In addition, piceatannol is more active in antioxidant, anti-inflammatory, and antiatherogenic activities than resveratrol (Ovesná et al. 2006). Piceatannol is also reported as an antiaging potential activity in *C. elegans* in terms of reducing locomotive activity, improving pharyngeal pumping rate, and protecting the worms from oxidative and heat stress through insulin/IGF-1 signaling and sir-2.1-dependent pathways (Shen et al. 2017).

6.2.4 Ursolic Acid

Ursolic acid (3β-hydroxyurs-12-en-28-oic acid, UA) is a lipophilic pentacyclic triterpenoid, the main component of herbal plants, found in a wide variety of vegetarian and medicinal foods. It has been reported as an antioxidant, anti-inflammatory, and antiaging activity and possesses many beneficial effects, notably hepatoprotection, antitumoral, antihyperlipidemic, and anti-inflammation (Liobikas et al. 2011). UA is one of these plant-based therapeutic metabolite groups that have separate extracellular and intracellular marks that play a role in metastasis, apoptosis, and inflammatory processes. In addition, UA's synthetic derivatives were also found to be active in a series of pharmacological applications related to age-related disease prevention (Kashyap et al. 2016). Ursolic acid regulates the aging process for better health span and lifespan in *Caenorhabditis elegans* via modulating JNK pathway (Bahrami and Bakhtiari 2016; Negi et al. 2016).

6.2.5 Acacetin

Acacetin is extracted in nature from *Premna integrifolia* (*P. integrifolia*) and is an essential flavanoid. It has been known for its potential actions such as antioxidant, immunomodulatory, anti-inflammatory, antidiabetic, antibacterial, hepatoprotective, antihyperglycemic, and anti-obesity (Mali 2014). Acacetin has been reported as a stress buster, antiaging, and ROS scavenger and also able to reduced aging marker lipofuscin level in *C. elegans* (Asthana et al. 2016).

6.2.6 Chlorogenic Acid

Chlorogenic acid compounds are the most abundant polyphenols typically found in apple peels and green coffee beans and have many biological properties, including antibacterial, antioxidant, anticarcinogenic, and anti-obesity activity and are capable of lowering blood sugar rates (Sato et al. 2011; Meng et al. 2013; Jeszka-Skowron et al. 2016). Chlorogenic acid has beneficial effects on human health and ameliorates aging diseases, and it also slows age-related decrease in body activity and increases stress tolerance via insulin/IGF-1 signaling pathway in *C. elegans.* Chlorogenic acid is also able to activate the FOXO transcription factors DAF-16, HSF-1, and SKN-1 but not SIR-2.1 (Zheng et al. 2017).

6.2.7 Specioside

Specioside (6-*O*-coumaroylcatalpol) is an iridoid glucoside isolated from the plant *Stereospermum suaveolens* (Bignoniaceae), commonly known as "patala." The plant produces apigenin, lapachol, dianatin-7-glucuroniside, dinatin, β-sitosterol, saponins, palmitic, stearic, and oleic acids that have multifunctional properties,

viz., analgesic, antidyspeptic, astringent, hepatic stimulant, antiaging, and wound healing (Asthana et al. 2015). The iridoids, present in a wide range of plants, are groups of natural molecules with a monoterpene cyclic ring. Iridoid glucoside has been reported to have many functions, such as antitumoral, hypotensive, sedative, and hepatoprotective (Garg et al. 1994).

6.2.8 Withanolide A

Withania somnifera, also known as ashwagandha, is an essential therapeutic medicinal plant worldwide. Withanolide A is a steroidal lactone important bioactive compound extracted from *W. somnifera* (root) (Baitharu et al. 2014). Many studies are reported for the human health benefits of *Withania somnifera* because it is one of the most important plants which has been reported that have antioxidant, antistress, anti-inflammatory, immunomodulatory, and rejuvenating properties (Alam et al. 2012). Withanolide A also has many therapeutic properties, such as neurological disorders, including Alzheimer's disease-associated amyloid pathology, neuritis regeneration, synapsis recovery, axonal outgrowth, etc. (Baitharu et al. 2014; Kurapati et al. 2013). Withanolide A is also reported as antiaging agent and promotes stress resistance via IIS pathway (Akhoon et al. 2016).

