

## Bioactive phytochemicals and aging in *Caenorhabditis elegans*

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### Abstract

Aging is a complex phenomenon, a sum total of changes that occur in a living organism with the passage of time and leads to decreasing ability to survive stress, increasing functional impairment and growing probability of death. Aging changes can be attributed to development, genetic defects, environmental factors, disease and an innate process- the aging process. Aging has been one of the most crucial menace factors for a number of socio-economic burdens, hence discovery of any new chemical that modulates aging in research model organisms could lead to a new strategy for working upon age related diseases like diabetes, cancer and neuro-degenerative disorders. The present review highlights the previous studies suggesting effective modulation of the life prolonging mechanistic pathways and lifespan by various phytochemicals. The free living nematode *Caenorhabditis elegans* is a well established multicellular model organism for aging in biological research, being used by different laboratories worldwide. The enormous characteristics of this animal model that has contributed to its success includes its genetic pliability, invariant and fully described developmental program, well characterized genome, ease of maintenance, short and fertile life cycle and small body size. Being a multicellular organism it goes through a complex developmental process, including embryogenesis, morphogenesis to grow into an adult so, any biological information from *C. elegans* may be directly linked with more complex organisms, such as human. The reports on life span extension on exposure to plant based compounds clearly depicts that aging can be slowed down and thus makes life span extension an interesting area for research. This review summarizes the current understanding on interaction of phytochemicals with signalling pathways of aging that provides potential application in human health improvement and development of anti-aging therapeutics.

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### Introduction

Medicinal and Aromatic Plants (MAPs), a rich repository for enormous bioactive phytochemicals in the form of their secondary metabolites have been used for decades in traditional system of medicine in the form of drugs, antioxidants, flavours, fragrances, dyes, insecticides, pheromones etc. by more than 80% world population [1]. In the recent years, a resurgence of the use of herbal drugs has once again been witnessed prominently, firstly because the synthetic

drugs have been found to be hazardous in many cases, and secondly because of the growing social awareness for the side effects associated with synthetic drugs. The world market for herbal medicines is growing at an annual rate of 10-15% and consequently, the current global herbal drug market has reached a level of US \$62 billion, which is expected to grow to US \$5 trillion by the year 2050 [2]. This immense importance of natural molecules has reallocated the unearthing of enormous phytochemicals (approximately one lakh) and almost 4,000 new

bioactives are being discovered every year from a variety of plant species [3, 4]. Presently these bioactives from different MAPs have gained much more significance and have become the foundation stone for the development of novel drugs for various ailments. Furthermore these bioactive phytochemicals also hold a promising field in perfumery, nutraceuticals, food and flavour industries owing to the growing social awareness about the risks involved in synthetic components in parallel products. This is an indication of a possible growing demand for plant-derived drugs in coming years [5]. The use of plant species and their active molecules for human healthcare cannot be avoided due to their low concentration and no side effects. The use of phytochemicals as food supplement has not only increased the quality of life but also reduced the human healthcare cost.

In general bioactive compounds or phytochemicals are secondary plant metabolites having pharmacological or toxicological effects in man and animals and have no significant role in plant primary metabolism [6]. Secondary metabolites are produced within the plants along with the primary biosynthetic routes of compounds aimed at plant growth and development, such as carbohydrates, amino acids, proteins, and lipids [6]. Thus secondary metabolites can be regarded as products of biochemical “side tracks” in the plant cells and not needed for daily functioning of the plant but hold important functions in plant defences against various types of stresses [6]. The important secondary metabolites include bioactives like flavonoids (protecting against free radicals), terpenoids (attract pollinators and inhibit competing plants) and alkaloids (defense from predators) [7]. Few plant secondary metabolites also play major role in cell signalling and metabolic pathway engineering [6]. Thus, plants producing bioactive compounds seem to be the rule rather than the exception serving as the warehouse for bioactive phytochemicals. Relationship between the bioactive phytochemicals intake and health has been an area of active exploration. Initially much of research was focussed on antioxidant activities of bioactive phytochemicals (Vitamin A, Vitamin E etc.) and their ability to prevent free-radical induced tissue damage [8]. The modern researches have proved that consumption of bioactive phytochemicals rich diet

(alkaloids, flavonoids, polyphenols etc.) reduces the risk of developing chronic disorders with ageing [9]. Evidences are growing that such bioactive phytochemicals may help to promote optimal health, slow down the ageing process and simultaneously reduce the risk of chronic diseases such as cancer, coronary heart diseases, and neurodegenerative disorders [9, 10]. The present review focuses on the major classes of bioactive phytochemicals with potential anti-ageing activities using the soil nematode *Caenorhabditis elegans* as the multicellular model system however, we will also highlight studies on other model system including rodents and humans that support role of phytochemicals in modulating aging.

