 doi:10.20944/preprints202208.0011.v1

Review

Polyphenol Rich Nutritional Supplement Derived from the West African *Sorghum Bicolor* Leaf Sheaths Has Evidence-Based Efficacy and Health Promoting Effects

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Abstract

Across different cultures around the globe, human beings have historically depended largely on medicinal plants for managing diseases that have hitherto threatened their optimal health, survival, and longevity. Evidently, the health-derived benefits of medicinal plants can be strongly attributed to the presence of secondary metabolites, particularly polyphenols. The health-promoting effects of Sorghum bicolor supplement **Jobelyn®** (SBSJ) —a unique supplement derived from the leaf sheaths of a West African variety of *Sorghum bicolor* (L.) Moench—have also been ascribed to its high levels of polyphenols. This review seeks to gather and synthesize findings from various experimental and clinical studies on the health benefits of SBSJ in arthritis, cancer, chronic viral infections, stroke, anaemia, and aging. SBSJ has been reported to contain potent bioactive polyphenolic compounds with polyvalent biological activities, including antioxidant, anti-inflammatory, immunomodulatory, chemopreventive, and neuroprotective activities. Moreover, the probable benefits of SBSJ in chronic viral infections (e.g., HIV/AIDS and COVID-19) have been attributed to its potent anti-inflammatory and immunomodulatory activities. As this supplement is increasingly becoming one of the fastest-selling herbal medicines in Nigeria, there is a need for more robust studies (including clinical trials) in order to replicate and validate the prior insights gleaned from experimental studies.

Keywords: SBSJ; polyphenolic constituents; antioxidants; anti-inflammatory; chemoprevention; immunomodulation; anti-aging; adaptogen

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1. Introduction

Historically, human beings have responded to infectious and non-infectious diseases that threaten their health and existence through the use of plant-based products which are available within their immediate environment. In modern times, laboratory screening of plant-based constituents has favourably shifted the therapeutic curve of modern medicines, as they have yielded the discovery of important biomolecules with activities such as anticancer (vincristine), antiglaucoma (physostigmine), antimalarial (quinine), muscle relaxant (tubocurarine), cardiotonic agent (digoxin), and analgesic (morphine) [1-3]. Furthermore, the discovery of calanolides (from *Calophyllum teysmannii* Miq.) with anti-retroviral activity, paclitaxel (*Taxus brevifolia* Nutt.) as an anticancer agent, artemisinin (*Artemisia annua* L.) as an antimalarial, St. John's wort (*Hypericum perforatum* L.) as an antidepressant, and ginseng (*Panax ginseng* C.A.Mey.) as an adaptogen further demonstrate the key roles of medicinal plants in contemporary healthcare [1, 4-5].

Over two decades ago, the WHO reported that herbal products are extensively used across the globe as alternatives to pharmaceutical medicines [6]. It was estimated that about 80% of the African population depends largely on herbs, as compared to 65% in India. The WHO report also showed that 50% of Canadians and 75% of people in France used alternative medicines, while 85% of Japanese doctors prescribed not only modern medicines but also traditional herbal medicines [6]. In the United States of America, it has been reported that over 15,000 herbal medicines are sold annually for nearly five billion dollars, thus constituting the fastest-growing sector of the pharmaceutical market [6]. These reports further indicate the central position of medicinal plants in primary healthcare delivery.

The therapeutic efficacy of medicinal plants is generally attributed to the presence of several potent bioactive constituents, otherwise known as secondary metabolites [7-9]. Various studies have established the capability of several phytochemicals to attenuate the de-regulation of the neuroendocrine–immune system, orchestrating downstream activation of oxidative and inflammatory pathways—the primary co-conspirators in the pathogenesis and progression of chronic human diseases in response to infections or abiotic factors [7-9, 10]. Thus, it is widely believed that medicinal plants with diverse phytochemical constituents with proven antioxidant and anti-inflammatory activities may provide a better option for the treatment and prevention of chronic diseases [7-8, 11]. The polyphenols, particularly flavonoids and phenolic acids, constitute a group of unique secondary metabolites that play roles in the defence mechanisms of plants against pathogenic attacks and abiotic factors [8,12]; for example, the response of the sorghum plant to pathogen attacks and abiotic stressors leads to the accumulation of high levels of secondary metabolites which enhance the survival of the affected cells [9, 13]. This defence mechanism also underpins the healing and health-promoting effects of

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SBSJ, a unique supplement derived from the leaf sheath of a West African variety of *Sorghum bicolor*.

SBSJ is an African-based herbal supplement, which has been widely acclaimed for its several health benefits, including chemoprevention and mitigation of arthritic pains, stroke episodes, and neuropsychiatric disorders, as well as promoting resilience against stressful situations [14-16]. It has also been reported to contain potent bioactive compounds [17] with multi-target and polyvalent pharmacological activities, including suppression of oxidative and inflammatory signalling pathways [8-9]. These bioactive constituents have also been shown to exhibit neuroprotective abilities and to inhibit cell proliferation in cancer cells through the stimulation of various apoptosis promoter genes, as well as down-regulation of certain apoptosis inhibitor genes which are critical players in the induction of carcinogenesis [13, 18]. Moreover, the possible benefits of SBSJ in chronic viral infections, such as HIV/AIDS and COVID-19, have been envisaged based on its ability to modulate the immune system by increasing the activity of natural killer cells and activation of macrophages [17]. This review seeks to provide experimental evidence of the health-promoting pleiotropic effects of SBSJ in certain medical conditions, such as cancer, chronic viral infections, stroke, arthritis, and premature aging. The probable underpinning mechanisms relating to its neuroprotective, antioxidant, anti-inflammatory, chemopreventive, and immunomodulatory activities, with the goal of eliciting more robust studies and clinical trials on SBSJ with respect to various associated medical conditions, are also discussed.

