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REVIEW article

Anti-aging potentials of a polyphenol-rich supplement from African *Sorghum bicolor* leaf sheaths: A narrative review

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Abstract: Aging is a complex biological process marked by a gradual decline in physiological functions and systemic deterioration, resulting in increased susceptibility to age-related diseases. There is increasing interest in the use of plant-based constituents in mitigating oxidative stress and inflammation, the major drivers of aging and age-related diseases. Polyphenol-rich plant-based constituents including *Sorghum bicolor* supplement (SBS) with potent antioxidant, anti-inflammatory and neuroprotective properties, have demonstrated anti-aging potential. The aim of this review is to provide documentation from published literature on the anti-aging potentials of SBS that may elicit the need for its clinical evaluation for age-related diseases. A literature search was conducted using PubMed electronic database with subject headings, related to the mechanisms of aging, age-related diseases, health burden of aging population, and polyphenols for a healthy life span. It also included the source, bioactive constituents, and antiaging potential of SBS. The findings obtained from the review showed that SBS mitigated age-related diseases in various animal models. The supplement extended the life span of *Drosophila melanogaster* and improved their motor functions. The SBS inhibited the activity of collagenase and elastase enzymes involved in premature skin aging and exhibited cytoprotection against hyposaline-induced red blood cells hemolysis. The anti-aging potential of SBS relates to its potent antioxidant, anti-inflammatory, immune-modulating, and neuro-protective properties. These findings provide a strong foundation for further preclinical and clinical studies to validate the therapeutic potentials of SBS in promoting a healthier lifespan and enhancing the quality of life of the aging population.

Introduction

Aging is a complex, irreversible, and inevitable biological process marked by a gradual decline of physiological functions and systemic deterioration, resulting in increased susceptibility to age-related diseases [1]. Oxidative stress and inflammation are key drivers of aging, contributing to telomere attrition, DNA damage, mitochondrial

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dysfunction, genetic instability, immune impairment, and metabolic disorders [2, 3]. Aging increases the incidence and severity of the debilitating nature of age-related diseases such as cerebrovascular disorders, neurodegenerative diseases, diabetes, visual impairment, musculoskeletal disorders, and cancer [4, 5]. Thus, when aging reaches a certain critical threshold, organ and tissue functions rapidly deteriorate, increasing the incidence and mortality of age-related diseases. However, the decrease in physical strength and cognitive impairments, particularly dementia, are the prominent features of the aging process. Interestingly, aging and chronic diseases are highly associated with increased oxidative stress, elevated chronic low-grade inflammation and increased DNA damage [6, 7]. Although the prospect of increased lifespan is desirable, there is a need to consider the challenges of disability and the burden of living with age-related diseases. Notably, the qualities of life of most elderly people are grossly impaired instead of a healthy life span [8].

Globally, the proportion of older people (aged 60 years and above) is rising, and it has been estimated that it will nearly double by 2050 [9]. Developing nations are undergoing rapid demographic transitions, with the rise of aging populations [10]. With the increase in the global aging population, age-related diseases have become the focus of attention worldwide for several reasons. For example, the functional decline in the elderly poses serious challenges, arising from the increased burden of age-related diseases and the shortening of healthy life span. Aging comes with financial pressure in terms of loss of economic productivity and medical expenses [1, 11]. Therefore, it is highly imperative to search for effective interventions that can positively prolong the healthy lifespan of the aging population. The current focus of aging research has shifted towards interventions targeting oxidative stress and inflammation to promote not just longevity but a healthier lifespan [1, 11]. Phytochemicals have shown promising efficacies in addressing the multifaceted pathways associated with aging [1, 12, 13]. The polyphenol-rich SBS derived from the leaf sheaths of the African *Sorghum bicolor* variety has demonstrated antioxidant, anti-inflammatory, immune modulating, and neuroprotective properties in various experimental models [14-16]. In addition, these bioactive constituents can mitigate aging-related diseases and promote healthy living among the elderly. Nevertheless, available experimental data on SBS have yet to be extensively reviewed to highlight its anti-aging potential for a healthy long life-span. Consequently, this review underscores its anti-aging properties, based on information from the PubMed electronic database. The findings obtained from the review can provide a strong foundation for further preclinical and clinical studies to validate the therapeutic potential of SBS in promoting a healthier lifespan and quality of life of the aging population.

Literature search strategy: This review analyzed information obtained from a comprehensive search of literature using the PubMed electronic database with the subject headings, relating to mechanisms of aging, age-related diseases, health burden of aging population, and polyphenols for a healthy life span. The search includes the source, bioactive constituents, and antiaging potential of SBS. We excluded studies with non-availability of the full-text articles, personal opinions and those not written in the English language.

Discussion of key findings: The published articles retrieved based on the literature search, were discussed, mainly on four broad categories, including health care burden for the elderly, biological basis of aging, polyphenols for aging and antiaging properties of SBS. The antiaging properties of SBS were further discussed under four broad subtopics.

Health care burden for the elderly: Globally, the proportion of older people, 60 years and above, is on the increase and it has been estimated that it will double by 2050 [9]. However, the aging population has several consequences on economies, social services and healthcare systems, and they are often associated with differing levels of disability and a deteriorating quality of life. The functional decline in the elderly poses serious challenges as well

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as financial pressures in terms of reduced productivity and cost of medical expenses [5, 17]. Financial and economic factors significantly affect health outcomes and well-being for elderly people. Specifically, studies have shown that disease burdens can lead to a decrease in economic growth and increased families' health-related expenditure [5, 18, 19]. In fact, the burden of diseases among the elderly people could increase families' caregiving liability, affecting resource allocation and labor employment within the household [18, 19]. The need for caregiving can affect household income and resources, particularly for families caring for elderly relatives with disabilities.

The impacts of the aging population on health systems have been documented in the literature. For example, it has been reported that in the United States, people aged 65 and above, accounted for 30% of healthcare expenditure in 2008, a figure expected to rise to 50% by the year 2030 [5, 20]. In Sub-Saharan Africa, the effects of aging would even be more devastating in countries like Nigeria, Ghana, Kenya, and Uganda, because of the projected increase in the number of older adults [21]. Taken together, these observations suggest the need to develop therapeutic strategies that can enhance the quality of life of the aging population.

Biological basis of aging: The remarkable influence of aging on the genesis of chronic diseases in humans and their progression highlights the need to understand the basic mechanisms that underlie the aging process and human longevity. Understanding the key molecular and cellular processes that are involved in aging may promote the development of therapeutic agents that could delay senescence and improve overall human health [22]. Although the dilemma behind why we age, and the causes of aging appear unfathomable, a plethora of theories have been propounded over the years to unravel the complex nature of the aging process [23]. These include telomere attrition, DNA damage, mitochondrial dysfunction, loss of nicotinamide adenine dinucleotide (NAD^+) levels, impaired autophagy, stem cell exhaustion, inflammation, loss of protein balance, oxidative stress, deregulated nutrient-sensing, altered intercellular communication and dysbiosis [1, 22, 24]. The deregulation of these interconnected pathways leads the cells to a state of senescence, which contributes to aging and the genesis of age-related diseases (**Figure 1**). Indeed, many of these interrelated mechanisms, especially DNA damage, have been touted as drivers of aging [24].