Ageing is the single largest risk factor influencing various chronic diseases and is consequently responsible for enormous societal and economical burden. The resulting need to understand and alleviate age-related decline has led to pharmacological manipulation of age-related degeneration in several species like *Saccharomyces cerevisiae* (yeast), *Drosophila melanogaster* (Fruit fly), *Mus musculus* (rodent) and (Nematode) *Caenorhabditis elegans* [11]. The nematode *C. elegans*, is a valuable model for studies of aging and age-related disorders [12] owing to its short 3-week life span, easy culture conditions and rapid generation time [13]. Additionally, its rapid growth and high fecundity make *C. elegans* well suited for high-throughput chemical screens. The organism’s relative simplicity and the wealth of knowledge of its biology, along with the large number of available genetic tools, make it an attractive organism for pharmacological research. Bioactive compounds that slow down the ageing process are highly sought after due to their potential for treating age related diseases. Although translation of life span extension from worms to human is unknown, substantial experimental evidence suggest that life span extending phytochemicals are useful in treatment of various neurodegenerative diseases [14, 15].

*C. elegans* is a multicellular eukaryote sharing its cellular, molecular and biochemical features with higher organisms. *C. elegans* is easy to maintain in the laboratory (in Petri dishes) and has a fast and convenient life cycle [11]. Embryogenesis occurs in about 12 hours, development to the adult stage occurs in 2.5 days, and the life span is 2-3 weeks. The development of *C. elegans* is known in great detail

because this tiny organism (1 mm in length) is transparent and the developmental pattern of all 959 of its somatic cells has been traced [13]. The life cycle is temperature-dependent. *C. elegans* goes through a reproductive life cycle (egg to egg-laying parent) in 5.5 days at 15°C, 3.5 days at 20°C, and 2.5 days at 25°C [13]. *C. elegans* eggs are fertilized within the adult hermaphrodite and laid a few hours afterward--at about the 40 cell stage [13]. Eggs hatch and animals proceed through 4 larval stages, and produce about 300 progeny at adulthood [13]. It goes through a complex developmental process, including embryogenesis, morphogenesis, and growth to form an adult. Thus, the resultant biological information from *C. elegans* may be directly applicable to more complex organisms [11, 13].

Various theories of aging have been proposed in past and some of them have been widely accepted which comprises well recognized Harman's free radical theory, Telomere shortening theory, Hayflick limit theory, mitochondrial decline theory and DNA damage theory [16-20]. Although many theories have been proposed focussing on phenomenon of aging but no single theory is able to account for all aspects of aging. Previous decade have been dedicated to investigation of mysterious world of longevity and aging where gerontologists have attempted to investigate aging mystery. With advent of various discoveries in field of bio-gerontology multiple cellular signalling pathways found to regulate phenomenon of longevity [13]. The discovery of single mutation in insulin signalling pathway (IGF-1/IIS) mediating lifespan extension suggested genetic manipulation directly or indirectly can regulate aging in organisms [13]. Presently, various genes and genetic mutation found to have effect on lifespan. The genes effecting lifespan in various organisms are found to be homologous to humans. Altogether it can be concluded that these genes directly or indirectly regulate lifespan by modulating cellular stress response, metabolism, growth and metabolism [13]. Furthermore, numerous phytochemicals interact with these genes regulating multiple cellular signalling pathways playing important role in lifespan extension and delaying aging [11].

## Multiple cellular signalling pathways effecting aging

The discovery of single gene mutation in insulin growth factor (IIS) in *C.elegans* has led to identification of various genes which modulate lifespan [13]. Apart from insulin signalling pathway various other pathways are found to regulate lifespan in various organism. The interaction of these pathways systematically regulates stress response, oxidative stress level and cellular redox homeostasis effecting lifespan. The disruption of cellular balance affecting these cellular signalling pathways leads to aging and age related pathologies [13].