2. Methods

Using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [**19**] standard, a systematic search was conducted using three primary databases (i.e., PubMed, Europe PMC, and Cochrane Library), in order to identify and screen the published literature on SBSJ and West African *Sorghum bicolor*. The inclusion criteria were reviews, experimental, clinical, and *in vitro* studies on SBSJ and West African *Sorghum bicolor*, as well as ethnomedicinal surveys on the therapeutic use of West African *Sorghum bicolor* published in the English language.

Articles describing the health benefits of polyphenols and their mechanisms of actions were also included. The exclusion criteria were plant-based, genome, and agricultural studies; studies that merely cite a SBSJ and *Sorghum bicolor*-related paper without being a primary study on them; clinical trials whose results have not been published; and studies/reviews/surveys that do not focus on SBSJ and/or West African *Sorghum bicolor*, but merely refer to them.

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The literature searches and analysis for selection and quality assessment were performed between June 1 and July 8, 2022. From the search terms selected from the three databases, a total of 349 articles were identified. Duplicates were removed manually. Two researchers reviewed the titles and abstracts of the remaining 345 articles, after which an additional 258 articles were removed based on the exclusion criteria. As a result, a total of 87 articles were selected. After reviewing the full texts of these 87 articles, 46 were excluded based on the inclusion and exclusion criteria, leaving only 41 articles. These search and selection steps are outlined in the PRISMA flow diagram below (Figure 1).

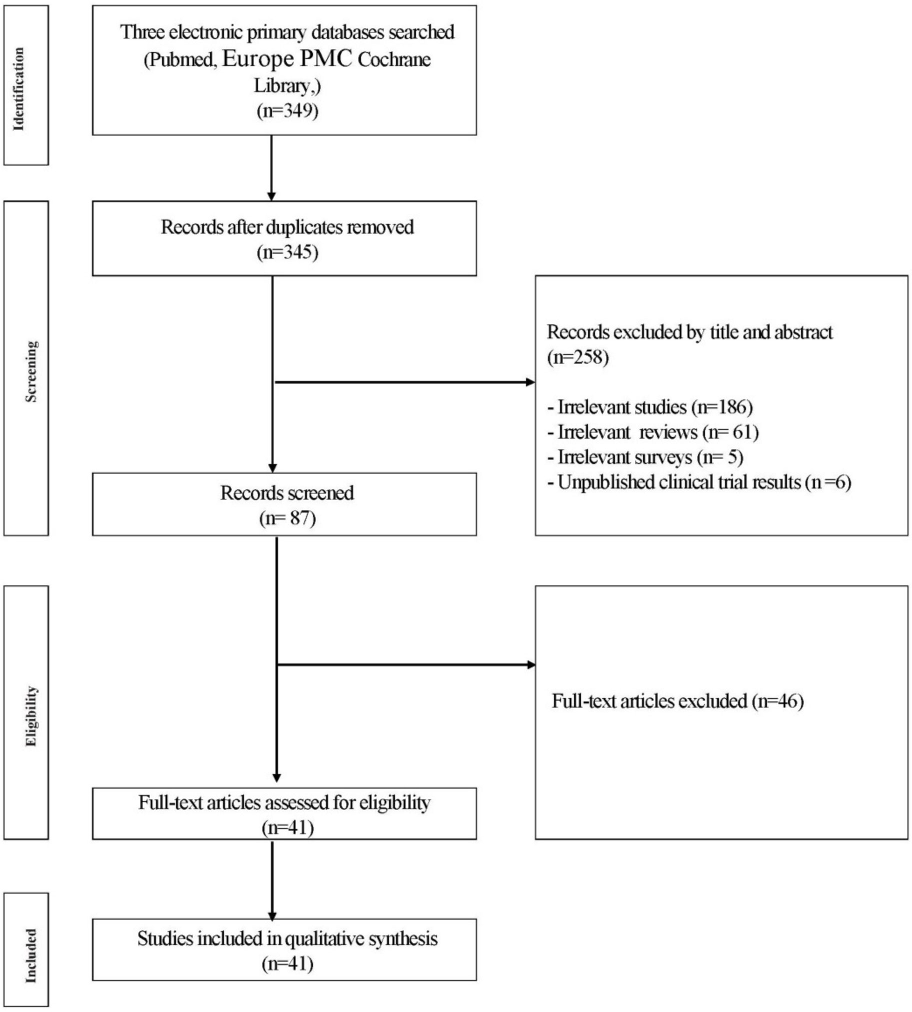


Figure 1. PRISMA Flow Diagram for the Literature Search.

2.1. Results

Of the 41 eligible articles found in the three databases, 3 were review papers (only 1, a mini-review, was focused exclusively on SBSJ), 5 were ethnomedicinal surveys, 31 were experimental studies, and only 2 were clinical studies. These findings clearly suggest that there has not previously been a rigorous synthesis of the extant literature on SBSJ. Therefore, it is against this background that the present review seeks to present the current state of research on SBSJ.

3. Discussion

Based on the 41 eligible articles retrieved from the three databases and other relevant literature identified from Google Scholar as a secondary source, the Jobelyn-related data are presented, in terms of its source, phytoactive/nutritional composition, potential therapeutic use in the treatment of anaemic conditions, arthritis, stroke disorders, chronic viral infections, and cancer, as well as its use as an anti-aging supplement and as an adaptogen.

3.1. Source of SBSJ

SBSJ is a uniquely formulated regimen manufactured by Health Forever Product Ltd., a Nigerian nutraceutical company based in Lagos. It is obtained from the polyphenol-rich leaf sheaths (Figure 2A) of a West African variety of *Sorghum bicolor* L. Moench (Poaceae). *S. bicolor*, commonly known as millet, sweet sorghum, broom, or guinea corn, is widely cultivated across many tropical countries of the world for its economic, nutritional, and medicinal values [14-15]. Accordingly, *S. bicolor* plant-based regimens have been used for well over a century in treating various ailments in African traditional medical settings [20-21]. In fact, folklore medical practices have revealed that herbal concoctions of the root are used as an antimalarial, especially by natives of Southern Rhodesia, while seed (grain)-based concoctions are used to treat diarrhoea and breast cancer, as well as for their anti-inflammatory effects [14, 21]. Extracts from the stem are used as an anti-tubercular oedema regimen, while the leaf is utilized for a wide range of ailments [9, 14, 21]. Of particular note, the extract from the leaf-sheaths component of *S. bicolor*—from which SBSJ is claimed to be exclusively obtained—tends to exhibit better therapeutic effects against diverse diseases over those derived from other parts of the plant [14].

