AGEING AND POTENTIAL ANTI-AGING PHYTOCHEMICALS: AN OVERVIEW

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ABSTRACT
This is the era, which aggressively corroding the life style, mental ability, discretion, semblance of humans. Today every human being wants to post-pone his/her ageing and different theories have been given time to time for aging. Regarding this many products are present in market, synthetic as well as natural molecule. Now days it is recommended to highly involved in anti-aging properties of Pharmacophore/phytochemicals of natural origin. This is because these phytochemicals have less side effects comparison with synthetic one and more easily trustable to human beings. The researchers are efficiently involved in assaying anti-aging procedures with different animals using different photochemical as well as their extracts and also study done at molecular level. Most of the study concluded that the Pharmacophore which contain large numbers of –OH group (Polyphenols) have greater property of anti-aging than having less numbers of –OH groups.

KEYWORDS: Ageing; anti-ageing, animal models, phramacophore; molecular ageing theory, phytochemicals.

INTRODUCTION
Aging is a natural phenomenon that affects the entire physiology of an organism. It is the accumulation process of diverse detrimental changes in the cells and tissues with advancing age. It can also be defined as an increase in the probability of death. Healthy aging (a late onset of disease) is associated with longevity. For example, centenarians’ peoples show
significant delay in the onset of age-related diseases, including cardiovascular disease, type 2 diabetes, cancer and Alzheimer's disease (AD). In other words, those who live longer are healthier and *vice versa*. \(^{1,2}\)

Many theories of aging have been proposed and some of the most widely accepted including DNA or genetic theory, free radical theory, neuroendocrine theory, membrane theory, Hayflick limit theory, telomerase theory and mitochondrial decline theory. Various phytochemicals obtain from different species have been proved for their anti-aging properties and prolonging life-span. In anti-aging research, caloric restriction (CR) is most widely accepted for health improvement and life-span extension. \(^3\) Many accelerating factor involved in ageing process (Figure No. 1).

### Causes of Aging

There are many causes of ageing such as metabolic damage, cellular senescence, cellular death and toxic and non-toxic garbage accumulation (Figure No. 1). Metabolic damage includes glycation, \(^4\) mitochondrial damage (somatic mitochondrial DNA) and respiratory chain dysfunction. Mitochondrial dysfunction automatically generates free radicals, highly responsible for ageing. Respiratory chain dysfunction accumulates different types of ageing phenotypes. \(^5,6\) Cellular senescence is irreversible cell cycle growth arrest and or irregular cell generation. Senescent cells never re-inter the cell cycle, so senescent cells proliferates tumor cells. \(^7,8\) Most of the cause of senescence is due to induction of tumor suppression genes *p53* and *p19Arf*. Another cause of senescence is *Skp2* E3-ubiquitin ligase act as proto-oncogene and induces cancer. \(^9\) Cellular senescence and cellular death induced by inflammation with chronic cell death including DNA, \(^10\) telomerase shortening, \(^8,11,12\) declining and inadequate anti-oxidant system, \(^13,14\) declining and inadequate DNA repair and autophagy, \(^15\) defective cell cycle control, \(^16\) defective proteasome, lysosomes and shock

![Figure No. 1 Factor Involved in Ageing Process.](image)
proteins. \cite{4,17,18} The atherosclerotic and amyloidal plaque, \cite{19} advanced glycation end products, \cite{20} cortisol, \cite{21} and lipofuscin \cite{22} are the garbage accumulated in body tissue and major cause of ageing (Figure No. 2).

![Figure No. 2 Causes of Aging Process.](image)

**Types of Aging Process**

The two major classifications of aging are ‘programmed aging’ and ‘wear and tear aging’.

**Programmed Aging**

This would be aging due to something inside an organism's control mechanisms that forces elderliness and deterioration, similar to the way genes program other life-stages such as cell differentiation during embryological development or sexual maturation at adolescence.

**Wear and Tear Aging**

It is not the result of any specific controlling program, but is the effect of the sum effect of many kinds of environmental assaults \textit{i.e.}, damage due to radiation, chemical toxins, metal ions, free-radicals, hydrolysis, glycation, disulfide-bond cross-linking, etc. Such damage can affect genes, proteins, cell membranes, enzyme function, blood vessels etc.