## Intracellular reactive oxygen species (ROS) and oxidative stress

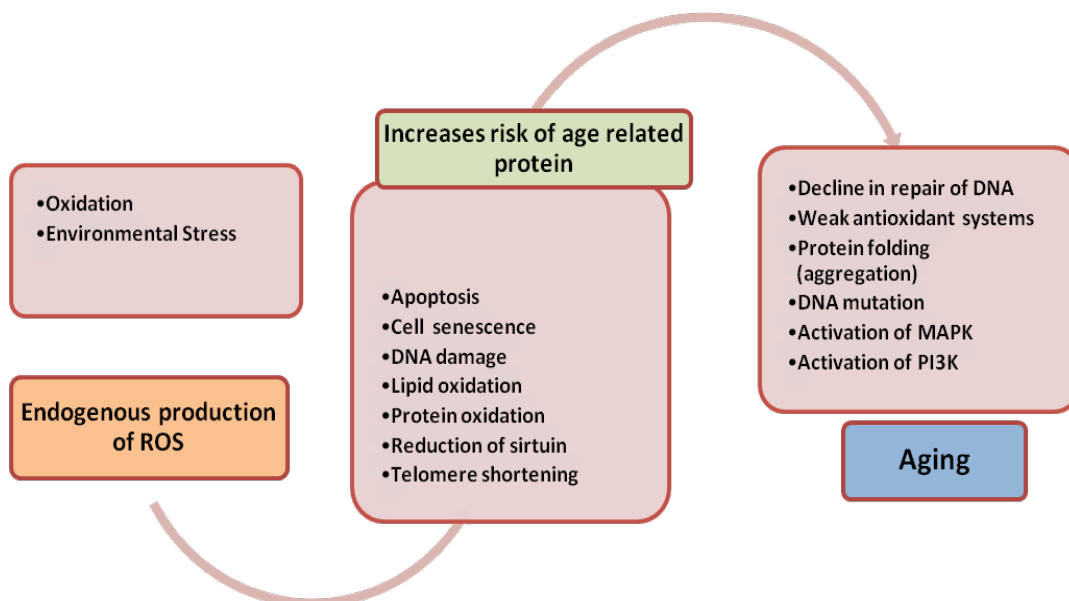
The progressive increase in intracellular ROS level with various metabolic activities occurring within the cell leads to enhanced oxidative stress effecting overall cellular health. The accumulation of intracellular ROS leads to oxidative damage of cell increasing morbidity and mortality. The Harman's free radical theory suggests increment in various cellular metabolic activities leads to increment in free radical levels and oxidative damage which leads to cellular death [17]. The antioxidant defence network counteracts with ever increasing intracellular ROS remediate deleterious effect of ROS induced oxidative stress. The cell system synthesizes cellular enzymes like superoxide dismutase (SODs), glutathione peroxidase (Gpx) and catalases (CAT) which regulates oxidative stress level [21]. In general the intracellular ROS is synthesized by mitochondrial processes, peroxisomes and cytoplasmic enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) as an outcome of various metabolic activities [17]. The mitochondrial electron transport chain (ETC) plays key role in ROS accumulation as it is considered as primary source of intracellular ROS [17]. The accumulation of intracellular ROS mediating oxidative stress is counterbalanced by antioxidant cellular enzyme defence system. The progression in age disrupts balance between ROS production and antioxidant enzyme levels effecting cellular redox homeostasis. The previous studies

demonstrated link between oxidative stress, mitochondria and lifespan.

The single gene mutation in *clk-1* gene encoding protein necessary for biosynthesis of coenzyme Q resulted in increment in lifespan by 40% in *C.elegans*, whereas, the up regulation of *clk-1* shortens lifespan in *C.elegans* [22]. The similar deletion in mouse model also demonstrated lifespan extension. Additionally, mutation in iron sulphur protein (ISP-1) of complex III mediated lifespan extension in *C.elegans* [23]. In contrast the mutation in *ctl-1* gene which encodes for cytosolic catalase enzyme have decrease in lifespan by 25% and the up regulation of catalase leads to reduced oxidative stress level and longevity [23]. The mechanism behind lifespan extension involving role of mitochondrial pathway still remain elusive but the mutation in genes involved in electron transport chain plays key role in managing oxidative stress level and lifespan extension [23]. The mitochondrial dysfunction has been associated with progression in age by previous researchers [24]. The increment in oxidative stress level due to various physiological and environmental factor leads to mitochondrial DNA damage (mtDNA) in age dependent manner [24]. The increment in intracellular ROS leads to mitochondrial dysfunction disrupts mitochondrial biogenesis, ATP synthesis and finally cellular death [24] (Fig. 1).

### Insulin signalling Pathway (IGF/ IIS)

In the roundworm *Caenorhabditis elegans*, mutations in the insulin-like signalling pathway extend adult lifespan [11] and are associated with up-regulation of stress response genes including those for heat shock proteins (HSPs). Insulin-like signalling is mediated by the receptor protein DAF-2 and mutation of the *daf-2* gene doubles worm lifespan [25-30]. Mutation of the downstream *age-1* gene, which encodes a protein similar to the mammalian p120 catalytic subunit of phosphatidylinositol 3-kinase, leads to a 65% increase in mean lifespan [31-33]. These effects depend on the integrity of the protein DAF-16, which has similarity to a family of mammalian fork head transcription factors [26-28, 34 and 35]. The components of insulin signalling pathway are well studied in *C.elegans* and overlap with other organisms like *Drosophila*, rodent and mammals [13]. Mammals possess different receptors with overlapping functions for insulin and IGF-1 that regulates the mammalian metabolism. An insulin-like signalling pathway also influences aging in *Drosophila* [36, 37].