SBSJ has an FDA (USA) *GRAS* certification with an organ systems tolerance profile [14, 23]. It has also has gained local and international recognition for the treatment of moderate to severe anaemia (as in sickle cell patients), as well as cancer and HIV/AIDS [19, 24]. It is also widely used to combat stress and to restore the much-needed energy during periods of recovery from debilitating diseases [16]. There have been reports that

SBSJ is helpful in arthritis, cancer, and neurological disorders such as stroke, psychosis, and convulsions [16]. In addition, it is known to modulate the immune system, enhancing the body's defence mechanisms in response to stress and infections, and to aid recovery from debilitating illnesses [16, 17].

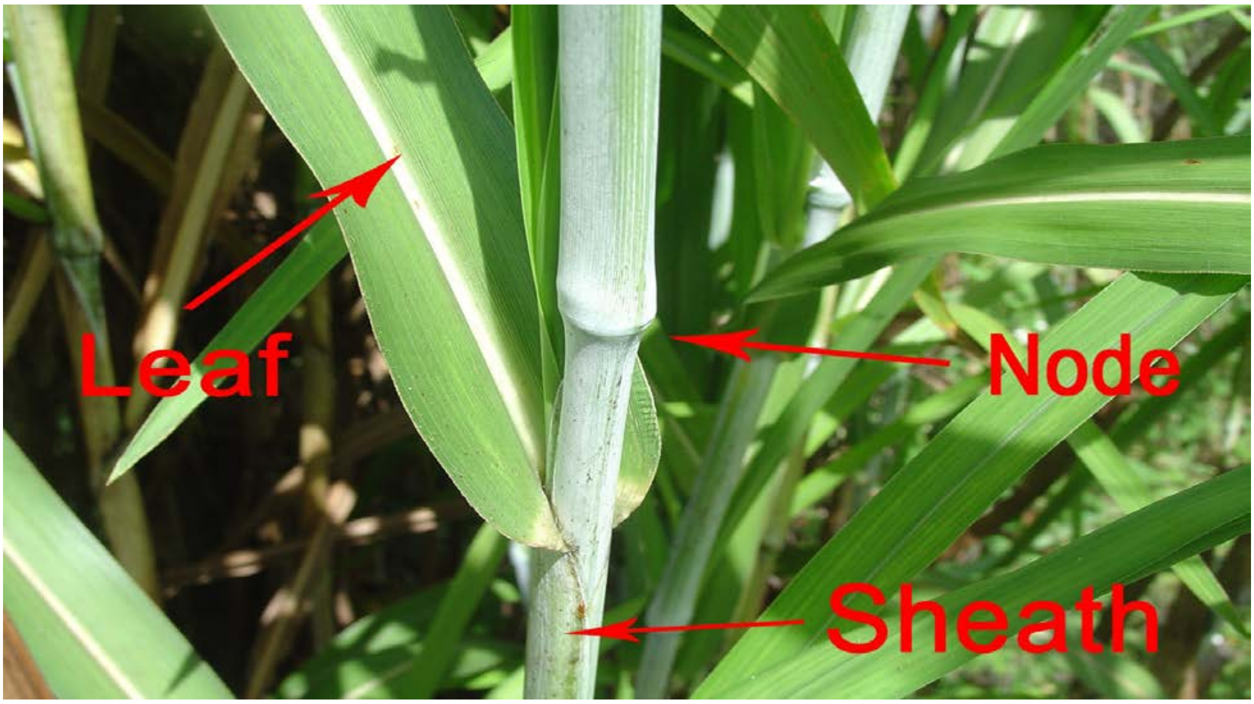


Fig. 2. *Sorghum bicolor* plant with leaf, sheaths, and nodes

3.2. Phytoactive constituents and nutritional composition of SBSJ

Some phytochemical studies have shown that SBSJ contains diverse bioactive polyphenol-rich constituents, which can be broadly divided into phenolic acids and flavonoids. Polyphenols are the main secondary metabolites known to exhibit antioxidant, anti-inflammatory, immunomodulatory, and chemopreventive effects; four key pillars of healthy living and wellness [9, 26-27]. It has been reported that all food plants, such as cereals, fruits, and vegetables, contain polyphenols in variable quantities [9, 27]. The leaf sheaths of the special domesticated West African variety of the Sorghum plant have been documented as having the highest concentrations of various polyphenols (especially 3-deoxyanthocyanidin) among food plants [17]. Thus, its unique properties have been ascribed to its high polyphenol content, when compared with other plant-based products (Figure 3). It is interesting to note that these unique properties, among other scientific reasons, explain the inclusion of SBSJ into the drug dictionary of the National Cancer Institute, USA, where it is described as a substance rich in polyphenols and polyphenolic acids with the potential for antioxidant, anti-inflammatory, immunomodulatory, and chemopreventive capabilities [28].