6.3 Other Phytochemicals

Many of the phytochemicals are secondary plant metabolites that are found in a wide range of fruits, vegetables, grains, nuts, tea, and wine as well as in beverages including juice and coffee. More than 1 g of phytochemicals per day is commonly ingested with diet (Septembre-Malaterre et al. 2018; Leitzmann 2016). Many natural antioxidants, nutraceutical, and functional foods have been identified as radical or reactive oxygen-free scavengers. Functional and nutraceutical foods with antioxidant activity may play a significant role in slowing aging (Liu et al. 2018; Pant and Pandey 2015). Various pathways interact with each other and modulate lifespan by controlling the cellular stress response (Pan and Finkel 2017). These nutrient-sensing pathways include IGF, TOR, AMPK, and SIRTs (Aiello et al. 2017). Numerous phytomolecules have been reported for their therapeutic effects without compromising the quality of life (Pant and Pandey 2015). The natural molecules extend lifespan and reduce age-related pathologies. Polyphenols, resveratrol, found, for example, in grape berry skins, increased lifespan in *Caenorhabditis elegans* and prolonged lifespan and reduced oxidative stress and appeared to occur via a dietary restriction (DR) mechanism and performed to validate SIR-2-dependent and prevent age-related disease (Bhullar and Hubbard 2015; Conti et al. 2016). Quercetin is the primary representative of flavonoids found in elevated levels in herbal edibles such as onions, apples, and broccoli, as well as in red wine, tea, and *Ginkgo biloba* extracts (Pant and Pandey 2015; Conti et al. 2016; Koch et al. 2014). These flavonoids extend mean lifespan by improving antioxidant potential, reducing

ROS level, and increasing *mev-1* mean lifespan and daf-16 translocation (Koch et al. 2014; Büchter et al. 2015; Kampkötter et al. 2008). Curcumin is also one of the active ingredients that has been widely used as a spice and herbal medicine found in turmeric (*Curcuma longa*). It has biological activities, such as anti-inflammatory, antioxidative, anticancer, and anti-neurodegenerative and chemopreventive properties. Curcumin 20 μM dose extends the lifespan by 39.28% as well as improves health span and enhances resistance to oxidative and thermal stresses and prevents the age-related disease in *C. elegans* (Liao et al. 2011). 4-Hydroxy-*E*-globularinin (4-HEG) is major component of *Premna integrifolia* and enhanced the mean lifespan of worms by over 18.8% at 20 μM dose and also reduced reactive oxygen species (ROS) levels and fat accumulation in the worms (Shukla et al. 2012a, b). Some other phytomolecules reported as antiaging agent are l-theanine, 10-*O*-trans-*p*-coumaroylcatalpol, ferulsinaic acid, and baicalin (Zarse et al. 2012; Shukla et al. 2012a, b; Sayed 2011).

6.4 The Mechanisms of Age-Promoting Factor of Phytomolecules

Over a few decades, aging research has seen a breakthrough, particularly in the fact that the rate of aging is regulated, at least partly, by genetic mechanisms and biochemical procedures preserved in evolution. On the other side, it is further distinguished that age-related developments developed by genetics can be strongly affected by environmental variables (Stephan et al. 2013; López-Otín et al. 2013). Aging is induced by mitochondrial dysfunction, telomeric attrition, genomic instability, epigenetic modifications, deregulated nutrient sensing, cellular senescence, and stem cell fatigue. Aging would describe procedures that offer promising outcomes in animal models or even in human studies, leading in lifespan elongation or health improvement with the positive impacts of plant-derived extracts on aging and age-related diseases. Many phytochemicals can encourage longevity and enhance health span by synthesizing to boost plant fitness by enabling it to communicate with its surroundings, including herbivorous pathogens and insects. Phytochemicals can stimulate a cellular stress response in animals that is useful for life and health through various stress response mechanisms and low-dose exposures and can then stimulate adaptive stress resistance, also called hormesis (Mattson 2008). Functional foods and nutraceutical/dietary ingredients are an enormous promise to promote health and longevity and to prevent age-related chronic diseases through bioenergetic pathways that encourage aging via well-characterized antiaging pathways (López-Lluch and Navas 2016; Aiello et al. 2017). The increase in DNA damage with the consequence of impaired DNA repair system efficiency is the primary cause of cellular senescence. However, age-related declines in AMPK (AMP-activated protein kinase) pathways have improved the lifespan of the model organism, and AMPK kinase can also control several signaling pathways engaged in senescence and aging, such as those involving p53, mTOR, and NFB (Salminen and Kaarniranta 2012). The principal applicants for targeted measures are the mTOR

signaling inhibitors. This signaling pathway has been related to lifespan and health span in model organisms because both of these events have benefited from decreased mTOR signaling (Johnson et al. 2013).

6.5 Conclusion

Many Ayurvedic nutraceutical products are available in markets which provide health benefits made by phytodrug for the management of aging. Different natural compounds are an attractive research area because of their beneficial effects on human health and preventing degenerative disorders of aging for their antioxidant as well as antiaging activity. Different natural compounds are an attractive research area due to their beneficial effects on human health and the prevention for their antioxidant and antiaging activity of degenerative aging disorders. It will be interesting to see if such long-term exposure of different model organisms to natural plant molecules can guide to a variety of species that live longer than their predecessors.

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