**Aging of Skin**

Skin is the most outer part of the body which has direct contact with outer environment. In this era the pollution reaches very high and UV-rays are very prominent. It is commonly divided into "chronological aging" and "photo aging", with up to 80% of skin aging attributed
to photo aging in non-smokers. [23] Photo aging is due to ultraviolet (UV) light, which activates inflammatory cytokines and metallo-protein collagenases as well as inducing free radicals. Collagen and elastin (ELN) also cross-link in skin, resulting in a loss of elasticity. The protein keratin in fingernails is also a component of the outer layer of skin (epidermis), which provides "water-proofing". The epidermis thins with age, leading to wrinkles. [24]

**Modern Aspect of Aging and Theory**

Biologists define aging as the sum total of all changes that occur in a living organism with the passage of time and lead to a decreasing ability to survive stress, functional impairment and death.[25] The most common theories include mutation accumulation and antagonistic pleiotropy theory. The two theories posit that aging is due to pleiotropic genes with beneficial early-life effects but deleterious late-life effects (antagonistic pleiotropy) or mutations with purely deleterious late-life effects (mutation accumulation). [26] Besides, programmatic theory states that aging is a preordained process due to an inherent genetic program, played out at a rate characteristic of each species; this theory takes in consideration aging genes, cellular senescence, telomere shortening, and failure of apoptosis and longevity genes. [27] Stochastic theory, which states that random cumulative environmental damage to genes and proteins produces aging and homeostatic failure, takes in consideration oxidative stress (free radical damage), amino acid racemization and non-enzymatic glycolysation. [28]

**Klotho Enzyme and Aging**

Genetic level Studies on the Klotho enzyme in human denoted as **KL** gene or **Fgf23** gene. The **KL** gene was identified by. [29] Klotho protein exists in two forms: the transmembrane form expressed primarily in renal tubular cells and the secreted form circulating in the blood 2011.[30,31] In living organisms down-regulation of **KL** gene accelerates whereas up-regulation or over-expression of the same gene retards aging process.

**Target of Rapamycin (TOR) and aging**

TOR is the target of antifungal drug, Rapamycin, which is a secondary metabolite of soil bacteria against fungal growth competitors. It is a central growth controller naturally as well as functionally in human which conserved from different worms. [32] In response to different nutrients and growth factors mTOR with protein kinases pathway controls the growth and metabolism in mammals. Jia et al. in 2004 has reported in their work that there was arrest in larval stage in *C. elegans*, after mutation in gene/factor responsible for growth (raptor/daft-15). [33,34]
Molecular Aspect of Aging
Molecular chaperones are abundant, well-conserved proteins responsible for the maintenance of the conformational homeostasis of cellular proteins and RNAs. Environmental stress is a proteotoxic insult to the cell, which leads to chaperone induction such as heat shock protein (HSP) and stress protein. The protective role of chaperones is a key factor for cell survival and in repairing cellular damage. \[^{35}\] Ageing is associated with a decrease in the ability of cells with environmental challenges. This is due partly to the attenuation of a primordial stress response, the so-called heat shock (HS) response, which induces the expression of HSPs, composed of chaperones and proteases. \[^{36}\]

Calorie Restriction (CR) and Anti-Aging
The main aim of CR diet is to reduce the intake of calories to a level 20-40% lower than typical, while still obtaining all the necessary nutrients and vitamins. CR is also known as calorie restriction with optimal nutrition (CRON). CR may exert anti-aging effects by inhibiting the growth hormone (GH) or insulin like growth factor-1 (IGF-1) axis. \[^{37}\] On the basis of other research the anti-ageing effects of CR may involve through the stimulation of macro-autophagy and lysosomal degradation in plants due to shortage of nutrients.\[^{38}\]

Pharmacophore Based Molecular Mechanisms of Anti-Aging
Anti-aging is the demand of life. Any person in earth wants to immortal but none is such as. So in this regarding many of studies have been going on and different theories has been also given by researchers. But the exact mechanism, through which aging can tarry, is still anagogic and scientists are more attracted toward natural origin pharmacophore.