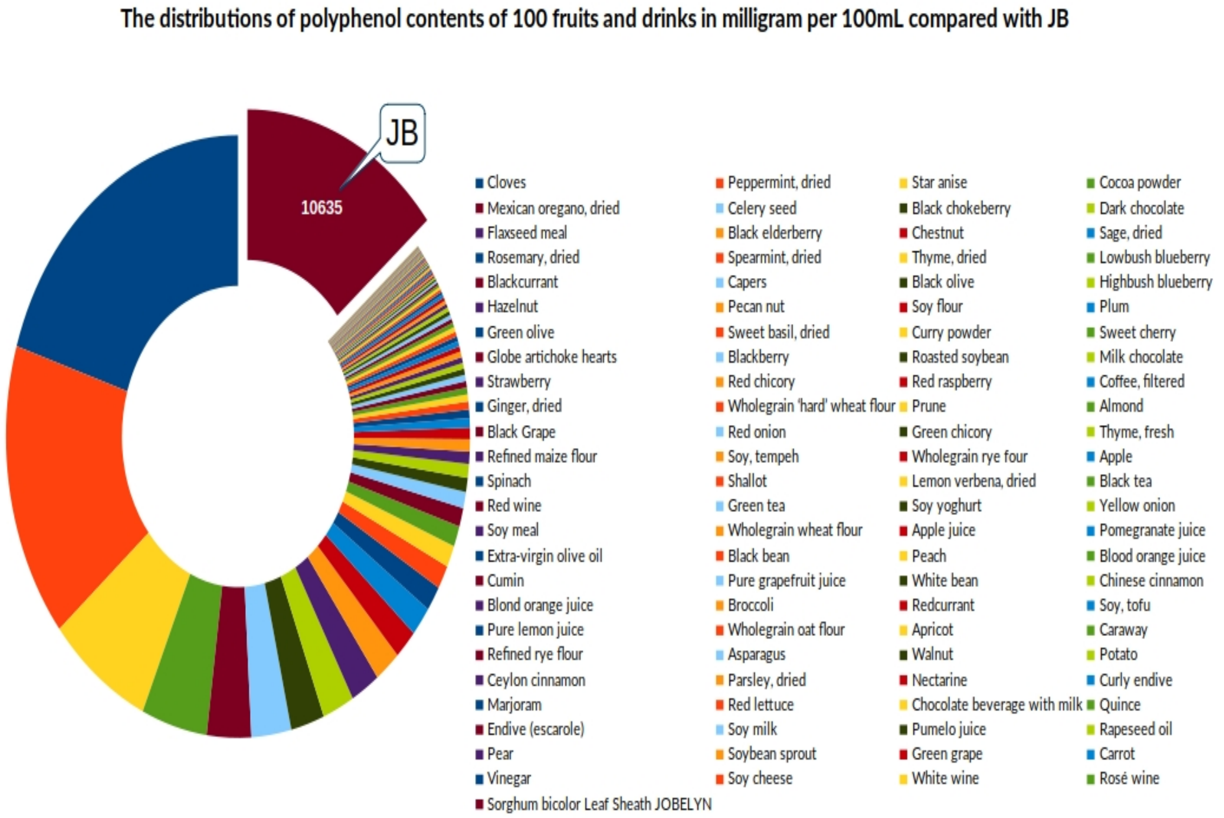
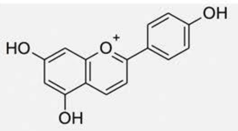
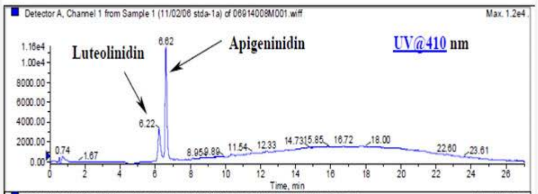
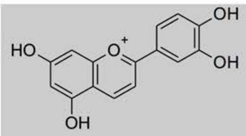
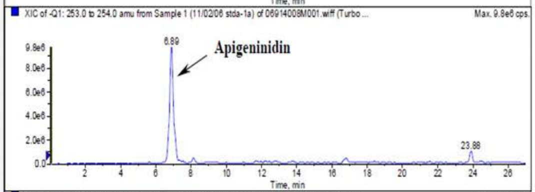
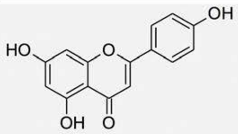
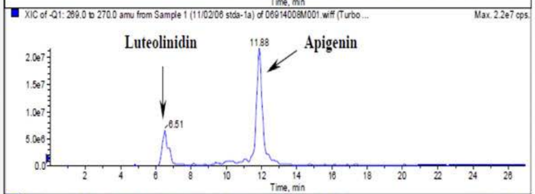
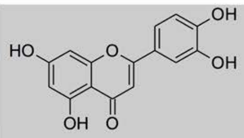
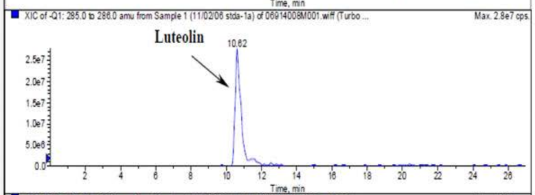
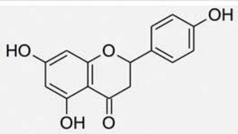
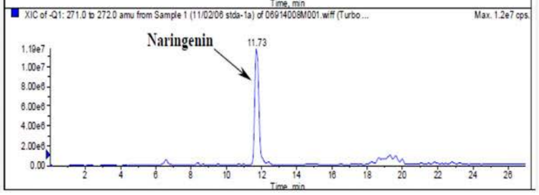


Figure 3. Comparison of polyphenol contents of SBSJ with other plant-based products.

High-performance liquid chromatography (HPLC)-UV spectral characterization studies have revealed that SBSJ contains apigenindin (stabilized 3-deoxyanthocyanidin, apigenin (flavone), luteolin (flavone), luteolinidin (anthocyanidin), and naringenin (flavone); see Table 1. Thus, flavonoids are the most bioactive polyphenolic compounds present in SBSJ [15, 17, 29]. A literature survey indicated that luteolin, naringenin, and apigenin are the most-studied bioactive flavonoids present in SBSJ, with diverse pharmacological activities including anti-inflammatory, antimutagenic, anticancer, immunomodulatory, antioxidant, and neuroprotective effects [17, 27, 30].

Table 1. Phytochemical constituents of leaf sheaths of *Sorghum bicolor* [29].