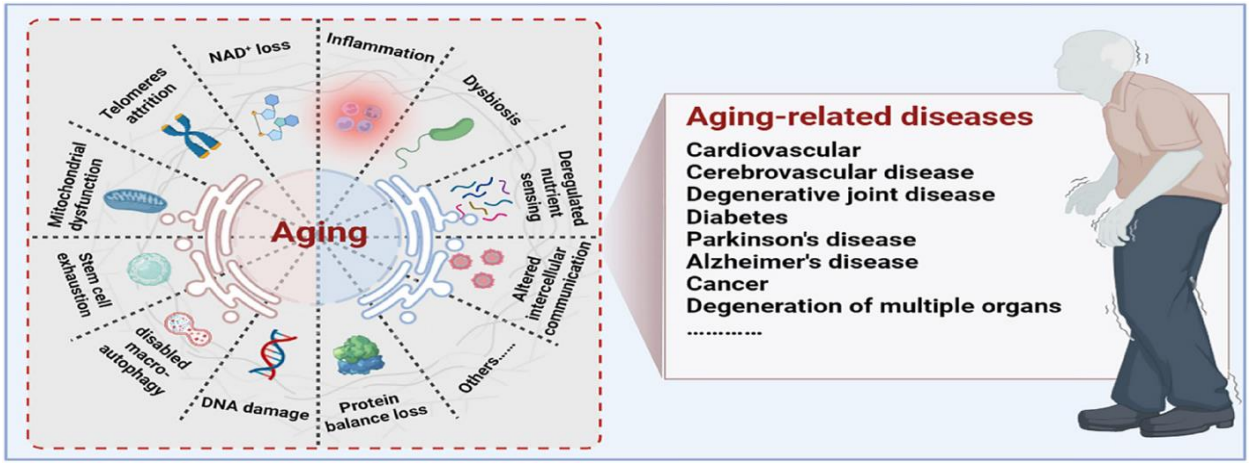

Figure 1: Key documented molecular basis of aging and age-related diseases

Telomere attrition, DNA damage, mitochondrial dysfunction, loss of nicotinamide adenine dinucleotide levels, impaired macro-autophagy, stem cell exhaustion, inflammation, loss of protein balance, deregulated nutrient sensing, altered intercellular communication, and dysbiosis are some of the key processes that underlie aging [1]. Aging leads to organ/systemic deterioration and an increase in susceptibility to age-related diseases such as cardiovascular, cerebrovascular, degenerative joint disease, diabetes, Parkinson's disease, Alzheimer's disease and cancer [1].

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DNA damage is the major internal factor that triggers genomic instability, epigenetic changes, protein stress, impaired mitochondrial function, and telomere dysfunction [1, 25]. Notably, the continuous accumulation of DNA-damaged cells triggers cell death and senescence, eventually leading to chronic inflammation, loss of function, atrophy, and aging of cells and tissues [26]. Nevertheless, the unanswered question about what factor triggers DNA damage, *ab initio,* suggests that identifying, which of the inter-related mechanisms are drivers or passengers of aging remains a big challenge [24]. However, the free radical or oxidative theory appears to be the most popular theory of aging, with several studies demonstrating the injurious nature of excessive reactive oxygen species (ROS) and oxidative stress via mechanisms, relating to the shortening of telomeres, mitochondrial dysfunction, and the initiation of aging-related inflammatory responses [27]. The theory also has a lot of evidence-based support [28]. Proposed by Harman in 1956, the free radical theory holds that aging is associated with the accumulation of ROS that exert oxidative damage to cellular biomolecules, especially the DNA (**Figure 2**), ultimately leading to a decline in physiological function and death [29]. The cellular degeneration and early apoptosis caused by free radicals produce oxidative stress, regarded as the main pathological culprit in premature aging [29]. Moreover, oxidative stress is further aggravated by a variety of stressors, which may accelerate aging and age-related diseases, as well as increased vulnerability to death [30].

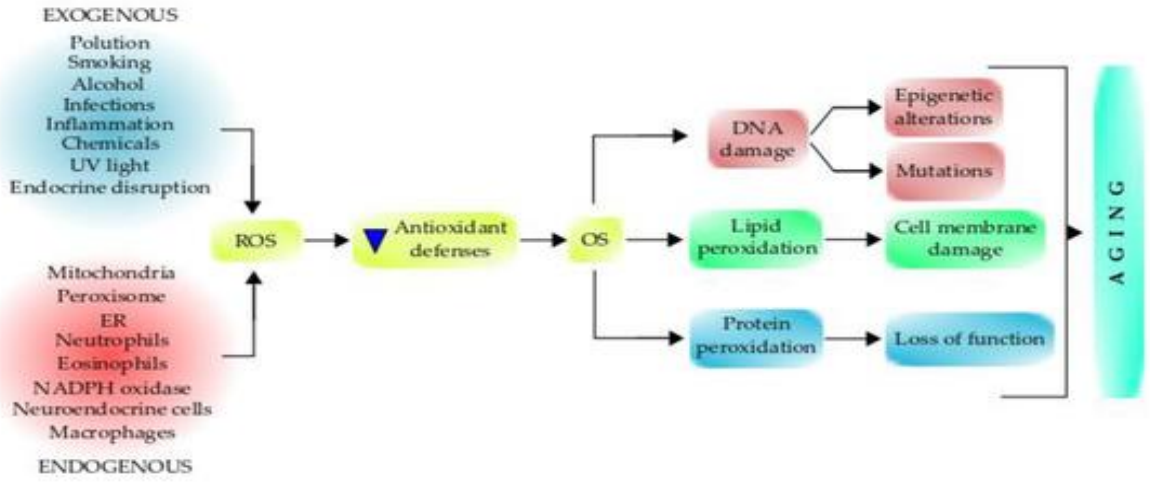

Figure 2: Role of free radicals in oxidative stress and the aging process [3]

The free radical theory holds that aging is associated with the accumulation of ROS that exert oxidative damage to cellular biomolecules, especially the DNA, ultimately leading to a decline in physiological function and causing cellular death [29]. The cellular degeneration and early apoptosis caused by free radicals produce oxidative stress, which is regarded as the main pathological culprit in premature aging [27, 29]

Indeed, oxidative stress and inflammation underlie the telomere attrition, DNA damage, mitochondrial dysfunction, genetic instability, impaired immune functions and metabolic deregulations (**Figures 3-5**) that underpin the aging process [1]. The accumulation of ROS that exerts oxidative damage to cellular biomolecules and apoptosis might be the primary initiator of the complex interconnected pathways that lead to deterioration in bodily function with aging. As shown in **Figures 4** and **5**, ROS induces telomere damage, leading to its shortening and decapitation, which further supports the central role of oxidative stress in the aging process. ROS and deregulated metabolites (NAD^+) contribute to mitochondrial dysfunction, and the development of several age-related diseases [1]. Studies have shown that increased ROS levels contribute to decreased replication of stem cells [31]. In addition, senescent cells secrete pro-inflammatory cytokines, and studies have shown that ROS and inflammation are all important inducers of cell senescence [32].