**Figure 1.** Factors responsible for generation of ROS and other cellular changes promoting ageing in worms

In the mouse, loss of a single copy of the *igf1r* gene (encoding the insulin-like growth factor type-1 receptor) results in a 26% increase in lifespan [38] and knockout of the insulin receptor specifically in adipose tissue increases lifespan by 18% [39]. The FOXO family of transcription factors play key role in maintaining cellular redox homeostasis by transcribing genes involved in glucose metabolism regulation (glucose-6-phosphatase), maintain energy homeostasis (Agouti-related peptide; AgRP, neuropeptide Y; NPY), detoxification of ROS (catalase and MnSOD), apoptosis (Bim and Fas ligand), autophagy (light chain-3; LC-3, autophagy related gene; Atg) and DNA repair (growth arrest and DNA damage inducible gene 45a; GADD45a) [40]. Similarly, the search for “ageing genes” has shown *Fox1* and *Fox3* gene variants to be associated with long life [41]. The complex interaction of sirtuin and Fox proteins has been investigated in many species, including humans. But it is still not known whether these proteins actually increase or reduce the longevity of mammals as apoptosis and senescence are essential requirements for cancer suppression. The insulin signalling plays important role in nutrient and stress sensing. The functional overlap between Jun N-terminal kinase (JNK) and AMP-activated protein kinase (AMPK) pathway modulate lifespan [42]. The stress mediated activation of JNK is known to regulate FOXO in organisms. The energy sensing AMPK directly phosphorylates FOXO promoting stress resistance and lifespan extension in *C.elegans*.

### Dietary restriction pathways

Nutrient sensing pathways regulate lifespan in different organism. The restriction of nutrient without causing malnutrition alleviates oxidative stress and extends lifespan in organisms [13]. The previous researches have identified lifespan extension due to dietary restriction regime. Various pathways interact with each other and modulate lifespan by controlling cellular stress response. These nutrient sensing pathways include IGF, TOR, AMPK and SIRT1 [13]. The up regulation of AMPK extends lifespan in *C. elegans* [42]. The AMPK senses energy deprivation like in case of lowered ATP or exercise induced hypoxia. It is also known to regulate activity of FOXO

and extends lifespan in *C.elegans* in DAF-16 dependent manner based on caloric restriction [43]. Another nutrient sensor and growth regulator is mTOR which controls lifespan in organism. The mTOR contributes in aging via protein synthesis, ribosome biogenesis, metabolism and autophagy. It is a serine/ threonine kinase which is highly conserved in yeast, *Drosophilla*, *C.elegans* and humans. The loss of function in TOR leads to lifespan extension in *C.elegans*, *Drosophila* and mice [44, 45]. The silent information regulator (*Sir 2*) is highly conserved protein deacetylases firstly identified in yeast and found to extend lifespan in yeast, *C.elegans* and *Drosophila* [13]. The SIRT1 is a key mediator in dietary restriction mediated longevity. Previous studies suggest it plays major role in nutrient sensing and regulating energy metabolism triggering stress response at transcriptional level. SIR-2.1, the histone deacetylase is widely known to modulate lifespan during DR and enhance stress resistance [46]. The stress tolerance and lifespan modulating effects via dietary restriction are mediated by sirtuins, which function as NAD<sup>+</sup>-dependent deacetylases [46]. The SIR-2.1 maintains cellular stress level and regulates heat shock response playing key role in longevity [47]. Another transcription factor HSF-1 known to play key role in longevity mediated by DR. Thermotolerance is a key feature of DR response and *hsf-1* plays key role in maintenance of cellular stress response essential for DR induced lifespan extension [47] (Fig. 2).

### The natural dietary bioactive phytomolecule: an emerging anti-aging therapeutics

The use of natural compounds and their derivatives has emerged as one of the alternative forms of medicine. As ageing is emerging as a major problem of today's world hence, anti-ageing compounds without side effects are need of hour. Numerous phytochemicals have been reported for their therapeutic effects without compromising the quality of life [48]. There is considerable interest in finding anti-ageing bioactive compounds from the huge reservoir of natural herbs.



**Figure 2.** Increased/Decreased cellular signaling response promoting longevity in *C. elegans*

The advancement in field of biogerontology unravels various multiple cellular signalling pathways and genes controlling lifespan [13]. The discovery of elicitors of lifespan extension has led to development of antiaging research. In recent years, several bioactive phytochemicals have been reported for their anti-ageing activity in *C. elegans* and due to higher homology of *C. elegans* with mammals these bioactive phytochemicals find their pharmacological application in mammals too [11]. Many of these bioactive phytochemicals directly or indirectly influence the aging in organisms and found to have protective effect against age related cellular stress [11]. These natural molecules alleviate age related pathology by targeting longevity promoting signalling pathways involving nutrient sensing and maintenance of mitochondrial redox homeostasis. These natural molecules extend lifespan and reduce age related pathologies [11]. The molecular mechanism and interaction of some selected natural bioactive phytochemicals (Table 1) are described below.