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

Based on the recommended daily allowance indices, SBSJ is known to be very rich in minerals such as iron, zinc, calcium, copper, magnesium, selenium, phosphorus, sodium, and potassium, which are essential for metabolism and neuronal communication [31]. It is also rich in various vitamins, including vitamin B_{12}, niacin, and riboflavin. In fact, the presence of iron and vitamin B_{12} are clinically relevant in anaemic and immune-related compromised conditions [32-33]. It is also rich in proteins, fats, carbohydrates, and omega-3 and -6 fatty acids (Table 2). Omega-3 and -6 fatty acids, for example, have been recognized as active promoters of anti-inflammation, anti-apoptosis, and modulation of neurotransmitters functions, as well as functioning in the maintenance of cellular membrane integrity and activation of neuroprotective mechanisms [34-35]. The rich phytochemicals, minerals, and vitamins with proven biological activities may account for the diverse health benefits of SBSJ when consumed routinely, especially in regimented doses.

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Table 2. Nutritional composition of leaf sheaths of *Sorghum bicolor* (SBSJ) [15].

Principle	Nutrient Value	Percentage of RDA
Energy	324 cal	-
Carbohydrates	75.3 g	-
Protein	4.87 g	-
Dietary fibre	50.30 g	-
Vitamins		
Vitamin B12	0.83 µg	0.345
Riboflavin	0.18 mg	0.1636
Niacin	3.55 mg	0.2535
Minerals		
Calcium	352 mg	0.352
Magnesium	183 mg	0.5903
Iron	51.20 mg	6.4
Zinc	1.09 mg	0.1362
Copper	900 µg	1.2777
Phosphorus	700 mg	0.2014
Selenium	15.40 µg	0.28
Electrolytes		
Potassium	0.5 g	0.1063
Sodium	1.15 g	0.9583
Total Omega-3 fatty acids	36 mg	-
Total Omega-6 fatty acids	110 mg	-

3.3. Therapeutic indications of SBSJ in anaemic conditions

SBSJ has gained significant recognition for its ability to boost haemoglobin (Hb) content and to cause rapid stimulation of the production of red blood cells (RBCs). This is particularly useful in reversing anaemia and its symptomatic presentations, including tiredness, dizziness, weakness, shortness of breath, headaches, and fainting [36]. Anaemia is most common in children, the elderly, and pregnant women [36]. The main causes of decreased production of RBC and Hb in anaemia include iron deficiency, vitamin B12 deficiency, and bone marrow tumours [36]. However, factors responsible for increased breakdown of RBC have been identified to include genetic disorders such as sickle cell anaemia, certain autoimmune diseases, stressors including chronic infections (e.g., malaria and HIV/AIDs), and haemolytic agents [36-37]. The most common clinical approach for the treatment of anaemia entails boosting RBC and Hb with iron, folic acid, and vitamin B12 supplementation [38-39]. Drugs and other agents that can stabilize RBCs may also be useful in certain anaemic conditions, especially those due to stressors such as chronic infections and exposure to haemolytic agents [37]. Severe anaemia in Africa has been described as a complex multi-factorial syndrome, for which a single conventional intervention may not be amenable [37].

The blood-boosting capability of SBSJ has been observed in facilitating the treatment of moderate to severe anaemia associated with sickle-cell disease, cancer (e.g., leukaemia), malaria, and helminthiasis [15, 40]. SBSJ is also prescribed as an adjuvant hematinic for pregnant women and patients with HIV/AIDs [14]. Pre-clinical studies have shown that SBSJ increased RBC count, Hb content, and packed cell volume (PCV) in rats and rabbits infected with trypanosomes [19, 24]. Interestingly, some clinical studies have also established its efficacy in anaemic conditions [15, 40-41]. In a randomized open label clinical trial, it has been reported that SBSJ increased RBC count, Hb content, and PCV in women with pre-operative anaemic condition without inducing significant changes in the white blood cell and platelet counts [41]. Indeed, the prophylactic importance of SBSJ in anaemia has been recognized beyond Nigeria [40, 42-43]. Taken together, these findings are of significance for public health.

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The high concentration of iron in SBSJ may be one of the ways though which it increases Hb content and PCV in clinical settings. The presence of vitamins B_{12}, niacin, and riboflavin may also contribute to its blood-rejuvenating effect and ability to combat anaemia in chronic debilitating conditions, such as sickle cell disease, malaria, and HIV/AIDs [15, 42]. The presence of omega-3 and -6 fatty acids, which are known for their antioxidant effects and maintenance of cell membrane integrity, may also act to protect RBCs from lysis in pathological conditions. Interestingly, SBSJ has been found to protect RBCs against lysis induced by hyposaline, suggesting the presence of phytochemicals with a cyto-protective effect [17, 43]. Additionally, oxidative stress has been implicated in the aging of RBCs and degradation of Hb molecules, which may contribute to the anaemic condition in individuals with chronic diseases [44-47]. Thus, the efficacy of SBSJ in several anaemic conditions may be related to its combined capacity to boost RBC and Hb production while reducing oxidative stress in RBCs. Nevertheless, more studies are necessary to elucidate the exact mechanism(s) underlying the capacity of SBSJ to boost RBC and Hb production in anaemic conditions.

3.4. Benefits of SBSJ in arthritic conditions

There have been claims that SBSJ is helpful in the management of arthritic pain and other inflammatory conditions [17, 43]. The recommended daily dose (1–2 capsules) of SBSJ has been reported to help in alleviating the excruciating pain associated with arthritis [48]. Arthritis is a common chronic inflammatory disease, which is widely known to impair the quality of life of the affected patients, and is a major cause of disability among the elderly [49-50]. It is characterized by chronic inflammation of the synovial membrane, pain, and joint immobility [48, 51-52]. Although the pathogenesis of the disease is yet to be fully known, the infiltration of inflammatory cells (leukocytes) into the joints appears to play a prominent role in the initiation of the tissue destruction that epitomizes the arthritic condition [50, 52-53]. The initiation and progression of the disease have been closely connected with the migration of inflammatory cells to the inflamed joint, in response to the release of chemical mediators such as cytokines, prostaglandins, and leukotrienes [54-56]. Furthermore, the activity of the inflammatory cells trigger the release of free radicals and other cytotoxic substances, including pro-inflammatory cytokines, which further enhance joint tissue damage [49-50, 54].