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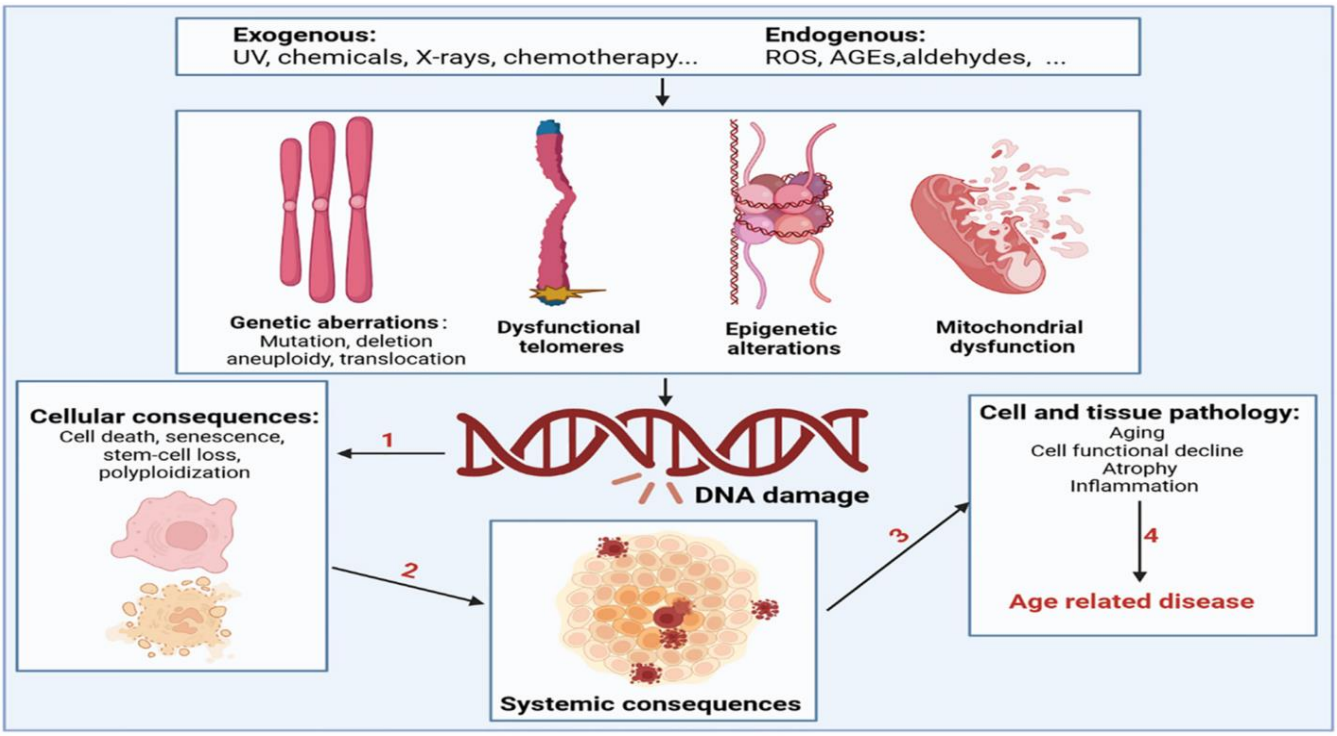

Figure 3: Drivers of DNA damage and the resulting systemic consequences of loss of cellular functions and the genesis of age-related diseases [1]

The sources of various injurious substances that cause genetic abnormalities, dysfunctional telomeres, epigenetic alterations, and mitochondrial dysfunction have been established in the literature [1, 3]. Ultimately, DNA damage leads to cellular dysregulations and promotes the development of age-related diseases [1]

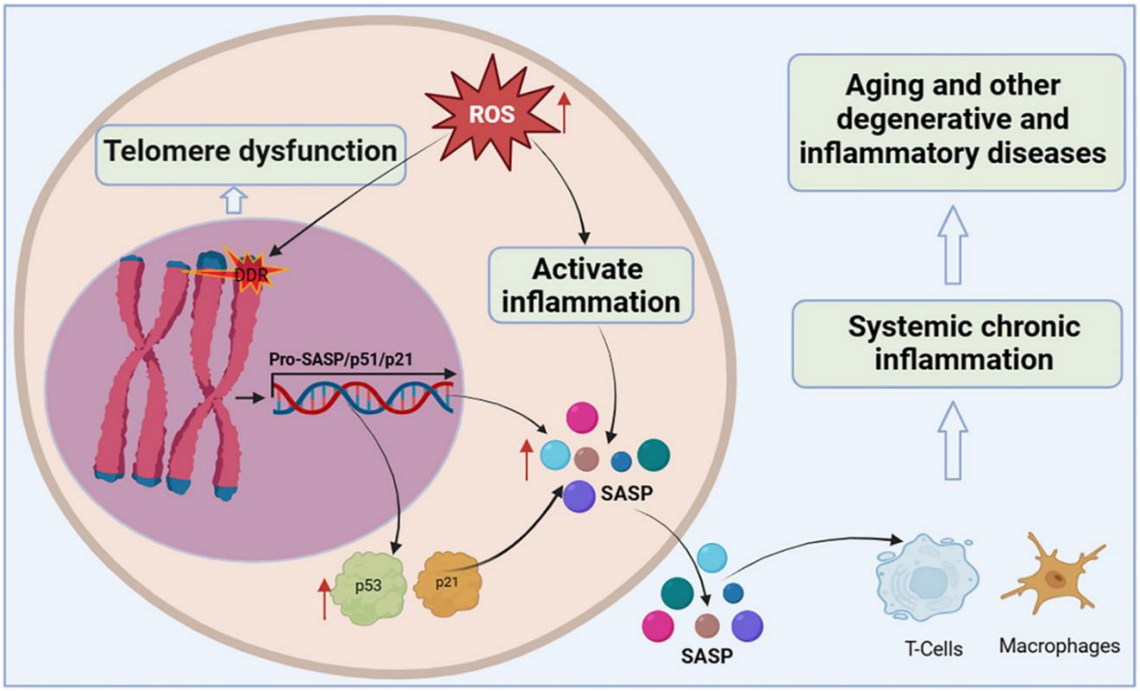

Figure 4: The role of ROS in telomere decapitation and accelerated cell senescence [1]

ROS have been implicated in telomere decapitation and accelerated cell senescence [1]. Accumulated senescent cells are known to secrete a complex set of pro-inflammatory cytokines, the senescence-associated secretory phenotype (SASP), which enhances T cells and macrophages, resulting in systemic chronic inflammation and inflammation-related diseases [1].

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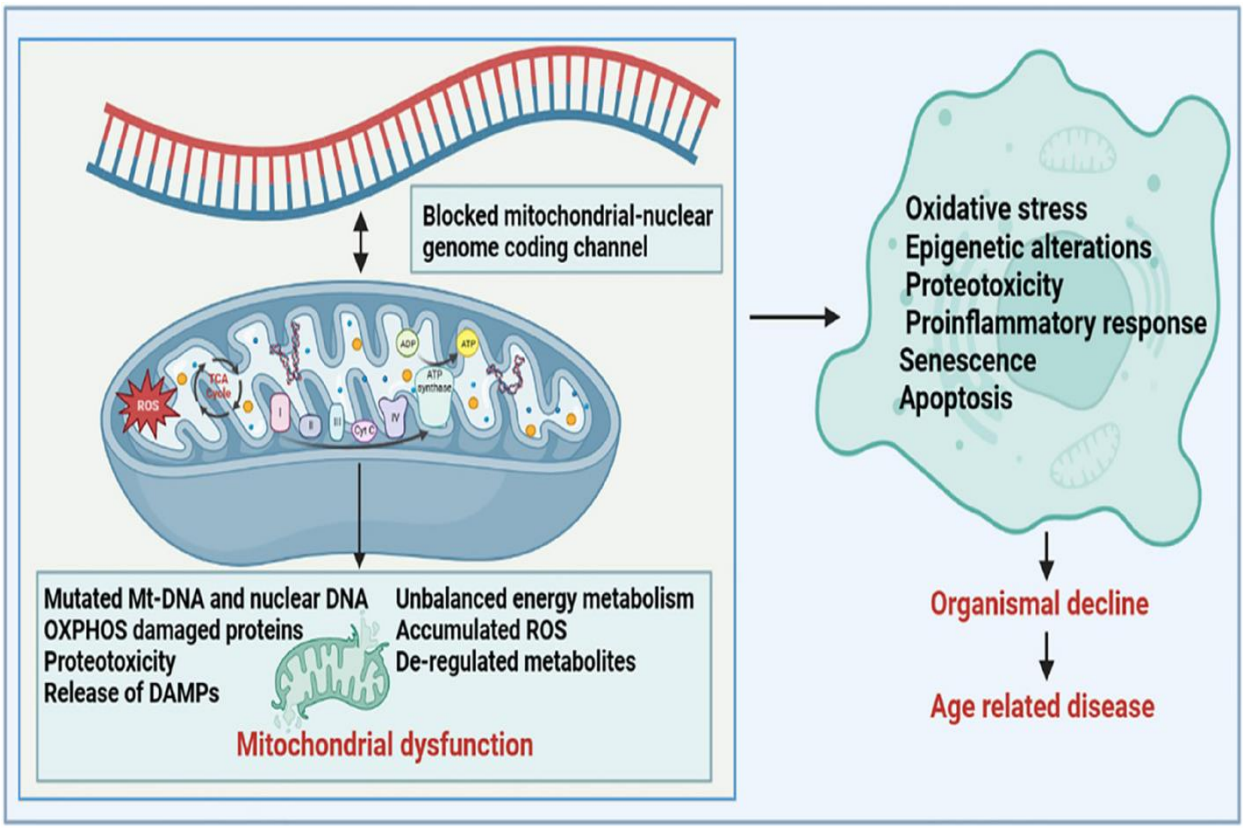