**Table 1.** Major bioactive phytochemicals associated with anti-aging activity

Bioactive phytochemical	Molecular formula	Source	Antiaging activity	Reference
Resveratrol	C <sub>14</sub> H <sub>12</sub> O <sub>3</sub>	Grapes, mulberries blueberries, and raspberries	Oxidative stress reduction, Chemo-protective, sir-2.1 regulation of ER stresses response.	66, 69, 71, 72
Curcumin	C <sub>21</sub> H <sub>20</sub> O <sub>6</sub>	Turmeric ( <i>Curcumin longa</i> )	Antioxidant, Modulation of Protein and lipid peroxidation, stress reduction	80, 81, 82
Epigallocatechin gallate	C <sub>22</sub> H <sub>18</sub> O <sub>11</sub>	White tea, Green tea and black tea	Neuroprotection, ROS scavenging, upregulation of stress response genes.	83, 87, 89
4-hydroxy-E-globularinin (4-HEG)	-	<i>Premna integrifolia</i>	ROS detoxification and induction of stress response	101
Beta-caryophellene	C <sub>15</sub> H <sub>24</sub>	Essential oil of Cannabis, Clove, oregano, <i>Ocimum basilicum</i>	Dietary restriction, Modulation of cellular stress response	102
Reserpine	C <sub>33</sub> H <sub>40</sub> N <sub>2</sub> O <sub>9</sub>	<i>Rauwolfia serpentina</i>	Neuroprotection and stress modulation	106
Harmene	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub>	Coffee	Modulation of innate immune response and lifespan extension	108
Allyl isothiocyanate	C <sub>4</sub> H <sub>5</sub> NS	Mustard, radish, horseradish, and wasabi.	Chemoprotection, anti-carcinogenic and ROS detoxification	109, 112, 113, 114

### Polyphenols

Polyphenols are abundantly found in berries, green tea, chocolate, apples and citrus fruits such as oranges, grapefruits, and lemons. Polyphenols (Polyhydroxyphenols) derive their name from the Greek word "Polus" meaning "many, much"; the word phenol refers to a chemical structure formed by attaching a hydroxyl (-OH) group to an aromatic benzenoid (phenyl) ring and thus consist of the structural class of chemicals characterized by the number of phenol structural units [49]. Polyphenols are one of the most significant secondary metabolites exhibiting natural antifungal, antibacterial, antiviral, and antioxidant (1-3) property [49]. They are generally involved in defence against ultraviolet radiation or aggression by a variety of pest and pathogens [49]. In recent years, there has been much interest in the potential health benefits of dietary plant polyphenols as antioxidant [49]. Recent epidemiological studies and associated meta-analyses strongly suggest that long term consumption of diets rich in plant polyphenols offer protection against ageing and age related chronic disorders such as development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases etc. [49]. Polyphenols contribute bitterness, astringency, colour, flavour, odour, and oxidative stability and are naturally found in the fruits, vegetables, cereals, and beverages [49]. Fruits like grapes, apple, pear, cherries etc. contain high amount (2-3 mg/g fresh weight) of polyphenols [50]. There are approximately 8,000 polyphenolic compounds derived from various plant species have been identified [50]. Broadly they occur in conjugated forms, with one or more sugar residues or other organic compounds linked to hydroxyl groups [51]. Polyphenols can be classified either on the basis of number of phenol rings or on the basis of structural elements that bind these rings into various groups [51]. This class of compound includes anthocyanins, catechins, flavanones, flavones, flavonols and isoflavones [51]. Flavonoids belong to subgroup of polyphenolic plant compounds. This class of compound possess potent biochemical and pharmacological properties which can be attributed to their antioxidant and free radical scavenging potential [50]. Flavonoids modulate an energy-intensive stress

response and repair system that results in reduced body length and an enhanced lifespan of *C.elegans* [29]. Some common dietary flavanones include the compounds such as hesperetin, naringenin, eriodictyol, daidzein, genistein and glycitein found chiefly in soybeans and other legumes [53, 54]. The antioxidant properties are responsible for scavenging of increasing intracellular ROS responsible for cellular oxidative stress [54, 55]. The health benefits of fruits, vegetable and herbs can be attributed to this plant secondary metabolite. The extract of *Ginkgo biloba*, apples, onions, red wine and tea are rich in flavonoids like Quercetin [56]. Quercetins have neuroprotective, anti-cancerous and chemoprotective properties [56]. Most of these properties are linked to its strong antioxidant potential of quercetin, additionally it is also known to modulate the expression of specific enzymes attributed to an inhibitory action on protein kinases and to a regulatory influence on gene expression [56]. The studies on cell culture system also demonstrated protective effects of quercetin observed as reduction in DNA strand break and apoptotic cell death due to oxidative stress [57]. Furthermore, quercetin also demonstrated intracellular ROS scavenging, reduced aggregation of lipofuscin and thermotolerance in *C.elegans* [58, 59]. Lipofuscin is the known as ageing biomarker which accumulates as a result of oxidative degeneration of cellular components [60]. This bioactive phytomolecule prolongs lifespan with enhanced stress resistance in *C.elegans* by translocating DAF-16 into nucleus [58]. It also demonstrated extended lifespan in oxidative stress prone and glucose treated *mev-1* mutant of *C.elegans* [61]. These antiaging and protective effects of quercetin can be attributed to up regulation of the phase II metabolism enzyme GST-4 (glutathione S-transferase) [58, 59]. Green tea and tea is known to provide health benefits due too presence of compounds like catechins, epigallocatechin-3-gallate and theaflavins [62]. The senescence accelerated mouse (SAM) model for spontaneous aging and age related disorders demonstrated improved learning and memory with reduction in beta-amyloid (Ab) accumulation on catechin treatment [63]. The green tea catechins reduced protein carbonyl levels in aging brain of mouse. The three black tea molecules

theaflavins, theaflavin 3-*O*-gallate, theaflavin 3'-*O*-gallate, theaflavin 3, 3'-di-*O*-gallate and thearubigins interact with insulin signalling pathway (insulin/IGF-1) modulating action of FOXO1a and PEPCK [64]. Myricetin is another naturally occurring flavonol found in many plant based food sources extends lifespan in *C.elegans* with nuclear translocation of DAF-16 [57, 65]. Some widely studied antiaging polyphenols are described below.