Elucidating the molecular mechanisms underlying this complex process remains a major challenge today. Most flavonoids possess anti-aging activity due to their pharmacophoric features. They contain enormous phenolic hydroxyl groups and oxygen-bridge or linkages which are responsible for antioxidant activity. Due to these pharmacophoric functional groups the compounds may possess anti-aging properties. Some terpenoids such as lycopenes, retinol and crocin possess antioxidant as well as anti-aging effects due to their isoprene structure in the heterocyclic ring. Aging process is controlled by a complicated and precise signaling network that involved in energy homeostasis, cellular metabolism and stress resistance. Some iso-flavonoids can produce their anti-aging properties through increase of collagen and ELN synthesis and decrease to metalloproteinase gene expression (anonymous).
An Antiaging and Regenerative Medicine Approach to Optimal Skin Health

The optimal health and appearance of the skin is the result of several factors: extrinsic aging (UV damage), intrinsic aging (genetics, lifestyle), and hormonal aging (primarily estrogen loss). By taking a functional approach to the evaluation and treatment of the skin, it is to elucidate the causation of the condition of the skin and provide targeted treatments to improve its quality. [39]

Pharmacophore Has Anti-Aging Property

Some pharmacophore having anti-aging property, compounds are following and chemical structures are shown in Figure No. 3.

Equol

Equol (7-hydroxy-3-[4-hydroxyphenyl]-chroman) is the major metabolite of the phytoestrogen. [40] It is a plant and soy-derived isoflavonoid with antiaging and antioxidant properties with potential human skin applications. As equol has been shown to mimic 17β-estradiol and bind specifically to 5α-dihydrotestosterone (5α-DHT). In quantitative polymerase chain reaction (qPCR) experiments, equol significantly increased collagen, ELN, and tissue inhibitor of metalloprotease and decreased metalloproteinases (MMPs) gene expression and caused significant positive changes in skin antioxidant and antiaging genes. In human monolayer fibroblasts cultures (hMFC), equol significantly increased collagen type I (COL1A1), whereas, 5α-DHT significantly decreased cell viability that was blocked by equol. Fluorescence activated cells scanning (FACS) analysis showed equol and 17β-estradiol significantly stimulated COL1A1, collagen type III (COL3A1), and ELN while MMPs were significantly decreased compared with control values. [41] Besides, another in vivo experiment strongly support that equol have strong antioxidant action against acute UV-A (320-400 nm) induced lipid peroxidation of mouse skin, this property accounting for its anti-photo aging mechanism. [42]

Oleuropein and Hydroxytyrosol

The main active constituents of olive oil include oleic acid, phenolic constituents, and squalene obtained from Olea europaea. The main phenolic compounds, hydroxytyrosol and oleuropein, contain extra-virgin olive oil (EVOO) having bitter and pungent taste. EVOO (i.e. the juice derived from the first cold pressing of the olives without any further refining process) naturally contains high levels of phenolic compounds associated with the health benefits derived from consuming an EVOO-rich Mediterranean diet, which have ability of an
EVOO-derived crude phenolic extract to regulate fibrogenic and oncogenic epithelial-mesenchymal transition (EMT) in vitro. Members of the seco-iridoid family of complex polyphenols, namely oleuropein aglycone, the bitter principle of olives and its derivative decarboxymethyl oleuropein aglycone.\(^{[43]}\)

**Emblicanin A, Emblicanin B, Punigluconin and Pedunculagin**

The effect of tannoid principles emblicanin A, emblicanin B, punigluconin, and pedunculagin of *Embelica officinalis* was assessed on chronic unpredictable footshock-induced, and stress-induced perturbations in oxidative free radical scavanging enzymes in frontal cortex and striatum of rats brain. The effect of this shows a significant reduction in catalase (CAT) and glutathione peroxidase (GPX) activity. The changes in the enzyme activities were accompanied by an increase in lipid peroxidation, in terms of augmented thiobarbituric acid-reactive species (TBARS).\(^{[44,45]}\)