Figure 5: Drivers of mitochondrial dysfunction and development of several age-related diseases [1]

Healthy mitochondrial metabolic function is a key factor in ensuring long-term health during the aging process and is susceptible to various environmental factors and endogenous metabolites. Alterations in mitochondrial function have widespread adverse effects on intracellular homeostasis and lead to systemic organ decline and the development of several age-related diseases through complex signaling mechanisms [1]

In terms of aging, exposure to sources of damage over the human lifespan varies among individuals and may partly explain why people age differently [33]. However, the free radical theory has recently faced severe criticisms [34] including failure in addressing some critical aspects of aging. This realization has led some authors to suggest that the free radical theory of aging needs to be modified and improved upon. It likewise echoes the notion that no single theory has been able to explain the mechanism of aging [34] and none is generally considered as the gold standard [35]. Although the extant theories on aging often compete and conflict with one another, a maximally correct theory may trigger significant breakthroughs in the discovery of antiaging interventions. This may come via the integration of some existing theories for a better understanding of the mechanisms of aging and development of antiaging therapy [34]. Nevertheless, the free radical theory of aging is still one of the most promising theories of aging and constitutes the primary target for antiaging research. An imbalance between free radical generation and antioxidative capacity causes oxidative damage to DNA, proteins, and mitochondria during the aging process. Interestingly, Auley et al. [36] had further highlighted the significant role of oxidative stress in the network theory of aging, as interactions between the different key mechanisms relating to defective mitochondria, oxidative stress, DNA damage, and dysregulation of cellular signaling (**Figure 6**). Additionally, antioxidant supplementation has been shown to retard the aging process and delay the onset of age-related diseases, as well as extend human health and longevity [3]. Owing to these packets of scientific knowledge, current antiaging research is primarily focused on the use of antioxidant polyphenolic compounds to promote not only longevity, but a healthier lifespan [3].

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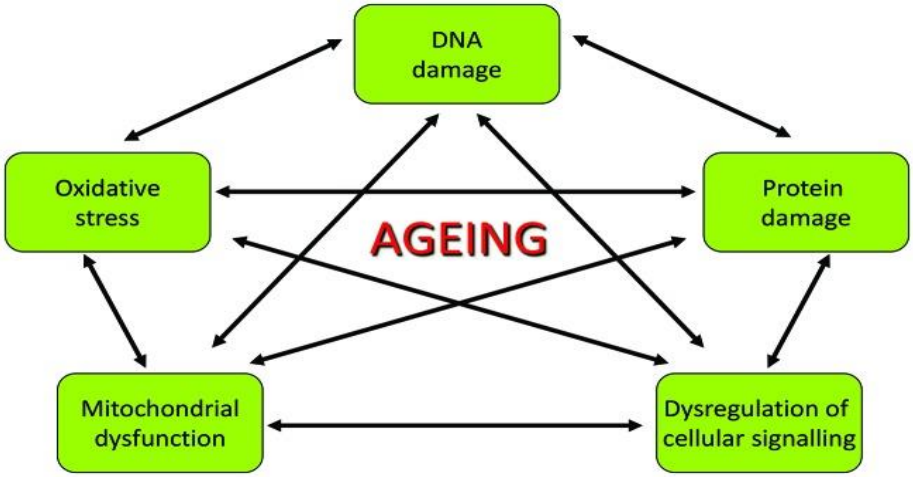

Figure 6: Complex patterns of interactions between oxidative stress, DNA, protein damage, mitochondrial dysfunction and dysregulation of cellular signaling in aging process [36]

The dysregulation of these interconnected pathways makes the cells senescent, contributing to aging and the genesis of age-related diseases [24]. The accumulation of ROS that exerts oxidative damage to cellular biomolecules and apoptosis might be the primary initiator of the complex interconnected pathways that lead to deterioration in bodily function during aging.

Polyphenolic plant-based preparations for aging

The desire to slow down the aging process and extend healthy life span has been the vigorous pursuit of the scientific field in recent times. The advocacy for lifestyle changes, including calorie restriction, sleep regulation, and exercise, has been reported to be insufficient in extending the healthy lifespan of older people or preventing age-related diseases [1]. Thus, many studies have focused on the mechanisms underlying the aging process and exploring ways of targeting the hallmark features of aging, particularly oxidative stress and inflammation. Polyphenolic-rich phytochemicals have shown promising antiaging properties by targeting the multifaceted pathways associated with aging. They exhibit numerous biological activities; including antioxidant effects, free radical scavenging, anti-inflammatory properties, neuroprotection, and immunomodulation pharmacological-key pharmacological targets for antiaging studies [37, 38].

Polyphenolic compounds, found abundantly in plant-based foods, are increasingly being recognized for their potential anti-aging properties. Polyphenols are essential components of human diets, and epidemiological data indicate that consuming foods rich in antioxidants lowers the incidence of oxidative stress-related aging disorders such as diabetes, cardiovascular diseases, neurodegenerative diseases and cancer [12, 13]. These compounds can help combat cellular damage, improve various physiological functions, and potentially slow down the aging process. Indeed, polyphenols protect cells from oxidative stress, delay cellular aging, and safeguard tissues from degradation [38]. Certain polyphenols can reduce inflammation, a key driver of age-related conditions, by suppressing inflammatory signaling pathways. In addition, polyphenolic compounds are generally regarded as safe and effective in preventing age-related diseases [38, 39].

Dietary polyphenolic components can extend the lifespan of various model species by removing senescent cells, maintaining mitochondrial homeostasis, suppressing inflammatory response, and countering oxidative stress [12, 13]. In fact, increasing evidence has demonstrated that dietary polyphenol intake can delay aging and age-related diseases [38]. The antiaging potential of these phytoconstituents is related to their anti-inflammatory and antioxidant capabilities and promotion of cellular repair [12, 40]. Also, polyphenols can regulate immune function and improve resistance to diseases by inhibiting the NF-κB pathway and pro-inflammatory gene expression,

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suppressing the enzymes related to the production of ROS, and up-regulating other endogenous antioxidant enzymes [41]. Polyphenols have shown protective effects on cognitive functions, alleviating neurodegenerative diseases by preventing cellular damage, and enhancing DNA repair machinery [42]. Epidemiological studies show that adhering to the Mediterranean dietary pattern, which is a plant-based diet, was associated with better health outcomes during aging [43]. These findings further suggest that diets rich in polyphenol-based food plants positively influence the hallmark of aging-related disease risks and longevity [43]. Remarkably, diets rich in vegetables and fruits with antioxidant and anti-inflammatory activities are linked to a low incidence of age-related diseases [44, 45]. Based on these findings, it is logical to think that the nutrients and bioactive molecules found in plant-based foods play a key role in acting synergistically to positively influence the different pathways of the aging processes.