### **Resveratrol**

Resveratrol (3, 5, 4-trihydroxy-trans-stilbene) is a stilbenoid phytoalexin providing plant defence against bacterial and fungal attack from the group of phenol [66]. The skin of red grapes and other fruits are rich in resveratrol [66]. It can be synthesized chemically and with the help of metabolically engineered microbes. It has a number of biological activity varying from anticoagulant [67], anti-carcinogenic [68], anti-ageing [69] to suppressor of oxidative DNA damage [70]. The health benefits of resveratrol are primary focus of many human and animal studies. Several experiments suggest that it triggers mechanisms that counteract aging-related effects in animals. It has been previously reported that resveratrol significantly extends the lifespan in yeast "*Saccharomyces cerevisiae*", *D. melanogaster* and *C. elegans* [69, 71, and 72]. It was suggested that lifespan extension involves a similar mechanism to that of dietary restriction involving the reduction of accessible nutrients and extending lifespan varying from yeast to mammals [13, 46].

### **Curcumin**

Curcumin (curcuminoid) is isolated from the rhizome of the common and popular Indian spice turmeric (*Curcuma longa* L.) from family *Zingiberaceae* [75]. The wound healing properties of curcumin are well known and it also used in traditional therapeutics for treating a variety of disorders viz. stomach dysfunction, flatulence, dysentery, ulcers, jaundice, arthritis, sprains, wounds, skin and eye infections [75]. Recently it has gained the attention as a non steroidal, anti-inflammatory drug with chemopreventive anti-carcinogenic, and antioxidant properties [76-78]. Curcumin works as a promising bioactive compound in cancer therapy due to its

strong inhibition activity against tumor formation, promotion, progression, and dissemination [79]. Curcumin has a potent antioxidant effect (eight times greater) than vitamin E [80] and thus is highly effective in preventing lipid peroxidation [80]. Recently the role of curcumin as anti-aging and antioxidant nutraceutical has been authenticated in *D. melanogaster* [81]. It has been reported that curcumin is able to increase lifespan in *C. elegans* through protein homeostasis modulation [82]. It was reported that genes such as *osr-1*, *sek-1*, *mek-1*, *skn-1*, *unc-43*, *sir-2.1*, and *age-1* play key role in curcumin mediated longevity in *C. elegans* [82].

### **Epigallocatechin gallate**

Epigallocatechin gallate (EGCG) is the ester of epigallocatechin and gallic acid. It is the main key ingredient of green tea [83]. Tea catechins are characterized by the di- or tri-hydroxyl groups on the B-ring and the meta-5, 7-dihydroxyl groups on the A ring [83]. EGCG has potent antioxidant activities due to the presence of phenolic groups that are sensitive to oxidation and able to produce quinine [83]. The trihydroxyl structure in the D ring of EGCG increases its antioxidant activity [83]. EGCG has been recognized as a potent neuroprotective agent [84] having free radical scavenging activity that protects from the oxidative damage [85]. Apart from these activities, EGCG also has iron-chelating and attenuation of lipid peroxidation capabilities [86]. EGCG has various biological activities and is used in the treatment of several disorders viz. cancer, atherosclerosis, diabetes, virus infection, and neurodegenerative diseases such as Parkinson and Alzheimer disease [83]. The anti-aging effect of EGCG has been explored in *C. elegans* [62, 87]. In stressed conditions, EGCG provides strong protection and extends the longevity of *C. elegans* by scavenging reactive oxygen species. In genetic analysis EGCG can up-regulate the expression of stress-resistance associated genes such as *sod-3*, *daf-16*, *skn-1*, and *hsp-16.2* [87]. The lifespan extending activity of EGCG might be due to its ROS scavenging or up-regulation of antioxidant genes [88, 89].



