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REVIEW

Aging and its treatment with vitamin C: a comprehensive mechanistic review

Shumaila Mumtaz[1] · Shaukat Ali[1] · Hafiz Muhammad Tahir[1] · Syed Akif Raza Kazmi[2] · Hafiz Abdullah Shakir[3] · Tafail Akbar Mughal[1] · Samaira Mumtaz[1] · Muhammad Summer[1] · Muhammad Adeel Farooq[1]

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Abstract

Aging and age-related disorders have become one of the prominent issue of world. Oxidative stress due to overproduction of reactive oxygen species is the most significant cause of aging. The aim of literature compilation was to elucidate the therapeutic effect of vitamin C against oxidative stress. Various mediators with anti-inflammatory and anti-oxidant properties might be probable competitors of vitamin C for the improvement of innovative anti-aging treatments. More attention has been paid to vitamin C due to its anti-oxidant property and potentially beneficial biological activities for inhibiting aging. Vitamin C acts as an antioxidant agent and free radical scavenger that can protect the cell from oxidative stress, disorganization of chromatin, telomere attrition, and prolong the lifetime. This review emphasizes mechanism of aging and various biomarkers that are directly related to aging and also focuses on the therapeutic aspect of vitamin C against oxidative stress and age-related disorders.

Keywords Aging · Oxidative stress · Reactive oxygen species (ROS) · Age-related disorders,vitamin C · Antioxidant

Abbrevations

RTKs	Receptor tyrosine kinases
TEWL	Transepidermal water loss
ROS	Reactive oxygen species
VLDL	Very-low-density lipoproteins
LDL	Low-density lipoproteins
HDL	High-density lipoproteins
SVCT	Sodium-dependent vitamin C transporters
MAPK	Mitogen-activated protein kinase
AP-1	Activatorprotein-1
oxLDL	Oxidized-low density lipoprotein
SOD	Superoxide dismutase
CAT	Catalase
GSH-Px	Glutathione peroxidase

✉ Shaukat Ali
dr.shaukatali@gcu.edu.pk

[1] Applied Entomology and Medical Toxicology and Laboratory, Department of Zoology, Government College University, Lahore, Pakistan

[2] Department of Chemistry, Government College University, Lahore, Pakistan

[3] Institute of Zoology, University of the Punjab, Lahore, Pakistan

Background

Aging is a complex multifactorial and permanent deterioration process that seems not only in body tissues, however, it is also associated with a decline in the physical functions of body organs e.g. poor immune reactions and loss of memory etc. There is a substantial amount of data supporting that aging is meticulously related to different lifelong disorders such as diabetes, multiple cancers, hypertension, Parkinson's disease, Alzheimer's disorder, and atherosclerosis [1]. The free radical principle of aging has been extensively concerned, initially offered by Denham Harman since the 1950s [2]. Oxidative damage triggered by the overproduction of reactive oxygen species (ROS) is the most significant determinant of aging. Excessive formation of free radicals is the consequence of oxidative stress and pro-inflammatory reactions, which directly lead to lipid peroxidation, oxidation of protein as well as impairment in DNA and mitochondria. These might prohibit the normal functions of cell and cause cell death [3]. Various studies showed that endogenous antioxidant systems comprising; glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT), can be directly or indirectly damaged by the ROS [4]. Also, more and more studies have revealed that the function of the immune system declines in aging which

affects the capability of the body to fight against outdoor infective agents, therefore, the probability of aging and disorders associated with aging might be increased as shown in Fig. 1 [5].

Molecular mechanism of aging

Molecular mechanisms of aging including cellular senescence, mitochondrial dysfunction, epigenetic alterations, accumulation of somatic mutations, telomere shortening, deregulated nutrient sensing, stem cell exhaustion, loss of proteostasis, a decline in the responsiveness to growth factors, formation of ROS, genomic instability, intercellular communication modifications, a rise in the concentrations and secretion of matrix metalloproteinases and inflammatory cytokines, an increase in the extent of oxidative damage to cellular macromolecules, and a delay in morphogenesis and maturation [6]. Molecular damage in cells can be recognized, repaired, or removed due to availability of quality control systems. Though, somatic maintenance is not 100% efficient due to the energy requirements of these systems [7]. Entirely molecular components including proteins, DNA, lipids and organelles are susceptible to damage and sources of destruction might be extrinsic factors (irradiation toxins and UV light) and intrinsic *e.g.* formation of reactive nitrogen species (RNS), and ROS. Physical activity, genetics, diet, and epigenetics are other contributing factors in aging [8]. The major causal factor in aging is the accumulation of unrepaired DNA damage [9]. Although, endogenous DNA repair and ROS removal systems have also been found in cells and organisms but in aging cells, these systems do not function effectively. Thus, the cause of premature aging is multiple damages to DNA or the repair system that leads to