The multi-dimensional nature of the disease, therefore, suggests that a non-conventional approach based on the use of agents with polyvalent actions that can target the multiple mediators involved in its pathology may be effective [49-50]. Interestingly, a number of polyphenol-rich medicinal plants are being investigated as new medicines for the treatment of arthritis-related pain [57-58]. In this regard, SBSJ has been extensively studied in various *in vitro* and *in vivo* models of inflammation [17, 43, 48]. In a carrageenan acute model of acute inflammation, SBSJ has been reported to potently reduce inflammatory paw oedema in rats [43]. This model has served as one of the rational tools in the pre-clinical screening of drugs with anti-inflammatory properties, as the reduction of paw oedema in rats is akin to the ability to attenuate acute inflammation in humans [59]. In another study, SBSJ has been evaluated in a granuloma air pouch model of chronic inflammation. This model has been shown to closely mimic the pathology of arthritic disorders, based on the pattern of disease progression, tissue destruction, infiltration of White Blood Cells (WBCs), and release of cytotoxic mediators [54, 60-62].

The efficacy of pharmacological ligands in the granuloma air pouch is based on reduction of inflammatory exudates, WBC count, concentrations of biomarkers of oxidative stress, and inflammatory mediators in the fluid exudates, as well as the histological cyto-architecture of the pouch tissue [61-62]. Notably, SBSJ was reported to decrease the volume of inflammatory exudates, WBC count, and positively modulated the altered fluid concentrations of biomarkers of oxidative stress in rats. More importantly, histological studies have revealed that SBSJ protected the pouch tissue of the rats subjected to carrageenan-induced granulomatous chronic inflammation [43]. These findings further provide experimental evidence supporting the efficacy of SBSJ in chronic inflammatory diseases such as arthritis. This observation has also been validated by the finding that SBSJ reduced the joint inflammation, oxidative stress, and pro-inflammatory cytokines induced by complete Freund adjuvant (CFA) in rodents [48]. It is important to note that CFA-induced chronic inflammation is a well-recognized model for studying molecular mechanisms associated with the pathophysiology of arthritis [63-64].

The *in vitro* anti-inflammatory activity of SBSJ has been evaluated using a rat RBC membrane stabilizing model. The erythrocyte membrane is considered to be similar to the lysosomal membrane, which plays an important role in inflammation [65-66]. This *in vitro* test was based on the release of haemoglobin from RBCs exposed to hyposaline, and the prevention of RBC lysis has been described as a biochemical index for evaluation of compounds with anti-inflammatory properties [65-66]. Thus, compounds with membrane-stabilizing capacity are expected to demonstrate anti-inflammatory activity by preventing the release of lysosomal phospholipases, which are prime mediators in the early phase of the inflammatory process [65-66]. Thus, the findings that SBSJ exhibits membrane-stabilizing activity lends credence to the experimental evidence supporting its anti-inflammatory effects and probable beneficial role in combating inflammatory diseases. Benson et al. [17] have evaluated the *in vitro* anti-inflammatory effect of SBSJ in cultured polymorphonuclear cells, and reported that it also showed anti-inflammatory activity through mechanisms relating to the suppression of leukocyte migration and an antioxidative protective effect. They further reported that the antioxidant protective capacity of SBSJ was several-fold higher than that reported for various cereal grains and vegetables [17]. As shown in Table 3, this sorghum-based supplement has also been shown to have demonstrated inhibitory activity against a variety of oxidant molecules, with a total oxygen radical scavenging capacity (ORAC) of 37,622 µmol TE/g **[17].** The authors concluded that SBSJ contained polyphenol-rich phytomolecules, such as luteolin, naringenin, and apigenin, which have been established as potent antioxidants and anti-inflammatory moieties [17]. Similarly, findings from the *in vitro* studies of Mankanjuola et al. [29] have revealed that the 7-methoxyflavone-apigeninidin and apigenin constituents of the sorghum formulation exhibited inhibitory activity against PG-E2 expression and COX-2 enzyme activity, further suggesting its role in inflammatory disorders.

Table 3. Antioxidant Capacity of West African *Sorghum bicolor* leaf sheaths [17].

	(µmol TE/g)
Antioxidant power against peroxyl-free radicals	3549
Antioxidant power against hydroxyl-free radicals	18,387
Antioxidant power against peroxynitrite	269
Antioxidant power against superoxide anion	11,417
Antioxidant power against singlet oxygen	4000
Total oxygen radical scavenging capacity (ORAC)	37,622

3.5. SBSJ as a potential remedy for stroke disorders

Some evidence has been presented in the literature that the established polyphenol-rich phytomoieties contained in SBSJ exhibit a wide range of neuro-protective effects against certain brain conditions, including stroke. It has been suggested that SBSJ may be protective against ischemic stroke through several mechanisms, including direct inhibition of the NF-kB signalling pathway [67-69]. Ischemic stroke is a fatal disease caused by sudden obstruction of the cerebral blood flow, with subsequent neuronal cell death [67, 70-71]. Occlusion of the carotid artery and the attendant inhibition of reperfusion are critical factors involved in ischemic stroke [67, 70-71]. The morbidity and mortality associated with stroke are alarming, resulting in huge losses of economic manpower and productivity [72-74]. Stroke is typically associated with neurological deficits with accompanying physical disabilities, and the belief that it is incurable may also lead to various psychiatric disturbances, such as anxiety, depression, and memory deficits [75].