Antiaging properties of the SBS supplement

Sorghum bicolor (L. Moench, family Poaceae), popularly known as millet, sweet *Sorghum*, or guinea corn, is widely cultivated in many tropical countries of the world for its economic, nutritional, and medicinal values [14]. *Sorghum bicolor* is a unique plant-derived food and ranked fifth after wheat, maize, rice, and barley in the world's cereal production [46]. Besides being used as a staple food by the natives of Africa, Central America and South Asia, the sorghum grain is used worldwide as animal feed [47]. In ethnomedicine, different parts of the plant, including the grain, are used for a myriad of chronic diseases [14, 47]. However, the leaf-sheaths portion of the plant have been recognized for the presence of high contents of polyphenolic bioactive compounds (**Table 1**). These bioactive compounds have exhibited potent antioxidant, anti-inflammatory, immunomodulating and neuroprotective, and chemopreventive properties [14, 16, 48], suggesting the potential roles of SBS in mitigating age-related diseases and as a possible elixir to healthy aging. In this review, we present evidence from the literature alluding to the antiaging potential of SBS and its capacity to promote healthy aging.

Therapeutic potential of SBS supplement in aging-related diseases

The antiaging potential of SBS is implied in its reported mitigation of age-related diseases such as stroke, arthritis, cancer, movement disorders, and memory deficits [14]. It is worth noting that ischemic stroke is the second leading global cause of death and physical disabilities among the elderly. It is due to the activation of oxidative and inflammatory pathways triggered by the obstruction of cerebral blood flow and subsequent neuronal cell death [49]. Thus, targeting oxidative and inflammatory pathways with bioactive constituents of plant origins offers promising therapeutic strategies for ischemic stroke [49-51]. Epidemiological data have revealed that regular consumption of plant-based foods rich in polyphenols can reduce the risk of stroke [51]. Lending credence to this, preclinical studies showed that SBS reduces the neurological deficits in a global ischemic stroke model through inhibition of oxidative stress, pro-inflammatory cytokines (IL-6 and TNF-α) and NF-kB reactivity in rats [52]. It protected the neurons of the striatum, prefrontal cortex, and hippocampus, as well as increasing the population of viable neuronal cells in these brain regions of ischemic rats [52]. The potential benefits of SBS in neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) have also been investigated in scopolamine-induced amnesia and rotenone-induced motor dysfunctions, respectively, [53, 54]. The findings showed that the supplement attenuated amnesia and motor dysfunctions by augmenting the neuronal antioxidant protective mechanisms. It reduced pro-inflammatory cytokines in rotenone-induced Parkinsonian-like motor dysfunctions in rats [54], indicating its therapeutic potential in movement-related disorders associated with aging.

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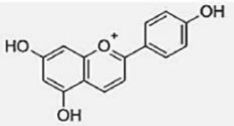
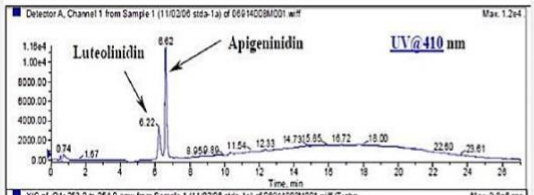
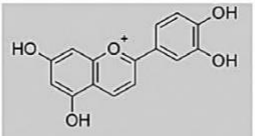
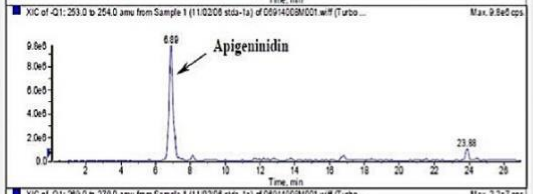
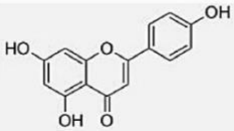
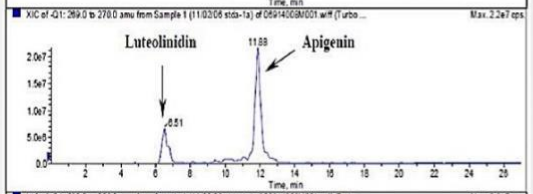
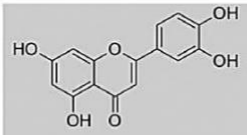
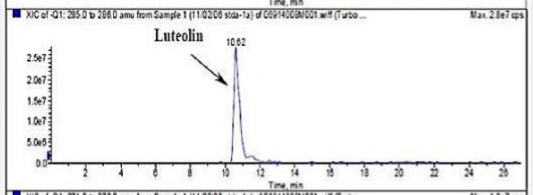
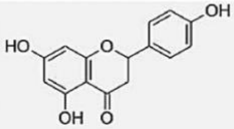
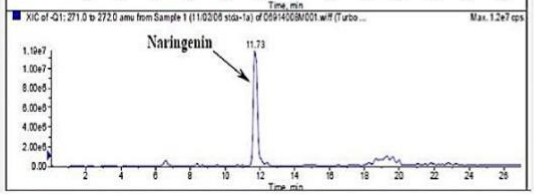
Rheumatoid arthritis is another age-related disease in the elderly. It is a chronic inflammatory autoimmune disease due to progressive inflammation of the synovial tissues, and cartilage destruction in the affected joints [55, 56]. The joints' health-promoting effects of SBS was demonstrated when it was tested in rats subjected to intra-articular injection of complete Freund's adjuvant (CFA). The supplement was shown to have reduced pain sensitivity in the hyperalgesia test and joint inflammation in rats with intra-articular injection of CFA. The supplement also positively modulated oxidative stress, pro-inflammatory cytokines, apoptotic factors (caspase 3 and caspase 9), NF-κB, myeloperoxidase, and nuclear factor erythroid 2-related factor 2 (Nrf_2), and articular tissue degeneration in the ankles of CFA-arthritic rats [57]. Notably, these biomarkers and transcription factors (NF-κB and Nrf_2) play pivotal roles in cellular aging and age-related pathologies, including arthritis [58-59]. Thus, the findings that SBS positively modulated these biochemical pathways and transcription factors further substantiate its anti-aging potential in promoting healthy joints in the elderly. Studies have shown that SBS is rich in diverse bioactive polyphenol-rich constituents (**Table 1**) such as luteolin, narigenin, apigenindin, apigenin and luteolinidin [16, 60], most of which exert diverse pharmacological activities; including anti-inflammatory, anti-mutagenic, anticancer, immunomodulatory, antioxidant, and neuroprotective effects [16, 61, 62]. SBS is rich in minerals such as iron, zinc, calcium, copper, magnesium, selenium, phosphorus, sodium and potassium, and omega-6 fatty acid [14], which are essential for metabolism and neuronal functioning [63]. Omega-3 and -6 fatty acids, for example, have demonstrable anti-inflammation, anti-apoptosis and neuroprotective properties [64, 65].