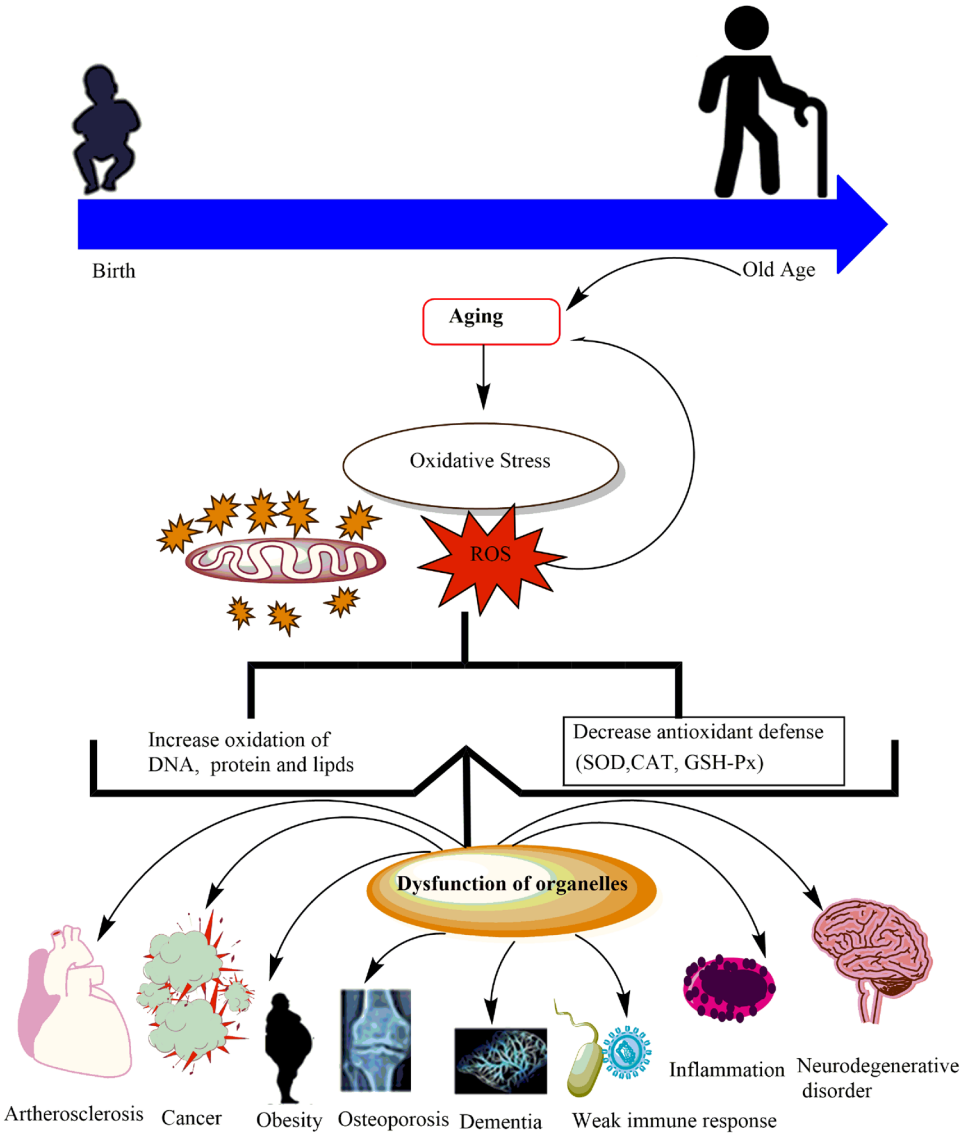

Fig. 1 Role of oxidative stress/ROS in aging and age related disorders. Reactive oxygen species enhances the oxidation of DNA, protein and lipids, decrease antioxidant defense system and the function of mitochondria which result in oxidative stress produce that might be subsequentltly lead to aging and disorders associated with aging

an accumulation of DNA damage which results in epigenetic alterations occurs [10].

Organ-specific biomarkers of aging

Vital organs such as the heart, brain, kidney, and lungs perform specialized functions while impairment in one of these organs can lead to death. Various biochemical tests evaluate the importance of specific tissues, which measure the concentration or presence of markers of disorder in urine or blood, saliva, peripheral blood lymphocytes, and buccal cells [11]. In this review, we focused on the biomarkers that are directly related to aging and age-related disorders.

The kidney

The currently accepted measurement of kidney function is the glomerular filtration rate. In healthy young men, the normal value of the glomerular filtration rate is 130–140 mL/min per 1.73 m^2. It is assessed that after the age of 40 years approximately 1 unit per year filtration rate declines. When the number of functioning nephrons decreases with age, it also causes a decline in the glomerular filtration rate [12]. Neutrophil gelatinase-associated lipocalin as a biomarker of the renal system, that is 25-kDa lipoprotein which is generally covalently associated with gelatinase. In healthy individuals, it is found at very low levels in serum but it is found at a high level in blood, urine, or serum of patients after acute kidney injury as well as with acute bacterial infections [13].

Cardiovascular system

In aging, the highest remarkable modifications that occur in the cardiovascular system are; rise in the stiffness of vessels as well as a consistent intensification in the number of atherosclerotic lesions. However, angiotensin and endothelin that regulate the endothelial function, as well as the progenitor cells of endothelial in plasma, might be measured via cell culture [14]. Fetuin-A and matrix Gla protein are probably remarkable markers of aging that defend the blood vessels from ossification [15]. Cardiac fibrosis is one of the age-related modifications in the vascular system that is associated with the accumulation of collagen in the extracellular matrix which might be lead to an increased ventricular stiffness [16]. Treatment and diagnosis of heart failure via natriuretic peptides have become a valuable component of medicinal training. Under stress or otherwise elevated pressure, N-terminal pro-brain natriuretic peptide and brain natriuretic peptides discharged from the wall of the heart ventricles. However, the amounts of these peptides are low in the blood of healthy persons [17].

Lungs function

The function of the lung has been found to decline with age consistently, as measured with a basic spirometer [18]. In arterial blood, the partial pressure of oxygen, as well as the physiology of the lung, also declines with age. A chronic obstructive pulmonary disorder that is particularly associated with "inflammatory processes" has been defined as the most prevalent age-linked lung disorder. At least one marker namely "surfactant protein D" that is produced through type 2 alveolar cells has been found in serum, related to lung infection [19]. It prevents the formation of lipid radicals by binding to dying and dead cells. Various biomarkers of lungs, heart, and kidney that can be assessed in plasma and offers references to human researches are mentioned in Table 1.