**Propolis**

The antioxidant properties of propolis, a hive product collected by honey bees mainly from poplar bud exudates, suggest that poplar buds also possess antioxidant properties. Here is reported the characterization of the antioxidant properties of an aqueous poplar bud (*Populus nigra*) extract. It presented a high total phenolic content, and moderate antioxidant properties as determined by oxygen radical antioxidant capacity (ORAC) assay. The plant has high antioxidant activity, caffeic and p-coumaric acids were identified as the major antioxidant components.\(^{[46]}\)

**Quercetin**

Quercetin (QUER) and its derivative, namely quercetin caprylate (QU-CAP) as a proteasome activator with anti-oxidant properties that consequently influence cellular lifespan, survival and viability of HFL-1 primary human fibroblasts. Recently, QUER has also been reported to exert preventive effect against aging.\(^{[47,48]}\) Apples (*Malus domestica*) possess phenolic compounds which may be cancer-protective and demonstrate antioxidant activity. The predominant phenolic phytochemicals in apples are QUER, epicatechin, and procyanidin B2.\(^{[49]}\)

**Ellagic acid and 4-O-Xyloside of Ellagic Acid**

*Platycarya strobilacea* fruit extract contains an active ingredient such as ellagic acid and 4-O-xyloside of ellagic acid (ellagic acid 4-O-xylopyranoside). The constituents were
investigated for their free-radical scavenging activity, elastase inhibitory activity, the expression of matrix metalloproteinase-1 (MMP-1), and type I collagen synthesis in normal human fibroblast cells. *P. strobilacea* fruit extract and ellagic acid increased the expression of type I collagen mRNA in a dose-dependent manner comparable to that of ascorbic acid. A clinical study of measurements using visual evaluation and image analysis showed a statistically significant difference (p < 0.05) between the effects of the test and placebo products. This result suggests that *P. strobilacea* fruit extract could be used as an active ingredient for antiaging cosmetics. [50]

**Retinol (ROL)**

ROL at high doses (0.4-1.6%) showed antiaging efficacy which has been clinically established in photo-protected skin sites. But a product containing a low dose (0.1%) of ROL promotes keratinocyte proliferation *ex vivo* and *in vivo*, induces epidermal thickening *ex vivo* and also alleviates skin aging signs, without any significant adverse reaction. [51]

**Alpha-Hydroxy Acids (α-HA)**

Alpha-Hydroxy acids are reported to reduce signs of aging in the skin and are widely used cosmetic ingredients. More recently, beta-hydroxy acids (β-HA), or combinations of α-HA and β-HA have also been incorporated into antiaging skin care products. [52]

**Resveratrol**

Grape polyphenol, resveratrol is very recent entry as an antiaging agent. Resveratrol is a stilbene compound produced by different plants derived from red grapes, berries, and peanuts with many biologic activities, including an antiaging effect, which has been demonstrated both *in vitro* in eukaryotic cells and *in vivo* in mice. Resveratrol increased insulin sensitivity, decreased the expression of insulin like growth factor-1 (IGF-1) and increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-c co-activator 1a (PPAR-co-1a) activity. There are experimental evidences that resveratrol can extend lifespan in the yeast *Saccharomyces cerevisiae*, the fruit fly *Drosophila melanogaster*, the nematode worm *C. elegans*, and seasonal fish *Nothobranchius furzeri*. [53,54]

**Curcumin**

Curcumin acts as a powerful antioxidant, neutralizing free radical’s damaging effects to every cell and especially the cell’s DNA. In aged people body’s antioxidant levels decline and the
free radical damage accelerates and the signs of aging start to appear. Wrinkles, liver spots, graying hair, muscle atrophy are the external signs. Internally our organs, vascular system, hormones, cellular and intracellular damage and inefficiencies no longer allow our body’s to keep up with the damage. It mobilizes the body’s repair and immune system to repair an injury or fight off an invader. Curcumin is looking to be one of the best anti aging supplement. \[55,56\]

**Lycopene**
Lycopene is obtained as a rich source from *Lycopersicon esculentum* Mill (Tomatoes). It is a powerful antioxidant and anti cancer agent that helps to prevent cell ageing. It reduces aortic cholesterol levels, cytokines production and lipid peroxidation in guinea pigs. It decreases diabetes-induced lipid peroxidation in cortex in rats.\[57,58\]

**Lutein and Polypodium Leucotomos**
Lutein, a carotenoid, and *Polypodium leucotomos*, a fern extract, are potent antioxidants and anticarcinogenic agents. Both are effective skin anti-aging agents. Lutein inhibits the MMPs and *Polypodium leucotomos* inhibits the proliferation and expression of MMPs in early and late passage fibroblasts. Identification of agents that inhibit MMPs can be beneficial in the inhibition of skin aging and cancer.