Table 1: Phytochemical constituents of leaf sheaths of *Sorghum bicolor,* Jobelyn® [60]

Marker	Structure	[M-H]- (*m/z*)	HPLC-UV/extracted ion chromatograms	Amount in leaf sheath powder (mg/g)*
Apigeninidin		253		29.87±9.85
Luteolinidin		269		0.34±0.21
Apigenin		269		4.90±1.29
Luteolin		285		0.52±0.16
Naringenin		271		0.15±0.05

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Several studies have shown that SBS is rich in various polyphenols with cancer prevention capabilities. It is pertinent to note that cancer is one of the common diseases associated with aging arising from alterations in DNA molecules and defects in DNA repair machinery. These changes lead to unchecked cell proliferation and neoplastic transformations [66, 67]. Oxidative stress and inflammation also play prominent roles in cancer pathogenesis and are robust targets for cancer prevention. Polyphenol-rich plant foods with chemopreventive capabilities have been documented in the literature. Epidemiological and animal studies have shown that phenolic compounds exhibit anti-cancer properties through multiple mechanisms relating to antioxidant activity, induction of cell cycle arrest and apoptosis, and the promotion of tumour suppressor proteins [68-70]. For example, luteolinidin and apigeninidin showed efficacy against colon cancer stem cells via reduction of cell proliferation [71]. Benson and others [16] and Makanjuola and others [72] reported that SBS is rich in 3-deoxyanthocyanins such as luteolinidin and apigeninidin with potential immunomodulatory properties, which may be central to its anticancer activity. These findings align with the report of the National Cancer Institute, USA, that reported that SBS is rich in various polyphenolic compounds with high capability for cancer prevention, owing to their immune-modulating, antioxidant and anti-inflammatory activities [73]. Besides, luteolin and naringenin have demonstrated anticancer properties in various cancer types in preclinical settings, and these anticancer effects have been found to be mediated through interaction with different molecular target sites and several signaling pathways in cancer cells [74-76]. These findings suggest that the presence of these bioactive compounds might be playing a significant role in the anticancer potential of the supplement. Nevertheless, more studies are necessary to further validate the efficacy of SBS for cancer prevention.

It is well established that aging is a key factor contributing to the development of neurodegenerative diseases such as AD and PD. Currently, there is no effective treatment for neurodegenerative diseases due to their multiple pathological mechanisms. Thus, discovering a multi-target agent is necessary to counteract these disorders. In this vein, natural compounds with anti-inflammatory, antioxidant, anti-apoptotic and neuroprotective effects hold promising benefits in the treatment of AD and PD [76]. For example, naringenin, luteolin and apigenin, the key constituents of SBS [14, 16], have been reported to exhibit neuroprotective properties [76-78]. Intake of naringenin interestingly improved spatial learning and memory in a rat model of AD through its anti-inflammatory, antioxidant, anti-apoptotic and neuroprotective mechanisms [76, 79]. Recent studies showed luteolin as a promising agent against AD, demonstrating neuroprotective and memory-enhancing effects in experimental models [78]. Apigenin has exhibited neuroprotective properties against neurodegenerative diseases in various experimental models. Apigenin and luteolin, in combination, rescue the dopaminergic neurons by reducing microglial activation, neuroinflammation and oxidative stress as well as enhancement of BDNF in the MPTP model of PD [80]. Based on the presence of these bioactive substances in SBS, it is logical to infer that they might be contributing to its neuroprotective properties in age-related diseases. As such, SBS by virtue of its neuroprotective ability might be a key towards healthy aging and longevity.

SBS supplement as a potential remedy for skin aging

There is a renewed interest in developing safer bioactive agents for skin health and against various harmful substances, including ultraviolet radiation (UVR) and free radicals. It is instructive to know that free radicals accelerate skin ageing through several mechanisms (**Figure 7**), resulting in disruption of the skin's protective mechanisms [13, 81]. In addition, oxidative damage caused by UVR promotes the formation of pro-inflammatory cytokines, including interleukin 1-β (1L-β), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) which are involved in skin disorders. The UVR-induced skin aging increases the activation and expression of certain

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proteases (collagenase and elastase) of the extracellular matrix of the dermis. Notably, these enzymes play significant roles in skin aging by causing degradation of elastin and collagen which are essential for skin elasticity and firmness. Increased activity of these enzymes leads to excessive degradation of collagen and elastin fibers, resulting in fragile skin with wrinkles and without elasticity [82]. Remarkably, free radicals can cause wrinkle formation and skin aging by activating these enzymes, leading to increased hydrolysis of elastin and collagen. Furthermore, activation of elastase and collagenase increases with inflammatory process and collagen degradation is a prominent feature of the inflammatory skin diseases [83]. Cosmetic products containing synthetic agents as the active substances are known to cause adverse effects such as allergic reactions. These findings have redirected the attention of researchers into plant-based preparations for skin care. Indeed, natural skin care products are easily absorbed from the skin layers and generally known to be hypoallergenic [83]. So, the inhibitors of these elastase and collagenase enzymes are being targeted as potential cosmetic ingredients in combating skin aging.

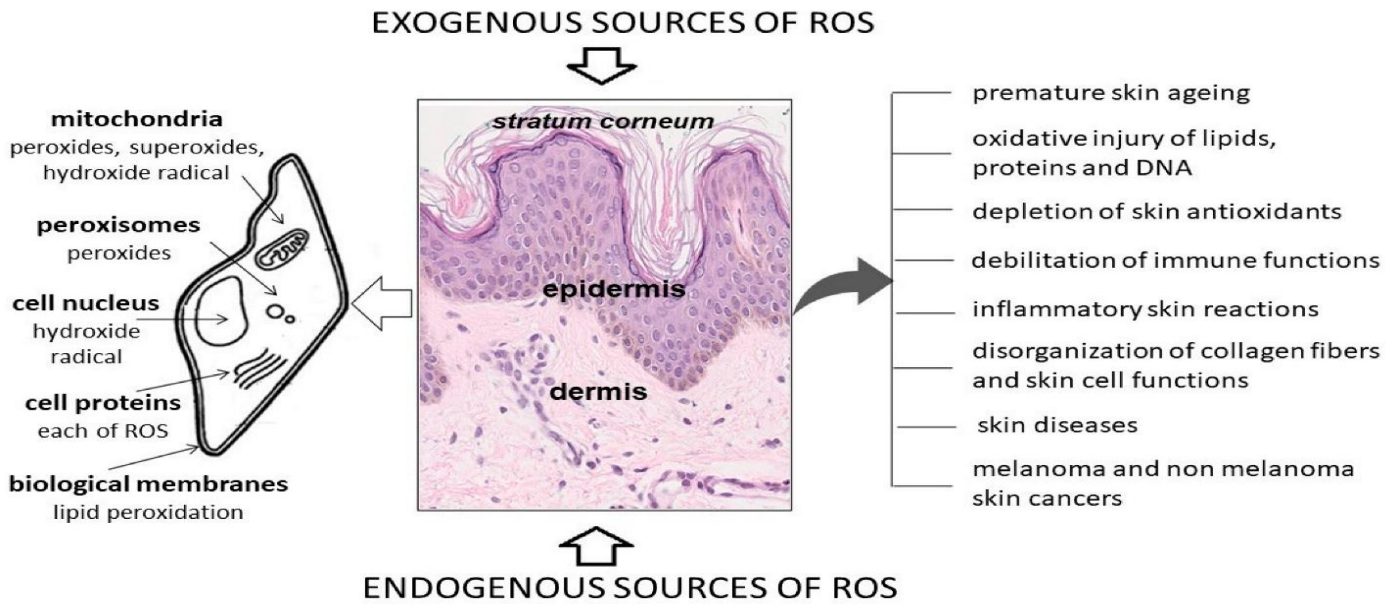

Figure 7: Potential cellular skin components attacked by ROS and the mechanisms underlying oxidative stress-mediated premature skin aging and skin-related diseases [13]

Recently, dietary phytochemicals have gained considerable popularity owing to their potential benefits in premature skin aging. They have been found to protect against skin damage due to oxidative stress by scavenging free radicals and reducing inflammation [84]. They can boost the health of the skin by decreasing the effects of sunburn and absorbing UVR, stimulating collagen production and reducing collagen breakdown [85]. The UV-protective effects of plant extracts are important as UV-induced photo-oxidative damage to cellular lipids, proteins and DNA is associated with premature skin aging and development of skin cancer [13]. The effectiveness of the cutaneous anti-aging preventive effects of SBS has been suggested based on its richness in polyphenolic constituents; noted for their antioxidant, anti-inflammatory, immunomodulating and neuroprotective properties. However, direct evidence on the potential of the supplement in promoting healthy skin has been shown from the study conducted on elastase-1 and collagenase-1 enzymes by Brunswick Laboratory, based in the USA [73], which found that the supplement inhibited the activity of elastase-1 and collagenase enzymes. The SBS was shown to be more effective than vitamin C and ferulic acid in inhibiting these enzymes, suggesting its capability to promote skin health [73]. It was concluded that elastase and collagenase inhibition might be related to the

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exceptional antioxidant activity of the supplement. Taken together, the findings that SBS inhibited elastase and collagenase enzymes suggest its potential usefulness in cosmetic ingredients for combating skin aging. The SBS polyphenolic constituents have been shown to delay skin aging and promote healthy skin via wrinkle reductions and skin moisture improvement. For example, luteolin and naringinin found in SBS demonstrated anti-aging effects on the skin [13]. A recent study by Iida et al. [86] reported that luteolin mitigated hair graying in a mouse model via a mechanism relating to a decrease in oxidative stress. It is important to note that hair graying creates a negative impression of senescence [87, 88], leading to a worldwide demand for interventions that can prevent hair graying or retard its progression [89]. The results of Iida and others [86] are encouraging and further suggest the need for the evaluation of the supplement for anti-graying effect with practical application in human hair, considering its richness in luteolin.