Ischemic stroke accounts for over 85% of all cases of stroke, and its pathology is known to be due to the activation of neuronal oxidative and inflammatory pathways [67, 76]. Both pre-clinical and clinical studies have reported increased biomarkers of oxidative stress and inflammatory cytokines after the onset of ischemic stroke [67, 76]. Interleukin-6 (IL-6), interleukin-1 (IL-1), and tumour necrosis factor-alpha (TNF-α) are some of the most studied cytokines in stroke pathology [67, 77]. In stroke patients, IL-6 has been linked to early neurological deterioration, greater infarct volumes, and poorer long-term outcomes [67]. High plasma levels of TNF-α have also been correlated with infarct volume and neurological deficits in various models of cerebral ischemia [67, 76]. During reperfusion there is an increase in serum cortisol, which further exacerbates neuronal damage by disrupting glucose homeostasis and increasing oxidative stress in the brain. Moreover, increased oxidative stress and leukocyte infiltration result in the formation of more pro-inflammatory cytokines, which perpetuate neurodegeneration in the brains of animals with ischemic stroke [67, 76-77]. On this basis, current approaches to the treatment of the disease using thrombolytic agents are quite limited in scope, as they cannot antagonize the injurious oxidative and inflammatory events that underpin ischemic stroke [67-68, 78]. Thus, oxidative and neuro-inflammatory pathways are currently being viewed as promising targets for the development of new drugs that could be used to antagonize the multiple mechanisms and mediators involved in ischemic brain injury [67-68, 78-79]. Bioactive compounds of plant origin with potent antioxidant and anti-neuroinflammatory activities are believed to hold promise for the development of therapeutic strategies [67-68, 78-79].

Indeed, several studies have shown that various phytochemicals have the ability to target the multiple pathways involved in the pathophysiology of stroke, including oxidative stress, inflammation, and apoptotic cell death [78-79]. Moreover, epidemiological data in the extant literature have evidenced that regular consumption of food rich in polyphenols can reduce the risk of stroke [78-79]. SBSJ has been experimentally evaluated against ischemic stroke induced through the occlusion of the bilateral common carotid artery by a group of scientists at the University of Ibadan [16]. The results of their investigations revealed that the neurological deficits produced by the occlusion of the bilateral common carotid artery in rats—which approximates the clinical characteristics seen in patients with ischemic stroke [80]—were attenuated by SBSJ

[16]. In addition, biochemical changes relating to increases in oxidative biomarkers and depletion of antioxidant defence molecules in the brains of rats subjected to ischemic stroke were mitigated by SBSJ [16]. The authors also reported that SBSJ reduced the brain contents of pro-inflammatory cytokines (IL-6 and TNF-α) and the expression of immunopositive cells of NF-kB in rats with ischemic stroke [16]. The neuroprotective effect of SBSJ is another major finding obtained from that study. It is well-known that stroke causes damage to several neuronal pathways which are crucial in the regulation of motor and cognitive functions [67-68]. Thus, the finding that SBSJ 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, corroborates its neuroprotective capacity. However, robust clinical trials using neurological and molecular markers are necessary, in order to establish its efficacy in stroke patients.

3.6. Anti-aging potential of SBSJ

Aging has been described as a universal and multi-factorial process characterized by a gradual decline of physiological functions. It occurs at the molecular, cellular, and tissue levels, and comprises a series of pathological mechanisms such as deregulated autophagy, mitochondrial dysfunction, telomere shortening, oxidative stress, systemic inflammation, and metabolic dysfunction [81-83]. The deregulation of these interconnected pathways leads cells to a state of senescence, which contributes to aging and age-related diseases. Although many theories have been proposed to explain the molecular mechanism associated with the aging process, the free radical theory, proposed by Harman [84] in 1956, appears to be highly insightful. According to this theory, aging is associated with the accumulation of reactive oxygen species that exert oxidative damage to cellular biomolecules and apoptosis, ultimately leading to a decline of physiological function and death [82-84]. The cellular degeneration and early apoptosis caused by free radicals produce oxidative stress, which has been regarded as the main pathological culprit in premature aging [82, 84]. Moreover, oxidative stress is often aggravated by a variety of stressors, such as chronic infections and abiotic factors, which may accelerate aging and aged-related diseases, as well as increasing vulnerability to death [78, 85]. The deterioration in bodily function with aging is the primary risk factor for most human pathologies, such as cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases [78, 85].

Strategic focus on interventions that increase lifespan in model organisms such as *Drosophila melanogaster*, and the potential of translating such discoveries into the development of therapies to combat age-related diseases, are currently being pursued [78]. Such interventions that are capable of slowing aging are likely to delay the onset of many human diseases, such as cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. In this regard, the consumption of foods rich in polyphenols has been reported to have probable preventive and therapeutic implications in the aforementioned non-communicable diseases [86-88]. Recently, food plants rich in polyphenols have been described as the 'Elixir of Life', as they possess the capabilities of promoting longevity [78].

The effectiveness of the anti-aging action of nutritional interventions has been advocated in the war against age-related diseases, promoting healthy living and longevity [81]. Mechanistically, natural supplements have been shown to exhibit polyvalent actions against oxidative, inflammatory, and degenerative processes, ultimately aiding immune functions and, thus, improving quality of life [78]. Indeed, food supplements with antioxidant-boosting capacity have been gaining attention for the prevention and treatment of chronic conditions linked to ROS [78], as they have relevant properties related to age-related and chronic syndromes [78, 86-88].