Skin aging

Skin aging is a multistage complicated process that is linked with physiological and morphological changes of the skin [20]. It consists of two distinctive progressions, intrinsic and extrinsic skin aging. An intrinsic skin aging affects all internal organs and even the whole organism as well as represents chronological aging [21]. Extrinsic skin aging is the consequence of environmental effect and external factors,

Table 1 Organ-Specific Biomarkers of Aging

Organs	Biomarkers	Type of sample	Analysis Technique	Quantity [Low /High]	References
Kidneys	Neutrophil gelatinase-associated lipocalin	plasma /Serum/ urine	Enzyme immunoassay	High	[13]
	Glomerular filtration rate creatinine, urea and Cystatin C	Serum/plasma	Autoanalyzer	High	[81]
Cardiovascular system	Natriuretic peptides	Serum/plasma	Autoanalyzer	High	[82]
	Endothelin	plasma /Serum	Enzyme immunoassay	High	[14]
	Collagen	plasma /Serum	Enzyme immunoassay	High	[16]
Lungs	Apelin	Serum/plasma	Enzyme immunoassay	High	[83]
	Surfactant D	plasma/ Serum	Enzyme immunoassay	High	[19]

mostly ultraviolet (UV) irradiation and chronic sun exposure but poor nutrition, smoking, and pollution are also causes of extrinsic skin aging [22]. Increased transepidermal water loss (TEWL), reduced activity of fibroblast and melanocyte, decline biosynthesis of elastin and collagen are perceived in the progress of aging [20]. Molecular mechanism of skin aging including; oxidative stress, the capacity of cellular DNA repairing declines, point mutations of extranuclear mitochondrial genetic material, and loss of telomeres, elevation in chromatic aberrations, cellular senescence, chronic inflammation, reduce the level of sugar, and single-gene mutations so on [23]. Now, various antiaging products can maintain the structure and function of youthful skin as well as can fortify the dermal matrix due to the presence of scientifically progressive constituents with anti-inflammatory, antioxidant, and anti-glycation properties. Vitamin C is a natural antioxidant that is found in the skin and possesses several biological important functions such as an anti-inflammatory, antioxidant, biostimulator of collagen synthesis, and photoprotective [24].

UV radiation and photoaging

Prolonged disclosure of UV radiation from the sun is the greatest significant ecological challenge to the skin. Ultraviolet radiations cause impairment in the skin via the generation of ROS, which might be damaged the extracellular matrix components of the dermis in intrinsic aging and photoaging as well as affect both function and the configuration of cells [25]. Reactive oxygen species might be generated from various origins such as the endoplasmic reticulum (ER) localized proteins, mitochondrial electron transport chain, peroxisomal, the Fenton reaction, and enzymes such as xanthine oxidases, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, cyclooxygenases, and lipoxygenases [26]. In normal situations without the presence of ligands, on the surface of a cell, the action of receptor tyrosine kinases (RTKs) is prohibited through receptor protein tyrosine phosphatase (RPTPs) which dephosphorylates the receptor tyrosine kinases (RTKs). Though, in the case of ultraviolet (UV) radiations, ROS and oxidation products are produced due to the fascination of energy from cellular chromophores. Reactive oxygen species bind to cysteine residues in the catalytic sites of receptor protein tyrosine phosphatases and inhibit the function of receptor protein tyrosine phosphatases (RPTPs). Reactive oxygen species activating the downstream signaling pathways comprising the activation of nuclear factor-kB (NF-Kb), mitogen-activated protein kinase (MAPK), and transcription factor activator protein-1(AP-1), as well as increasing the level of phosphorylated receptor tyrosine kinases [27]. When AP-1 and NF-kB are activated, increase transcription of the MMP gene and suppress the production of collagen in photoaged skin as shown in Fig. 2 [28].

Various endogenous antioxidant defenses especially vitamin C and E, as well as antioxidant enzymes, are also present in the skin to reduce these oxidants then renovation the resultant impairment, while repeated exposure to the sun causes consumption of these antioxidants and the skin's defenses might be distrustful [25]. Impairment to the dermal extracellular matrix, redness, swelling, sunburn immune suppression, altered pigmentation, early skin aging, and disruption to the structure of skin might be lead to the cause of skin malignancy that is a result of an acute acquaintance of UV radiation to the skin. The utmost apparent features of photoaging are hyperpigmentation wrinkles, as well as obvious modification, which occurs in the elasticity of skin [29]. The chest, face, and upper surface of the arms are most susceptible to photoaged skin. Most obvious modifications arise in the extracellular matrix of the epidermis such as loss of collagen fibrils [30]. Photo aged individuals have increased inflammation as well as neutrophil infiltration into the dermis while a decline in the concentration of natural enzymatic and non-enzymatic antioxidant defensive system has been found [31]. Recent studies showed that various endogenous antioxidant enzymes diminished in intrinsic aging and photoaging which regulates the antioxidant defense system of skin and alters the reactive oxygen species (ROS) to non-toxic water and atomic oxygen. Endogenous antioxidants, for example, glutathione, ascorbic acid, tocopherols, and function of anti-aging enzymes (CAT, and GSH) that perform a significant role in the inactivation of free radicals formed by ROS are decline in photoaging and intrinsic aging [32].