**Nordihydroguaiaretic Acid**
Nordihydroguaiaretic acid (NDGA) is a natural phenolic (resin) and prevents UV induced skin damage by inhibiting UV-B-induced *c-fos* and *AP-I* trans-activation in the human keratinocyte cell line HaCaT. NDGA blocks UV-induced gene activation of inflammatory cytokines in the skin.\[59,60\]

**Xanthohumol**
Xanthohumol is a prenyl flavonoid derived from the female flowers of the hops plant *Humulus lupulus* L. Xanthohumol, directly inhibits MMPs and elastase activities while dramatically increasing the expression of types I, III, and V collagens, ELN, fibrillin-1, and fibrillin-2 in dermal fibroblasts.\[61,62\]

**Epigallocatechin-3-gallate**
Epigallocatechin-3-gallate, is a primary constituent of *Camellia sinensis* (Green Tea) found to have a strong antioxidant and protecting skin cells against photodamage\[63\]. It reduces the
lipid peroxidation significantly which is helpful in reducing UVA-induced skin damage (roughness and sagginess) and also protects from the decrease of dermal collagen and collagenase mRNA level in fibroblast culture.\cite{64}

**Safranal and Crocin**

Safranal and Crocin is obtained from methanol extract of *Crocus sativus* exhibited high antioxidant activity and free radical scavenging activity responsible for ageing process, anti-inflammatory, anticancer and wound healing activity.\cite{65}

**Ginsenoside Rb1**

"Ginsenosides" is a saponin triterpenoid glycosides obtained from *P. quinquefolius* which includes Rg1, Rb1 and others constituents). The Rb1 groups, predominant called as diol series, are reported to have an ability to improve stamina and learning capacity. American ginseng has also been reported to have anti-aging effects in laboratory animals and human subjects. One laboratory animal study reported an increase in learning capability. Fu and Ji found that *P. quinquefolius* supplementation could prevent age-associated increases in oxidant production and oxidative protein damage in the homogenates of various tissues in rats. *P. quinquefolius* is known to directly scavenge hydroxyl radicals, 1-diphenyl-2-picrylhydrazyl (DPPH) and to chelate metal ions.\cite{66,67} A study on effects of total saponins and ginsenoside Rb1 isolated from Red Ginseng roots on skin thickness, elasticity, and wrinkle formation caused by long-term, low-dose UVB irradiation in mice. These results suggest that the protective effect of ginsenoside Rb1 on skin photoaging may be due to the increase in collagen synthesis and/or the inhibition of MMPs expression in dermal fibroblasts.\cite{68}

**Caffeic and Ferulic Acids**

Caffeic acid (3, 4-dihydroxycinnamic acid) and ferulic acid (4-hydroxy-3-methoxycinnamic acid) are largely present in grains, fruit and vegetables where they are conjugated with saccharides. Caffeic acids have protected phospholipidic membranes from UV-induced peroxidation by inhibiting propagation of the lipid peroxidative chain reaction and to react with nitrogen oxides. Ferullic Acid acts as a potent antioxidant *in vitro*, due to its ability to scavenge free radicals and induce a robust cell stress response through the up-regulation of cytoprotective enzymes such as heme oxygenase-1 (HO-1), HSP-70, extracellular signal-regulated kinase 1/2 and Akt.\cite{69-71}
**Apigenin**
Flavonoids, naturally occurring polyphenolic compounds, are known to inhibit both lipopolysaccharide (LPS) stimulated tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) release which modulate the pro-inflammatory molecules that have been reported in many progressive neurodegenerative disorders, including AD, viral and bacterial meningitis, AIDS dementia complex, and stroke. [72]