### Terpenoids

Terpenoids is found in natural sources such as plant leaves, flowers and fruits. Terpenoids are bioactive phytomolecules made up of isoprene (C<sub>5</sub>) units. Based on the number of isoprene units, they are classified as monoterpenes (C<sub>10</sub>), sesquiterpenes (C<sub>15</sub>), diterpenes (C<sub>20</sub>), triterpenes (C<sub>30</sub>), carotenes (C<sub>40</sub>), polyterpenes (C<sub>n</sub>) [90, 91]. The carotenes present in pumpkins and carrots, limonene and menthol present in oils of cherries, grapes, apricots and citrus fruits, saponins from leguminous plants and isothiocyanates belong to this class of bioactive phytomolecule [92]. The metabolic pathology and increment in lipid peroxidation enhance oxidative stress which is associated with aging [93]. The supplementation of d-limonene ameliorates pancreatic and metabolism related pathology in rats by reducing lipid peroxidation rate with up regulation of phase II enzymatic activity [94]. Another terpene menthol interferes with RANKL signalling and inhibits osteoclastogenesis which is commonly observed with progression in age [95]. The major component of vitamin A i.e. retinoic acid which is a diterpene alleviates age related macular degeneration and modulates glucose metabolism by activating AMPK signalling [96]. The retinoic acid promotes neuronal regeneration which is a major concern as aging is often associated with neurodegeneration which leads to various cognitive disorders [96]. Ferulsinic acid (member of class of sesquiterpene “coumarins”) attenuates lipid peroxidation, intracellular ROS formation, carbonyl production, formation of AGEs mediating lifespan extension in *C.elegans*. An iridoid, 10-O-trans-p- Coumaroylcatalpol (OCC), a major ingredient of *Premna integrifolia* Linn. alleviate age related  $\alpha$ -synuclein aggregation and modulate oxidative stress levels promoting longevity in *C. elegans* via DAF-16 activation [98]. The  $\alpha$ -synuclein aggregation is associated with age related neurodegenerative disorder Parkinson’s disease [98].

### 4-hydroxy- E-globularinin

4-hydroxy- E-globularinin (4-HEG) is an iridoid which consist of a cyclopentane ring fused to a six-membered oxygen heterocycle. This class of compound play important role in plant defence system and traditionally used in the treating hepatic

dysfunction, stimulation of bile acid excretion and tumours due to its high antioxidant and anti-inflammatory activities [99, 100]. Recently the antiaging activity of 4-HEG has been reported in *C. elegans* [101]. The study exhibited activation of an endogenous ROS detoxification pathway and several stress-inducible genes, viz., hsp-16.2 and sod-3 by 4-HEG [101]. The nuclear localization of DAF-16 and its up regulation were responsible for the 4-HEG-mediated longevity in *C. elegans* [101].

### Beta-caryophyllene

Beta-caryophyllene (BCP) is a natural bicyclic sesquiterpene and is a FDA approved food additive, found as an active ingredient in essential oils of numerous spices and edible plants. This bioactive phytomolecule possesses a wide range of biological activities like anti-oxidant, anti-inflammatory, anti-cancerous and local anaesthetics actions [102]. BCP was able to modulate lifespan and stress level in *C.elegans*. The administration of BCP resulted in decline of intracellular ROS level and enhancement in stress tolerance. The intake of BCP reduced aggregation of age pigment lipofuscin in *C. elegans*. BCP act as dietary restriction mimetic as it interacts with genetic elicitors of dietary restriction like *sir-2.1* and *skn-1* [102]. BCP interacts with SIR-2.1, SKN-1, DAF-16 and mediates longevity promotion [102]. The dietary intake of this bioactive molecule intervenes with various cellular signalling pathways and modulates cellular stress response promoting lifespan extension [102].

### Alkaloid

The term “Alkaloid” coined by pharmacist Carl Meissner derived from Arabic word “*al-qali*” the plant from which soda was first isolated [7]. Alkaloids are pharmacologically active basic nitrogen atoms containing chemical compounds of plant origin. In addition to carbon, hydrogen, and nitrogen, alkaloids may also contain elements such as oxygen, sulphur, chlorine, bromine, and phosphorus [7]. Alkaloids have pharmacological effects and are used for therapeutic and recreational purposes as anaesthetic (cocaine), psychedelic psilocin (caffeine, nicotine), analgesic

(morphine), anti-bacterial (berberine), anticancer (vincristine), anti-ageing (reserpine), cholinomimetic (galantamine) etc [7]. Caffeine inhibits TORC1 and releases Rim15 extending lifespan in yeast cell [103]. This kinase cascade is evolutionarily conserved in most of the organisms, suggesting that caffeine may prolong lifespan in other eukaryotes, including man [103]. The alkaloids isolated from *Lycoris radiata* viz. galanthamine and haemanthidine and their synthetic derivatives 1,2-Di-*O*-acetyllycorine and 1-*O*-acetyllycorine mediates lifespan extension and attenuate  $\beta$ -amyloid aggregation reducing paralysis in transgenic *C. elegans* strain CL4176 [104].

### Reserpine

Reserpine is an indole alkaloid derived from *Rauwolfia serpentina*, is the first modern drug for hypertension treatment [105]. In traditional herbal medicine, the root is used in the treatment of cholera, snakebite, insanity, and hypertension. Reserpine irreversibly binds to the storage vesicles of neurotransmitters, particularly norepinephrine, serotonin, and dopamine [105]. Reserpine is used as a sedative and hypnotic for reducing blood pressure [106]. It shows antipsychotic and antihypertensive activity and has been used for the control of high blood pressure and for the relief of psychotic symptoms [106]. Reserpine treatment from embryo to young adult stage extended lifespan in *C.elegans* significantly [106]. As Reserpine is a FDA approved drug for hypertension it can be evaluated for lifespan extension in higher model organisms like mice and finally humans [106].