Aging cells and tissue renovation

A fraction of the cells decreases in most tissues, and is substituted after some period from a group of hematopoietic stem cells. Once the capacity of hematopoietic stem cells to differentiation and replication loss then it becomes aging cells and overall efficient cells will decline which results in tissue dysfunction as well as a loss of homeostasis. Cell senescence is categorized into two forms, for instance, stress-induced premature aging and replicative aging [33]. Length of telomeres can be measured in replicative senescence while, oxidative stress stressful stimulus can enhance the stress-induced premature senescence which can be measured through antioxidant enzymes. Stressful stimulus stimulates the triggering of the p21/ p53 mechanism which results in cell cycle arrest permanent or can fetch the cells to that position when cell death begins [34]. A significant moderator of advanced aging had been identified as the upregulation of caveolin-1 expression in the past few years. This protein might be premeditated in blood and cells that developed in cell culture. Numerous forms of hematopoietic stem cells

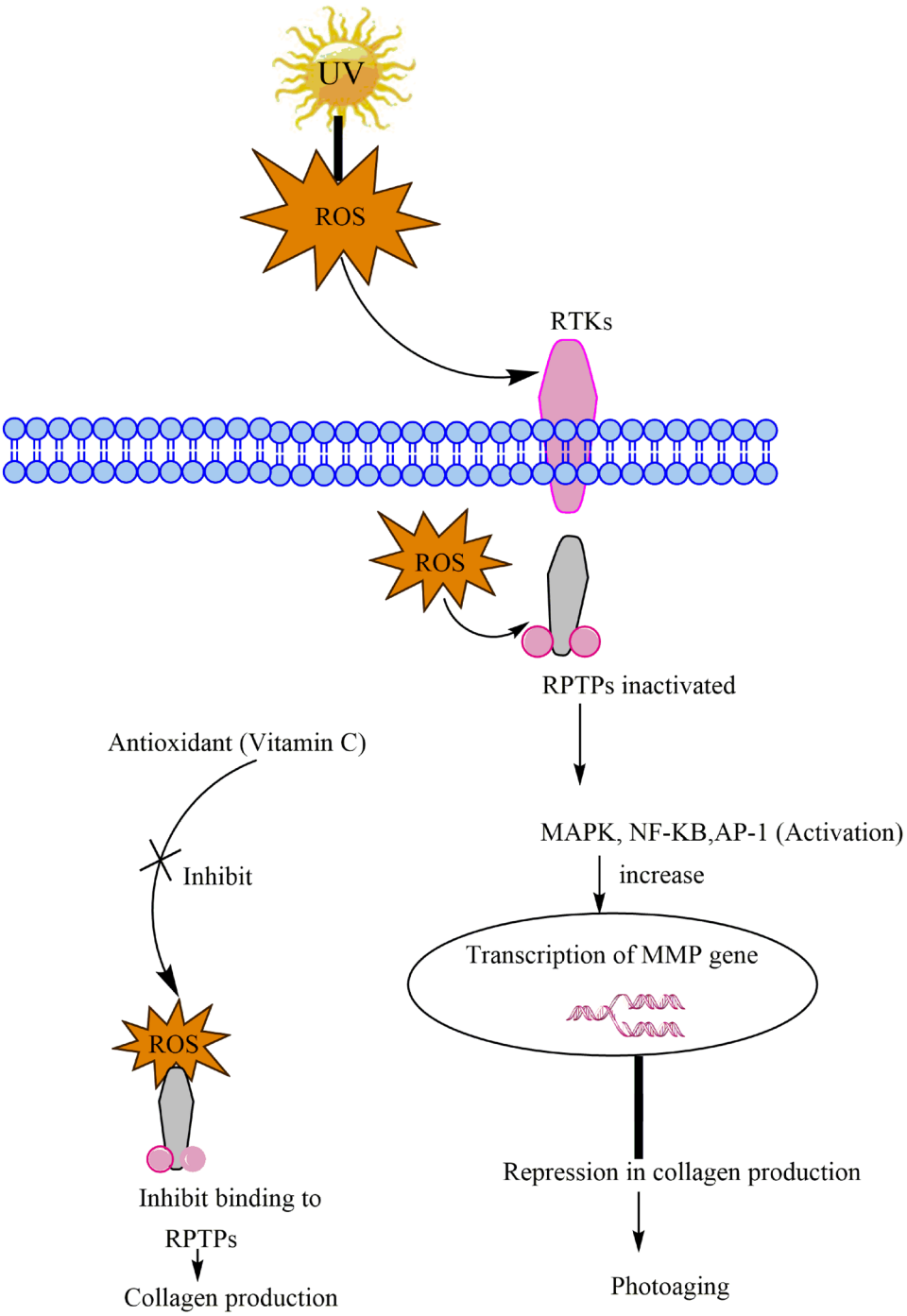

Fig. 2 Mechanism of reactive oxygen species (ROS) in photo aging. In case of ultraviolet (UV) radiations, ROS bind to cysteine residues in the catalystic sites of receptor protein tyrosine phosphates and inhibit the function of receptor protein tyrosine phosphates (RPTPs), Reactive oxygen species activating the nuclear factor-kB(NF-kB), mitogen-activated protein kinase (MAPK) and transcription factor activator protein-1 (AP-1), When Ap-1 and NF-kB activated, increase transcription of MMP gene and suppress the production collagen. Vitamin C can inhibit binding of ROS to (RPTPs) and enhance the collagen production

can be quantified as well as detected in plasma *e.g.* blood stem cells and other endothelial progenitor cells which can be changed with age [35].