**Genistein**
Genistein is found to be effective against ovariectomy (OVX), rats decrease in transforming growth factor-beta1 (TGF β1), tissue trans-glutaminase 2 (tTG2) and vascular endothelial growth factor (VEGF) by improving skin healing and wound tensile strength. [73]

**Nordihydroguaiaretic acid (NDGA)**
*Creosote bush, Larrea tridentata* (Zygophyllaceae) Coville is a common shrub of North American warm deserts. It is a notable source of natural products with approximately 50% of the leaves dry weight as extractable matter. The resin that covers the leaves yielded 19 flavonoid aglycones, as well as several lignans, notably including the antioxidant NDGA. [74] Derived from a pungent desert shrub, this reduces inflammation, irritation, and sebum, and boosts protection against UV damage. It may even help prevent the loss of collagen. However, the studies have mostly been on mice, so experts say more are needed on human skin. NDGA is a natural phenolic (resin) and prevents UV induced skin damage by inhibiting UVB-induced c-fos and AP-1 transactivation in the HaCaT keratinocyte cell line. NDGA blocks UV-induced gene activation of inflammatory cytokines in the skin. [75]
**Carnosic acid**

Carnosic acid is obtained from *Rosmarinus officinalis* L. which have an enhanced synthesis of nerve growth factor (NGF). UVA irradiation of the human skin fibroblasts led to a 10–15-fold rise in MMP-1 mRNA. This rise was suppressed in the presence of low μM concentrations of carnosic acid. [76,77]
Plant Sterols (PS) and Stanols for Healthy Ageing

Plant sterols, a group of naturally phytochemical resembling cholesterol are water insoluble. Cholesterol an essential fat produced by liver and or intestines used by your body to produce hormones and cell membranes, and aid in manufacturing bile acids, steroid hormones, and vitamin D. [78] Plant sterols and stanols (PS) consumption is known to decrease low-density lipoprotein-cholesterol (LDL-C) levels by 5–15%, and thus lower CVD risk. PS have recently been investigated for the prevention of other age-related diseases. PS have the ability to significantly lower LDL-C; yet, the large inter-individual variability in the lowering of LDL-C may be due to subject characteristics, food matrix of PS, dose of PS, dietary background, frequency of intake of PS, the additive effect of other foods or drugs, as well as genetic factors. Further, PS may also have other potential beneficial effects including anti-atherogenic, anti-inflammatory, antioxidant and anti-cancer activities. [79]

A brief of the some phytochemical (PC)/Extracts (E) used as anti-ageing are given in Table No. 1.

Bioinformatics in Aging Research

Computational approaches offer a powerful set of tools to study human aging. Computer methodologies will play a crucial role to reconstruct the genetic network of human aging and the associated regulatory mechanisms. Model organism data, next-generation sequencing are the upcoming tasks and challenges in the bioinformatics and systems biology. Use of bioinformatics and systems biology type of approaches provides a framework to start dissecting this complex biological phenomenon. [100-102]

Different Anti-Aging Models Currently Used by Researchers

In growing interest of anti-aging among researchers, scientists and normal human personality, there is a great trend in the development of these drugs. As the aging process in human is very slow and it takes more time to prove any scientific hypothesis and assay about the aging process. The animal models are very specific and useful to insure this process because they have an average short life against humans. The different models used against aging by the researchers are tabled in Table No. 2. In these models small animal are very useful. [103,104]
### Table No. 1. Some phytochemical (PC)/Extracts (E) used as anti-ageing.