Antiaging properties of SBS based on Drosophila survival time

Drosophila (fruit flies) are used as model organisms in aging research due to their relatively short lifespan and similarities to humans in some cellular and molecular aging processes [90, 91]. The ability of test substances to extend the lifespan of Drosophila is always taken as evidence of anti-aging properties [92, 93]. The findings from Drosophila studies can provide valuable insights into the mechanisms of aging and potential targets for interventions to promote longevity and address age-related diseases in humans. Studies on Drosophila have demonstrated that SBS significantly prolonged the lifespan of fruit flies (**Figure 8**) and improved age-related health biochemical indicators such as antioxidant defense profiles [15]. This finding provides direct evidence, which suggests that the supplement has anti-aging properties and can promote longevity. Too, SBS extended the lifespan of fruit flies exposed to lipopolysaccharide (LPS) (250 µg/g diet). In this study, LPS reduced the life span of Drosophila, with most of the flies dead before day seven post-exposure (**Figure 9**). LPS is a known neurotoxin widely used to induce complex neurological disorders such as AD, movement disturbances and depression [94, 95], and its lethal effect on Drosophila has been ascribed to the induction of oxidative and inflammatory damage to cellular constituents [96]. The remarkable finding that SBS extended the lifespan of the flies exposed to LPS holds significant implications as a potential antiaging remedy in clinical settings.

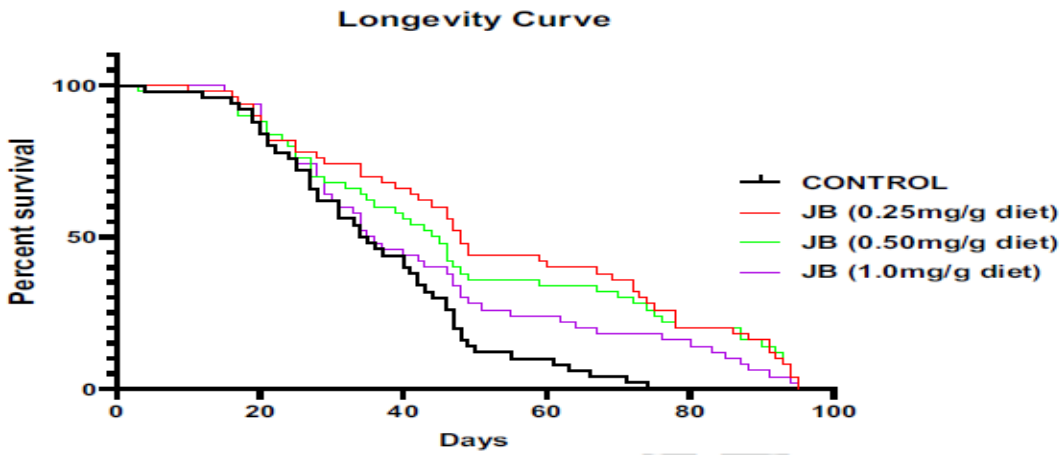

Figure 8: Effect of Jobelyn® (JB) on the survival curve of adult *D. melanogaster* [15]

[Figure first published in Metabolic Brain Disease, 37: 1031-40, 2022]. The supplement otherwise known as JB, extended the lifespan of Drosophila [15], suggesting anti-aging properties [92, 93].

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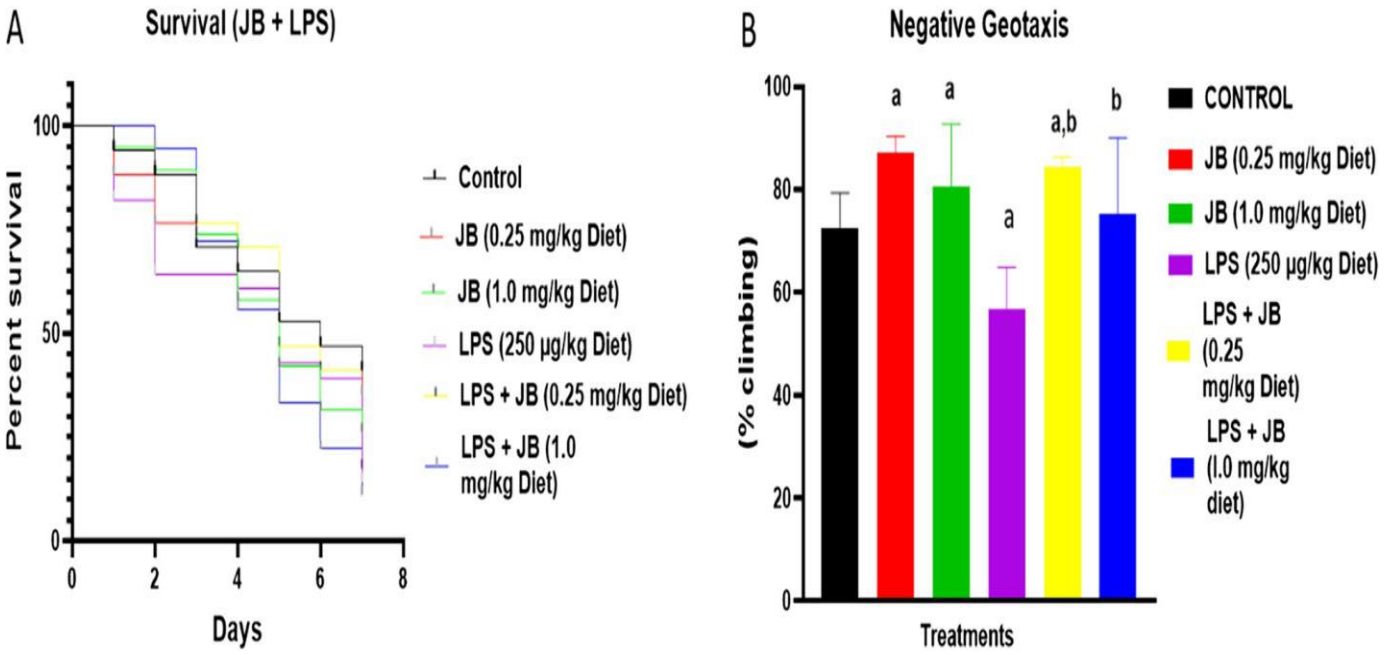

Figure 9: Effect of Jobelyn® (JB) on the survival curves (**A**) and negative geotaxis (**B**) of *D. melanogaster* exposed to lipopolysaccharide (LPS)

[a] $p<0.05$ relative to control; [b] $p<0.05$ compared with LPS (One-way ANOVA followed by Newman-Keuls *post-hoc* test) [15] [Figures first published in Metabolic Brain Disease, 37: 1031-1040, 2022].