Many apparent fluctuations are closely associated with age such as cardiac remodeling, changes in the extracellular matrix, and increased arterial stiffness. For instance, when stimulation occurs by development factors, cardiovascular fibroblasts produce and discharge the extracellular matrix proteins viz tissue prohibitor of matrix metalloproteinases and collagen, while, excretion of matrix metalloproteinases stimulated by proinflammatory mediators [36]. The higher levels of galectin-3, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinase-1 in serum certainly signify the more dynamic cell renovation. Various biomarkers of tissue renovation that can be assessed in plasma and offers references to human researches are mentioned in Table 2.

Generally, a balance between antioxidants and oxidants might be the more significant and the antioxidant status of

Table 2 Biomarkers involved in the general mechanism of aging

Biological process	Biomarkers	Sample	Analysis Method	Quantity [Low / High]	References
Aged cells and tissue renovation	Endothelial progenitor cells e.g. hematopoietic stem cells	Fresh anti-coagulated blood	Flow cytometric assay	Low	[84]
	Caveolin-1	Blood serum/plasma	Enzyme immunoassay	High	[33]
	Matrix metalloproteinase-1, metalloproteinase-9 and galectin-3	Plasma/Serum	Enzyme immunoassay	High	[85]
Oxidative stress	Glutathione, Superoxide dismutase, Glutathione reductase, and Glutathione peroxidase	Red blood cells	Auto analyzer	High	[33]
Metabolism of protein	Eotaxin, Carbonyls, Michael adducts, Nicotinamide	Plasma/Serum	Enzyme immunoassay	High	[52]
	Amyloid (inflammatory response protein)	Serum	Enzyme immunoassay	High	[86]
Metabolism of lipids	LDL, VLDL, HDL, triglycerides, Total cholesterol	Plasma/Serum	Auto analyzer	High	[41]

individuals can be measured via main elements included in chemical reactions mainly glutathione in lymphocytes or blood serum [37]. Creatinine, albumin, bilirubin, uric acid, and numerous vitamins [A, E, C, and D] are constituents of the physiological antioxidant defense mechanism and antioxidant enzymes that are related to oxidative stress, for instance, GSH-Px and SOD can be determined in erythrocytes or plasma/serum. Thioredoxin reductase-1 is also an antioxidant that can be assessed in lymphocytes. Certain disorders like atherosclerosis, prolonged inflaming disorders, and diabetes mellitus are closely related to oxidative stress and aging [38]. Chronic inflammation is one of the conditions, causes oxidative-stress and is an integral part of aging. Inflammation and oxidative stress both are related to hypoxia. Hypoxia also shows a vigorous role in aging, malignancy, cardiovascular disorders, lung infection, and various other infections. Numerous markers of oxidative stress with relevant references are mentioned in Table 2.

Proteins and metabolism of protein

Within cells, modification of proteins occurs constantly including; posttranslational modifications [oxidation, nitrosylation, and glycosylation] surveillance, protein folding, removal, repair, and typical reactions to stress [39]. In older organisms modifications in the homeostasis of protein are communal in most tissues as well as modifications in a group of proteins (chaperones) have also been found in nearly entire tissues and organisms. Proteins are mostly affected due to the presence of excessive amounts of oxygen radicals that are responsible for the oxidation of proteins. Protein carbonyl is a consequence of the oxidative reaction of the side chain atoms of lysine, proline, threonine, and arginine. When carbonyls accumulated in blood plasma it causes agedness and disorders related to age due to innovative glycation production [40]. Biomarkers associated with the oxidation of proteins are provided in Table 2.

Lipids and metabolism of lipid

Changes in various forms of lipid in plasma with age have been considered in several epidemiologic studies. In cardiovascular disease, lipid profiles in plasma have been considered expansively as risk impacts. In clinical practice the utmost significant parameters that are assessed comprising; triglycerides, free fatty acids, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL). The evidence of these biomarkers concerning human beings is provided in Table 2 [41]. These lipid profiles have limited value, as biomarkers of aging e.g. the total cholesterol level raises in women till 70 years of age while in males until the age of 50 years. Recently more than 600 distinctive molecular classes of lipids are identified in the plasma of humans among these 6 are characterized in main categories of lipid and their ratios are associated with aging including sphingolipids, fatty acyls, glycerolipids, sterol lipids, glycerophospholipids and prenol lipids [42].

Anti-aging compounds

Various mediators with anti-inflammatory, immunomodulatory, and anti-oxidant properties might be possible entrants for the improvement of innovative antiaging rehabilitations [4]. More attention has been paid to various natural

compounds [carotenoids, tocopherols and flavonoids, as well as vitamins [A, C, D, and E] due to their anti-oxidant properties as well as potentially beneficial biological activities for inhibiting or treating this subacute aging. The well-accepted anticipation stratagem in contradiction of the hurtful effect of free radicals is a well-adjusted nutritious food containing anti-oxidative rich foodstuff as well as a well-structured regime such as body care, caloric restriction, and physical exercise for the body [43].

Vitamin C (ascorbic acid)

Vitamin C, or ascorbic acid, is an essential dietary nutrient and is one of the naturally occurring antioxidants in nature for a variety of biological roles [44]. At biological pH states, it frequently occurs in ascorbate anion form [45]. It has also the competency to chelate the metal ions [Fe++] due to the existence of hydroxyl groups on an adjacent side of carbon atoms. It acts as a free radicals searcher and reduces the free radicals of oxygen and gives hydrogen to an oxidizing system to inhibit the oxidation. It possess the capacity to protect the macromolecules [Nucleic acids, proteins, carbohydrates, and lipids] from revelation to chemicals, and pollutants such as cigarette smoke, and also defend from damage through oxidants, which are formed in the common breakdown of the cell [46]. Most animals and plants can endogenously synthesize vitamin C from glucose. Humans are unable to in vivo biosynthesis of vitamin C due to the absence of the enzyme L-glucono-gamma lactone oxidase, therefore it is necessary for a healthy human diet and sufficient nutritional consumption of vitamin C is mandatory [47].