<table>
<thead>
<tr>
<th>Name of PC/E (Conc.)</th>
<th>Biological source</th>
<th>MOA</th>
<th>Other pharmacological uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silibinin</td>
<td><em>Silybum marianum</em></td>
<td>Burchard (Patch) tests</td>
<td>Antioxidant, anti-cancer, hepatoprotective [^{80-83}]</td>
</tr>
<tr>
<td>Black Currant (0.027 μmol/kg/day)</td>
<td><em>Ribes nigrum</em></td>
<td>learning and memory, GSH↑, ↓MDA.</td>
<td>anti-cancer, myopia [^{84-86}]</td>
</tr>
<tr>
<td>Extra Virgin Olive Oil Extracts (6 mg/kg)</td>
<td>Olive plant</td>
<td>AMPK/mTOR, xenohormetic nature, NF-κB activity activity</td>
<td>anti-cancer, anti-inflammatory, antioxidative, cardio-protective, [^{87-89}]</td>
</tr>
<tr>
<td>Kacip Fatimah extracts (0.006%)</td>
<td><em>Labisia pumila</em></td>
<td>free radical scavenging activity</td>
<td>Antifungal, anti-inflammatory and anti-cancerous [^{90,91}]</td>
</tr>
<tr>
<td>Extract of <em>Polyalthia longifolia</em> (100%)</td>
<td><em>Polyalthia longifolia</em></td>
<td>free radical scavenging activity</td>
<td>Antifungal, anti-inflammatory and antioxidative with hepato-protective [^{92,93}]</td>
</tr>
<tr>
<td>Apple fruit skin extract (584 mg/l)</td>
<td><em>Malus domestica</em></td>
<td>free radical scavenging and H₂O₂ sensitivity on yeast cells</td>
<td>Anti-cancerous, neuro-degenerative, cardio protective [^{94}]</td>
</tr>
<tr>
<td>Herbal Teas (extracts mixer)</td>
<td><em>Lagerstroemia speciosa + Rubus suavissimus + Sasa veitchii + Diospyros kaki</em></td>
<td>free radical scavenging property, Advanced glycation end product assay</td>
<td>Cosmetics, anti-inflammatory [^{95}]</td>
</tr>
<tr>
<td>Rhodiola herb (30 mg/ml)</td>
<td><em>Rhodiola rosea</em></td>
<td>Anti-oxidant effect on fly</td>
<td>Anti-fatigue, ↑ mental performance [^{96,97}]</td>
</tr>
<tr>
<td>Gall extract (0.1 mg/ml)</td>
<td><em>Terminalia chebula</em></td>
<td>DPPH radical scavenging activity</td>
<td>Anti-oxidant, radio-protector, anti-cancerous, hepato-protective, nutritional power [^{98,99}]</td>
</tr>
</tbody>
</table>