Besides lifespan extension, Drosophila is used to assess other aspects of aging such as locomotor activity and resistance to oxidative stress. Indeed, studies have shown that aging of *D. melanogaster* is accompanied by declines in motor and cognitive abilities [92, 93]. Interestingly, John et al. [15] reported that the flies fed with LPS exhibited locomotor deficit as evidenced by impairment of negative geotaxis (**Figure 9**). Negative geotaxis has been used to study movement disorders associated with PD in Drosophila [96, 97]. Thus, the finding that the supplement ameliorated movement disturbance in Drosophila fed with LPS suggests its potential usefulness in age-related disorders such as PD. The supplement mitigated LPS-induced elevation of acetylcholinesterase activity in the flies [15], an indication of cognitive decline associated with aging [98, 99]. Taken together, these findings further suggest the antiaging properties of SBS and its potential benefits in neurodegenerative diseases such as PD and AD. Drosophila is used as a model organism for elucidating the role of oxidative stress underlying the aging process and the potential of antioxidants to promote longevity and mitigate age-related diseases in humans. It has been documented that a substance can be adjudged to have anti-aging properties if it reduces lipid peroxidation and elevates antioxidant status in Drosophila [91, 100]. E.g., increased activity of antioxidant enzymes such as catalase and superoxide dismutase resulted in an increase in the lifespan of Drosophila [101]. In addition, the long-lived strain of *Drosophila* has been shown to exhibit higher activity of superoxide dismutase (SOD) and catalase throughout its lifespan than the short-lived strain, further supporting the notion that oxidative stress plays a prominent role in aging [102]. Interestingly, SBS supplementation reduced hydrogen peroxide accumulation and boosted antioxidant contents in the flies exposed to LPS. Previous studies have shown that LPS causes accumulation of hydrogen peroxide, leading to tissue injury by damaging key cellular molecules such as DNA and lipids, resulting in the depletion of antioxidant protective mechanisms [103, 104]. Thus, LPS-induced Drosophila lethality is associated with increased vulnerability of the flies to oxidative damage. Thus, the lifespan extension effect of SBS might be related to its potent anti-oxidative property, in preserving the cellular constituents of the flies against oxidative damage that typifies the aging process.

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SBS and hyposaline-induced red blood cell hemolysis aging model

Changes in aging red blood cells (RBCs), such as a decrease in enzymatic activities, loss of membrane integrity, reduced hemoglobin (Hb) concentrations, increased oxidative stress, and metabolic dysregulations have been regarded as potential indicators of the human aging process [105, 106]. Specifically, Remigante and others [107] revealed that the RBC membrane is an excellent biomarker for studying age-related changes. The RBCs *in vitro* model of hyposaline-induced hemolysis is being considered as a unique cellular aging model for investigating the molecular changes in the aging process and detection of agents with antiaging properties, as it is associated with changes in membrane properties and fragility that are observed in cellular aging [106]. This is largely related to the membrane of RBC as an important component responsible for its vitality and any damage to its membrane can elicit loss of functions that underlie the aging process [108]. The hemolytic effect of hyposaline solution is due to the accumulation of excessive fluid in the cells resulting in rupture of the RBC membrane. When the red cell membrane is injured, it will make the cell more susceptible to secondary damages via oxidative stress and the release of inflammatory mediators [109]. Growing evidence portrays a time-dependent oxidative assault to the Hb, indicating that oxidative injury is a key part of RBCs hemolysis [110]. Studies have shown that oxidative stress plays a significant role in damaging the RBC membrane and impairing its functions. RBCs are continuously exposed to endogenous and exogenous sources of ROS such as superoxide and hydrogen peroxide. The bulk of the ROS are neutralized by the RBC antioxidant system consisting of non-enzymatic and enzymatic antioxidants including catalase and glutathione peroxidase [110]. Lysis of the membrane leads to increased susceptibility of Hb to oxidative stress destruction. Agents with membrane stabilizing and antioxidant properties will prolong the life span of the RBCs. SBS has been found to inhibit hyposaline-induced RBC hemolysis [111], suggesting cyto-protective effect, which is a feature of antiaging substances. Studies have shown that exhibition of anti-hemolytic property is an indication of membrane stabilization in preventing the release of lysosomal phospholipases that are primary initiators of the inflammatory responses [112, 113] that typify aging. Earlier studies have revealed the abilities of polyphenols in targeting these changes in RBCs [114]. So, the capability of SBS to protect the RBCs from the damaging effects of hyposaline solutions further suggests its cellular antiaging potential.

Conclusion: Despite the extensive research, no effective pharmacological agents have been discovered to promote longevity and healthy aging. The complex pathophysiological mechanisms of aging, along with the lack of safe and efficient therapies for age-related diseases, underscore the need for novel multi-target therapies. Current research efforts focusing on natural products, and their bioactive compounds with the capabilities of targeting multiple pathways orchestrated by activation of oxidative stress and inflammation as a panacea for an increased healthy life span. Among the natural products, SBS supplement has shown promising antiaging properties by targeting multiple pathways, including oxidative stress and inflammation. The SBS supplement is reputed for the presence of phytochemicals, with antiaging properties and capabilities of addressing age-related diseases by targeting the multifaceted pathways of aging (**Figure 10**). Although numerous *in vitro* and *in vivo* studies have established the ability of SBS to alleviate several layers in the processes that underpin models of age-related diseases, the lack of clinical trials and pharmacokinetic studies are major limitations that need to be addressed. Due to its potential to prevent premature skin aging, SBS is potentially of importance in the cosmetics industry. Thus, further research on SBS as a potential additive in skincare products with the aim of mitigating premature skin aging is also necessary. Taken together, the insights generated in this review highlight the need for preclinical and clinical studies for further validation of the anti-aging potential of SBS and developing therapeutic strategies that can enhance the quality of life of the aging population.

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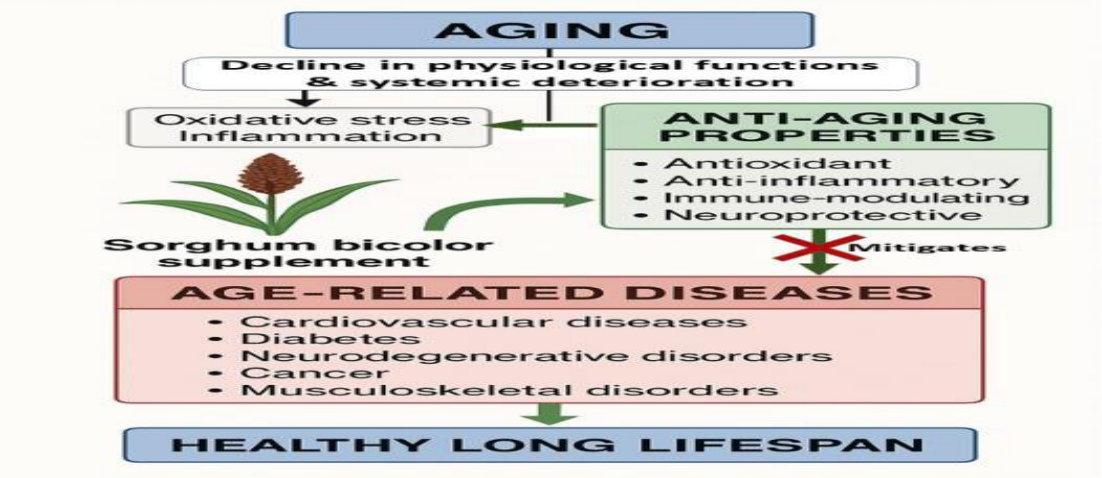

Figure 10: Schematic diagrammatic representation of the target sites of healthy long life-span promoting effects of *Sorghum bicolor* supplement

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