Sources of vitamin C

Natural sources of vitamin C are citrus fruits, green leafy vegetables, fresh fruits, papaya, blackcurrant, chili pepper or parsley, broccoli, strawberries, guava, and rosehip [48].

Topical formulations of vitamin C

Ascorbic acid is accessible in various formulas however L-ascorbic acid is the most biologically and chemically energetic and well-studied form of vitamin C. It is found in D-ascorbic acid as well as L-ascorbic acid in nature which are mutually interchangeable and fundamentally isomeric molecules. Though, only L-ascorbic acid is expedient in medical practice, due to its biologically active form [49]. L-ascorbic acid is a hydrophilic antioxidant and defends the dermis from oxidative impairment as well as act as a free-radical scavanger. It also actively restores vitamin E in the skin by neutralizing the reactive oxygen species including superoxide anion, hydroxyl radical, and singlet oxygen which are destructive to the skin. Two-thirds of the L-ascorbic acid in the dermis is destroyed during acquaintance to ultraviolet light because ROSare stimulated with ultraviolet light [50]. Reactive oxygen species are also stimulated by cigarette smoking. Premature wrinkling occurs due to cigarette smoking than extensive sun exposure. Constituents of skin comprising proteoglycan, collagen, elastin, as well as nuclear and cell membranes constituents can be damaged via reactive oxygen species. Intrinsic aging and photoaging variations including brown spots, wrinkles and skin cancers are visible signs of this destruction. L-ascorbic acid is found to be used in various products of cosmetics such as in anti-aging, lightening of skin depigmentation as well as sun protection formulations. L-ascorbic acid defends skin and diminishes the harmful effects caused by ultraviolet radiation [51].

Adsorption and deficiency of vitamin C in humans

Deficiency of vitamin C can cause scurvy, a disorder that is associated with some signs such as thickening of the stratum corneum, fragility, gum bleeding, skin lesions in form of petechiae, poor wound healing, fatigue, and even death [52]. In elderly age, kidney failure, peritoneal dialysis, hemodialysis, and various malabsorption disorders are also well-known risk factors for a low level of endogenous vitamin C and poor dietary intake of vitamin C. Consumption of vitamin C 10 mg/day is suitable to preclude scurvy. The recent recommended intake of dietary vitamin C is 75 mg per day for women while, for the adult men it is 90 mg/day [53].

The sodium-dependent transporters of vitamin C

Sodium-dependent vitamin C transporters (SVCTs) show an essential function in adsorption and transportation of vitamin C across the skin, which are found all over the body as well as accountable for transference into various soft tissues. In humans, SVCT1 and SVCT2 express in epidermal cells [54]. While SVCT2 is related to sustaining ascorbate homeostasis inside the cell as well as sensitive to the fluctuations in intracellular ascorbate levels. The expression of SVCT1 in the human being is mainly limited to the epidermal cells in the kidney and duodenum [55].

Antioxidant action

Vitamin C acts as an antioxidant agent and free radical seeker that can protect the cell from oxidative stress formed by ROS by an electron transfer or donation process. It can also support the antioxidant enzymes of a cell e.g. SOD, GSH-Px, and CAT, as well as non-enzymatic, defend systems of cells such as uric acid, glutathione, carotenoids and vitamin E [56].

Vitamin-C-mediated defense against photoaging and UV impairment

Vitamin C shows an indispensable function in protecting the cells from oxidative stress as well as significantly suppresses the formation of free radicals triggered by UV light [57]. It also increases the production of pro-collagen and collagen which stimulates the establishment of the skin barrier, an additional role in wound healing. Various readings on the skin of humans revealed that vitamin C improved the skin hydration and considerably increased the moisture content of the epidermis [58]. Vitamin C defends the keratin from the apoptotic process as well as rises the survival of the cell. It also prevents peroxidation of lipid in cultured keratinocytes after exposure to UV radiation. In numerous studies, it is found that resistance of the skin to UV exposure can be enhanced by supplementation with vitamin C [59].

During chronological aging, wrinkles are formed and significantly enhanced due to peripheral factor for example smoking, and acquaintance to ultraviolet radiation. Various natural compounds including vitamin C have efficacy against wrinkle formation [60]. Vitamin C can protect the skin against the formation of wrinkles via the biosynthesis of collagen. It also shows a vital role in enhancing the expression of the collagen gene and stabilizes the tertiary structure of the collagen molecule [61].

Vitamin C and oxidative stress

Oxidative stress is a result of enhanced production of ROS/free radicals or declines the ability of antioxidant defenses against ROS [62]. The ROS are formed in living organisms as a consequence of common cellular uptake. They perform the function in physiological cell processes at low to moderate concentrations however, at high concentrations cause adversative variations in cell components e.g. DNA, proteins and lipids [63]. Vitamin C functions as a proper boundary between life span, aging, and disorders linked with aging. It is capable to repair DNA and oxidative stress, bioenergetics, modulate the activity of telomeres as well specifying a nutrigenomic role in the aging process, leads to longevity as presented in Fig. 3 [64]. In recent times, it has been found that aged individuals possess decreased antioxidant capacity and antioxidant parameters in lower concentrations comprising vitamin C and are more vulnerable to frailty, disability and higher mortality [65]. It is also found that consumption of star fruit juice (*Averrhoa carambola*) daily, a fruit that consists of high content of vitamin C act as a free radicals rummager, restoring GSH levels and maintaining low levels of lipoperoxidation [66].