### Harmane

Harmane is the  $\beta$ -Carboline (9*H*-pyrido [3, 4-*b*] indole), also known as norharmane, is a nitrogen containing heterocyclic compound and is widely spread in plants and animals [107]. This molecule play important role act as benzodiazepine receptor agonists thus used as anxiogenic and memory enhancing drug [107]. This bioactive phyto molecule belongs to group of indole alkaloids consisting of pyridine ring fused to an indole skeleton [107]. The harmane was able to extend lifespan in *C.elegans* by modulating innate immune response [108]. The

nematode was infected with human pathogen the Shiga toxin-producing *Escherichia coli* O157:H7 strain EDL933 and several other bacterial pathogens and harmane treatment upregulated the expression of immune effector gene F35E12.5 [108]. The aging is correlated with compromised defence response against pathogenic infection and harmane prolonged lifespan during infection by modulating innate immune response [108]. The p39 MAPK pathway regulates the expression of F35E12.5 and innate immune response [108]. Harmane was able to modulate immune response thereby prolonging lifespan in *C.elegans* [108].

### Organosulphides

Organosulphides are sulphur containing organic compounds and are known for their peculiar foul smell [109]. These compounds found abundantly in cruciferous vegetables and are responsible for the pungent taste of garlic, onion, mustard, horseradish, wasabi, etc [109]. This naturally occurring phyto molecule possess medicinal properties which prevents platelet aggregation and cancer and are essential for normal functioning of living beings [109, 110, 111]. Organosulphides like allicin (ALI), diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) found in garlic are well recognized as chemopreventive agents [109, 111]. The organosulphides maintains cellular redox environment and known to induce apoptosis [112]. These compounds inhibit cancer proliferation by detoxification of carcinogenic agent and cancer cell growth owing to its antioxidant and anti-carcinogenic properties [109]. The dietary intake of diallyl sulphide demonstrated anti- carcinogenic effect and glutathione-dependent detoxification enzymes of female CD-1 mouse tissues [112]. The organosulphides include cardiovascular protective effects, stimulation of immune function, reduction of blood glucose level, radioprotection, improvement of memory loss, protection against microbial, viral and fungal infections, as well as anticancer effects [109]. The recent studies have demonstrated cancer inhibitory effects of organosulphides analogues *in vivo* in female CD-1 mouse tissues. [113]. The organosulphides modulates lifespan in *C.elegans*

promoting cellular ROS detoxification and longevity [114].

### *Allyl isothiocyanate*

Allyl isothiocyanate (AITC) is an organosulfur, colourless and oily bioactive having the chemical formula as  $\text{CH}_2\text{CHCH}_2\text{NCS}$  [110]. Isothiocyanates are widely found in various cruciferous vegetables viz. such as broccoli, cabbage, and cauliflower and mustard as the main source [110]. AITC induces phase II detoxification cascade *in vitro* and *in vivo* defending mammalian cells against oxidative damage [115]. This bioactive molecule extends lifespan in *C.elegans* by stimulation phase II detoxification and cellular defence system [115].

### Conclusions

After several years of waning enthusiasm towards herbal medicines interest in bioactive phytomolecule based therapeutics for age and age related disorders is suddenly on upswing. This area got boost with advancement in field of biogerontology and discovery of bio-active phytomolecules promoting longevity and stress tolerance [11]. The gerontologists are deploying a range of model organisms in solving the aging mystery and anti-aging effect of phytomolecules [13, 46]. The ultimate focus is on lifespan and multiple cellular signalling pathway modulation using dietary interventions. Earlier achieving longevity dividend was elusive but advancement in aging research has revived optimism in dietary intake of bioactive phytomolecules that can attenuate age-related declines in various physiological and functional indices. The discoveries demonstrating natural phytomolecules (EGCG, resveratrol, curcumin, quercetin and reserpine etc) and their dietary intake can modulate lifespan and stress level in range of model organisms can be utilized for development of anti-aging therapeutics [11]. These plant based bioactive molecules not only alter stress level and lifespan but also play role in maintenance of vitality of later life health [Table 1]. Some phytomolecules mediates lifespan extension by dietary restriction while some modulates cellular redox response [11]. The dietary intake of these plant based molecules in humans can be an alternative to chemically synthesized drug

having various side effects. These molecules can prove an option for treating age related chronic disorders like cardiovascular and neurodegenerative diseases [11]. The studies determining complex realm of interactions between genetic factors, nutrients and potent antiaging phytomolecule can identify genetic factor and metabolic pathways targeted by these phytomolecule. These results of previous studies provide insights of phytomolecules gerontological research exploiting *C. elegans* as a model system [11]. The higher homology of *C. elegans* to human analogues makes these studies significant as dietary intake of these bioactive phytomolecules can have similar effects on average lifespan of human beings, which can be subjected to future investigations.

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