### Table No. 2. Recent animal models used by researchers on anti-aging processes.

<table>
<thead>
<tr>
<th>Model representative</th>
<th>Assessable phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird model</td>
<td>Oxidative and glycoxidative damage, caloric restriction and in vitro oxidative stress [^{105}]</td>
</tr>
<tr>
<td>Bivalve (mollusks) models</td>
<td>Calorie restriction, shell size, growth, development and metabolic strategies [^{106,107}]</td>
</tr>
<tr>
<td>Canine brain model</td>
<td>β-amyloid accumulation, age-related cognitive dysfunction [^{108-109}]</td>
</tr>
<tr>
<td>Fly (<em>Drosophila melanogaster</em>)</td>
<td>Locomotor activity [^{110}]</td>
</tr>
<tr>
<td>Exotic mice (F₂ hybrid)</td>
<td>Oxidative damage to DNA, lipid, protein carbonyl content and protein [^{111-114}]</td>
</tr>
<tr>
<td>Flamingo (<em>Phoenicopterus ruber roseus</em>)</td>
<td>Oxidative stress [^{115}]</td>
</tr>
<tr>
<td>Model Type</td>
<td>Biomarkers and Characteristics</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Guinea pig osteoarthritis model</td>
<td>Transforming growth factor β, Synovial fluid levels of cartilage, histology</td>
</tr>
<tr>
<td>Guppies (Poecilia reticulate)</td>
<td>Swimming performance, degenerative histopathological study of liver and, neuromuscular functions</td>
</tr>
<tr>
<td>Hormesis and diet restriction rodents model</td>
<td>Corticosterone level</td>
</tr>
<tr>
<td>Japanese medaka (Oryzias latipes)</td>
<td>Biomarkers of normal aging like histopathology of liver, age associated changes in skin, muscles and heart</td>
</tr>
<tr>
<td>Klotho mouse model</td>
<td>Density and convolution of the fragmented collagen fibers and other skin aging factors oxidative base damage, in synaptosomes of</td>
</tr>
<tr>
<td>Metabolic syndrome model of mice</td>
<td>Mouse brain MDA, Vitamin C in plasma and tissues</td>
</tr>
<tr>
<td>Mouse (mimetic aging model induced by D-galactose)</td>
<td>Stress biomarkers like MDA, SOD, etc.</td>
</tr>
<tr>
<td>Mouse model (Alzheimer’s disease)</td>
<td>Base excision repair capacity</td>
</tr>
<tr>
<td>Mouse model of Werner syndrome</td>
<td>Age related biomarkers: NF-κB, protein kinase Cδ and Hif-1α transcription factor</td>
</tr>
<tr>
<td>Nothobranchius furzeri</td>
<td>Expression of senescence-associated β-galactosidase and accumulation of lipofuscin ↑ with age</td>
</tr>
<tr>
<td>Rat (F344xBN hybrid) aorta model</td>
<td>Morphometric and global gene expression</td>
</tr>
<tr>
<td>Rat brain model of caloric restriction</td>
<td>Neural circuits involved in pain, emotions, feeding learning and memory power</td>
</tr>
<tr>
<td>Rat liver and brain model</td>
<td>NF-kappa B a major transcriptional factor and regulation of cytokines</td>
</tr>
<tr>
<td>Rat model (Alzheimer’s disease)</td>
<td>Interleukin (IL)-1β, IL-6, and TNF-α</td>
</tr>
<tr>
<td>Rat Model cognitive abilities</td>
<td>mRNA expressions in gene and methylation analysis of age related genes</td>
</tr>
<tr>
<td>Rat model of oxidative stress</td>
<td>Oxidative stress parameters: MDA, peroxides</td>
</tr>
<tr>
<td>Rat model of work related musculoskeletal disorders</td>
<td>Grip strength, and IL-1alpha, IL-6, IFN-gamma, TNF-alpha, MIP2, IL-10</td>
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<tr>
<td>Rhesus monkey</td>
<td>Calorie restriction on testicular gene expression</td>
</tr>
<tr>
<td>Senescence-accelerated mouse (SAM)</td>
<td>Life span study of plasmid mice with vector (containing the lacZ reporter gene) clusters</td>
</tr>
<tr>
<td>Transgenic mouse</td>
<td>Oxidative stress induced ASK1-signalosome → p38 MAPK pathway</td>
</tr>
<tr>
<td>Transgenic mouse model</td>
<td>Age related problems such as learning and memory, emotional disorders, abnormal circadian rhythms, brain related problems</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>Lipofuscin analysis, Telomerase assay, Necropsy and histopathology</td>
</tr>
</tbody>
</table>
Current Concept on Age Related Problems

According to population reference bureau the world population has been grew 7.06 billion since 2012. In developed countries like The United State population increased in less percentage; younger growth rate declined and older age rate has been increased. There was 87 % deaths occurs in The U.S. due to non-communicable diseases such as cardiovascular, diabetes, cancer, lung and others. The mortality in different age groups has been shown in Figure No. 4. \[146\]

The population reference bureau report shown that the mortality cases are more prominent in aged group peoples cause of major diseases; frequently occurs in aged persons.

![Figure No. 4 Lead causes of death, by age group: United State 2011.](image)

CONCLUSION

This review provides modern and Ayurvedic perspectives of different natural compounds and management of aging. Notwithstanding most of these natural dietary compounds are yet to be investigated in clinical. Hence, additional extensive research of natural dietary compounds is needed in the future for improving human health and preventing degenerative disorders of aging. So, the various phytochemicals possess antioxidant as well as anti-aging activity has been proved by different model either \textit{in vitro} or \textit{in vivo} or even \textit{ex vivo}. The chemical moieties possess this activity due to their pharmacophoric structure. Most of polyphenols and bio-flavonoids show excellent anti-aging properties even plant extracts rich in polyphenols have efficient power of anti-aging. However, more consistently scientific studies to establish the safety and efficacy of natural therapies in both reawakening and detoxification procedures are needed. Thus, this
review may be most fascinated to modern scientists to understand different approaches and mechanism that may be useful to boost research on various degenerating conditions and aging.

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