Oxidative stress in the body is characterized by imbalance between the production of free radicals including reactive oxygen species (ROS) and reactive nitrogen species (RNS) and antioxidant defenses [67]. According to Liguori et al., when body is exposed to the higher levels of ROS and RNS, it leads to the cellular senescence, that ceases the proliferation of cells in response to the damage occurred during replication, consequently accelerating the aging process [68]. Thus the down-regulation of these reactive species could be an alternate to minimize the aging process.

Vitamin C is a powerful antioxidant that could act by providing protection against oxidative stress-induced aging by scavenging free radicals. The strong antioxidant effect of Vitamin C could be attributed to its electron donating capability from both second and third carbons of the six carbons molecule. During free radical scavenging, vitamin C neutralizes the free radicals by donating its high energy electron and itself oxidized to dehydroascorbic acid [69, 70].

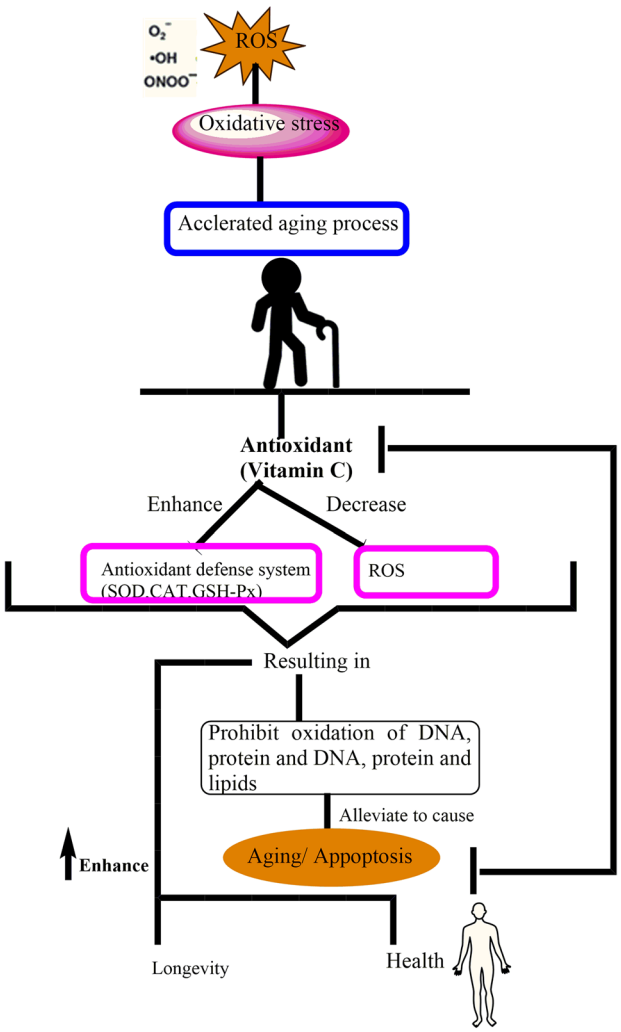

Fig. 3 Antioxidant effect of vitamin C to alleviate the oxidative stress in aging

Role of vitamin C in the prevention of age-related disorders

Vitamin C act as a cofactor in numerous biochemical reactions of enzymes such as enhances the biosynthesis of collagen, and absorption of iron, neuroprotection, maintaining the integrity of connective and vascular tissues, hydroxylation of proline and lysine, and moderating the leukocyte and hematopoiesis functioning. Both population and animal-based researches have revealed that there is a strong relationship among reducing ascorbate levels in soft tissues as well as the process of aging [71]. For example, in individuals at the age of 85 and above compared to those at age 60, reduction in the level of ascorbate was found approximately 50% in white blood cells. A previous study has shown that individuals at age of 80 and above, nearly 77% decline the level of ascorbate in the cerebral cortex,when contrasted with a person at age 50 and more youthful as shown in Table 3 [72]. Administration of ascorbate significantly increases the distinction of dopaminergic neuron which is originated from midbrain neural pluripotent stem cells [45].

Various studies showed that vitamin C can defend against melanoma. The high concentration interrupts the progression of tumors in xenograft mockups as well as prompts cytotoxicity in vitro against carcinoma. It is also found that vitamin C plays a fundamental function in antitumor activity in a clinical study [73]. Intravenous vitamin C has also been characterized to have therapeutic influence in progressive tumors. Numerous appliances of vitamin C in anticipation and management of carcinoma are; triggering the biosynthesis of collagen, averting metastasis (spreading) via prohibiting the enzymes, improving the immune system, improvement of deficiency of vitamin C which is related with individuals who have cancer, precluding viruses that can cause cancer, after surgery wound healing in patients of cancer, neutralizing some carcinogens,and preventing free radical damages, reducing the toxicity of chemotherapy, and improving the efficiency of chemotherapy. Adults who augmented with vitamin C are negatively associated with adiposity rather than the individuals who seldom or deficient in nutrient [74]. Numerous studies have supported that vitamin C inhibited the stimulation of leptin from adipocytes; predominantly the islet of langerhans beta cells which secreted the insulin [75]. Diminution in leptin might be the cause of initiate a predominantly decline in high blood pressure. Interestingly, excessive activation of leptin is associated with early-beginning of fatness which is signifying that the relation of leptin and insulin is essential in the homeostatic stability of glucose catabolism as well as fat [76].

It is estimated that high intake of vitamin C > 500 mg/dl is negatively associated with the cardiovascular disorder, and indicates an improvement in the function of the endothelium. It has been also found that individuals with more consumption of vitamin C have relatively no threat for the occurrence of myocardial infarction. Biochemical markers of dysfunction of endothelial alongside inflammation are cellular adhesion molecules. The activity of oxidized-low density lipoprotein (oxLDL) that is responsible for the stimulation of inflammation in the endothelium cells, and causes atherosclerosis can be neutralized by supplementation of vitamin C [77]. Markedly, some researchers suggested that in diabetic patients, administration of vitamin C upgraded the endothelial role. Former research indicated that diabetic patients have relatively low amount of vitamin C with respect to healthy individuals which might be cause of the scurvy [78].

Vitamin C shows a fundamental function in enhancing the immune system and requires for normal immune function. It can modify the defense system through directly protecting the important cell structural components or by modulation of redox-sensitive cell signaling pathways [79]. It also performs a significant role in various functions of neutrophil comprising; defense against the noxious properties of superoxide anion radical, improved chemotaxis, enhanced particulate ingestion, and increased lysozyme-mediated non-oxidative killing. In elderly individuals, it is found that supplementation of vitamin C improves the particular immune responses. When vitamin C 500 mg daily given intramuscularly in elderly individuals for 1 month which results in the proliferative response of lymphocyte enhanced in vitro [80]. It is also found that vitamin C can decline the inflammation from lungs; therefore, it can prevent the occurrence of asthma in susceptible individuals or might decline the severity of asthma.

Table 3 Vitamin C content in various organs of humans

Tissue	Vitamin C content [mg/100 g wet weight]	References
Brain	13–15	[87]
Kidneys	5–15	[25]
Liver	10–16	[88]
Heart muscle	5–15	[55]
Spleen	10–15	[89]
Pituitary glands	40–50	[68]
Adrenal glands	30–40	[87]
Skeletal muscle	3–4	[90]
Skin-dermis	3–13	[57]
Lungs	7	[25]
Skin-epidermis	6–64	[57]

Conclusion and future recommendations

The current study revealed that oxidative stress is the most significant cause of aging, triggered via the surplus formation of ROS. Destruction of the endogenous antioxidant

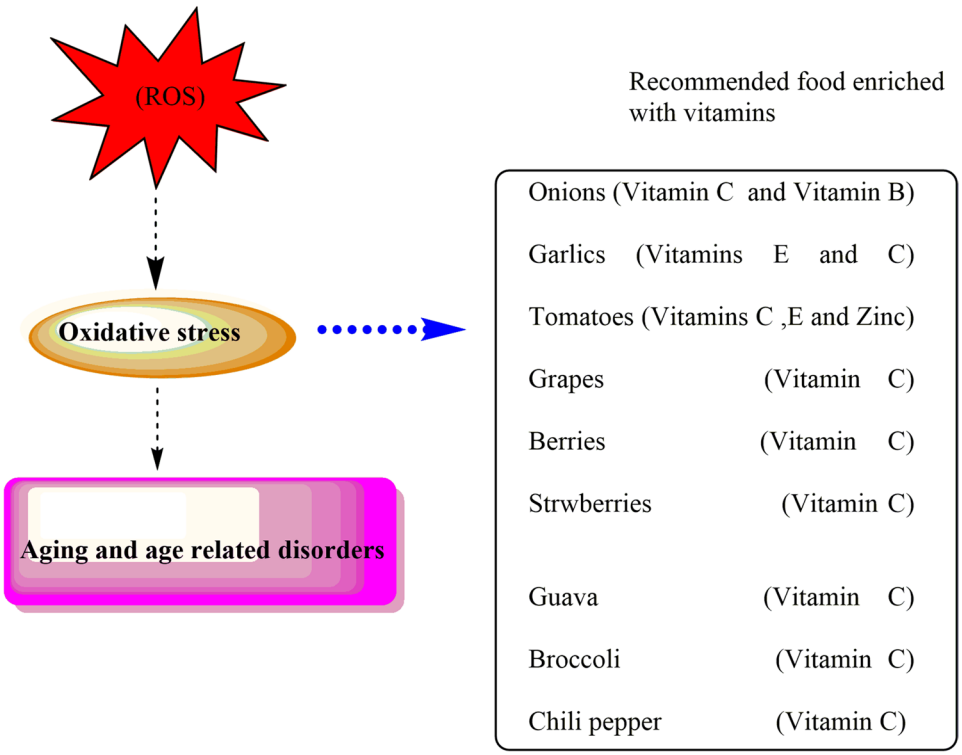

Fig. 4 Recommended food enriched with antioxidant (Vitamin C) for alleviation of oxidative stress in aging

system directly or indirectly occurs via reactive oxygen species (ROS). The immunity also declines in aging, therefore, the possibility of aging and age-related diseases might be enhanced. Vitamin C acts as a proper borderline between life span, aging, and disorders associated with aging through quench the free radicals that are produced by ROS. Therefore, a suitable approach for the mitigation of aging and extension of lifespan are antioxidant-based therapies. However, long life is not only limited to the genes but antioxidants enriched food (fresh fruits, green leafy vegetables, blackcurrant, papaya chili pepper or parsley, guava, broccoli, and strawberries) that can scavenge the ROS, enhance the immune system and production of cellular energy. Although antioxidants not function as a medication but offer leads in the future use to fight against age-related ailments. Oxidative stress biomarkers related to age might be valuable as a therapeutic target or analytical tool. Therefore, it should be recommended to control a high level of oxidative stress by consumption of various natural compounds carotenoids, tocopherols and flavonoids, as well as vitamins [A, C, D and E] due to their anti-oxidant properties as well as potentially beneficial biological activities for inhibiting or treating the age-related disorders as presented in Fig. 4.

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Declarations

Conflict of interest Biographers have no conflict of interest to this article.

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