The probable anti-aging potentials of SBSJ lie in its antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective effects in experimental models [22, 43, 89]. Studies have shown that the polyphenolic constituents of SBSJ, such as apigenin and luteolin, exhibit anti-aging activity through neuroprotective mechanisms related to anti-inflammatory, antioxidant, and anti-apoptosis effects [78, 82, 90]. Interestingly, the first concrete evidence regarding the anti-aging effect of SBSJ came from a study conducted at Brunswick Laboratory, USA, which revealed that it inhibited the activity of elastase-1 and collagenase-1 [15]: enzymes that have been implicated in premature aging, especially of the skin [91]. Specifically, SBSJ was shown to more be efficacious than vitamin C and ferulic acid in inhibiting collagenase and elastase, suggesting its capability to promote skin health [15]. The potential of SBSJ in age-related diseases, such as Alzheimer's disease, has also been investigated in a scopolamine-induced amnesia model [92]. The study found that SBSJ attenuated amnesia through neuronal antioxidant protective mechanisms [92]. A more recent study using *Drosophila melanogaster* showed that SBSJ extended the lifespan and improved motor function of the flies (Fig. 4), through augmentation of the antioxidant status [93]. In addition, it also extended the lifespan of *Drosophila melanogaster* exposed to lipopolysaccharide (LPS) [92]. SBSJ has also been shown to exhibit a neuroprotective capability against neurodegeneration in a binge-alcohol rat model through modulation of cellular apoptosis (p53) neurotrophin-positive expression and decreased inflammatory signalling cascade in specific brain regions [22, 89]. These experimental findings lend further credence to the potential of SBSJ to promote cellular survival and longevity.

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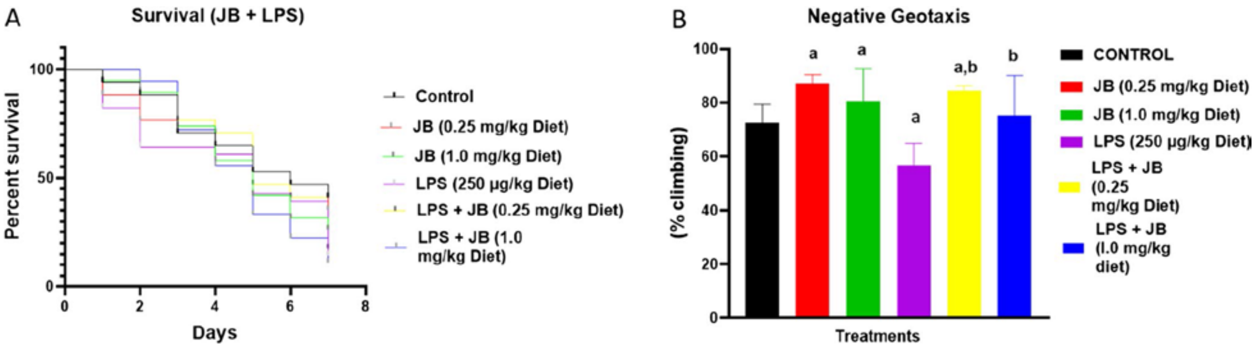

Figure 4. Effects of SBSJ (JB) on the survival curves (**A**) and negative geotaxis (**B**) of *D. melanogaster* exposed to LPS [93].

3.7. Potential of SBSJ in chronic viral infections

The possible beneficial effects of SBSJ in chronic viral infections, such as HIV/AIDS and COVID-19, have been envisaged based on its potent anti-inflammatory capacity, as well as its ability to modulate the immune system by increasing the activity of natural killer cells and activation of macrophages [15, 17]. The pathogenesis of HIV is known to be associated with the depletion of the immune function, which predisposes infected individuals to secondary infections [94-95], with the ensuing immunocompromised state threatening survival [95-97]. Although the impact of COVID 19 infection is closely related to chronic inflammation, commonly described as the cytokine storm [97], the severity of the disease also depends on the functionality of the immune system [96-97]. The pattern of invasion and infectivity is also similar to the HIV, as the SARS-CoV-2 virus exhibits receptor attachment, cellular entry, replication, cellular outlet, and cytokine induction [94-97]. The complex nature of HIV and COVID-19 suggests a need for the development of interventions with polyvalent actions that can mitigate the inflammatory mediators while also strengthening the immune system against viral replication and infectivity [97-98]. In this regard, the therapeutic potentials of several polyphenolic compounds in controlling the key cellular mechanisms involved in the infectivity of these viral infections are actively being investigated [97]. This is not surprising, as polyphenols are well-known to modulate the immune response and boost resistance to chronic viral infections [15, 17, 26, 97, 99].

The anti-inflammatory, antioxidant, and immunomodulatory effects of SBSJ [15, 17, 42] are strongly indicative of its anti-viral action against HIV/AIDs and COVID-19. Pre-clinical studies have shown that SBSJ up-regulates the expressions of chemokines and increases CD4 cell counts in cultured human monocytes and macrophages [41] which are known to be severely affected in HIV infection [17, 95, 100]. Specifically, Benson et al. [17] have shown that SBSJ causes several-fold increases in the expression of chemokines (e.g., RANTES/CCL5, Mip-1a/CCL3, and MIP-1b/CCL4) known to inhibit HIV entry into CD4+ T-cells. Interestingly, increases in chemokine production exert protective effects on the host immune response against HIV infection and disease progression [95, 100]. SBSJ has also been reported to exert immunomodulatory actions on a wide range of both pro- and anti-inflammatory cytokines, such as IL-1β, IL-6, IL-8 and TNF-α and, in particular, interferon-α [17], suggesting effective viral suppressive capabilities in patients with HIV/AIDs [95-96]. It has also been reported that SBSJ increased interferon-alpha (IFN-α) levels by 12-fold [17], further suggesting its immunomodulatory and viral suppressive capacities. It is important to note that IFN-α has been reported to inhibit HIV replication [95]. Interestingly, naringenin—one of the prominent phytoactive constituents of SBSJ—has been reported to show a strong inhibition of SARS-CoV-2 infection *in vitro [101]*. The inhibition of pro-inflammatory cytokines, such as IL-6 and TNF-α, by naringenin has been ascribed to a synergistic action that enhances its antiviral effects [101]. Thus, the potential benefits of naringenin in COVID-19 may be ascribed to its ability to inhibit or slow down the viral infection and the associated cytokine release/cytokine storm syndrome [101]. It is interesting to note that the leaves of *Sorghum bicolor*—the principal source of SBSJ—have been listed as one of the plants used for treating respiratory infections in an ethnomedicinal survey [102], lending further credence to its therapeutic potential in COVID-19. Indeed, Alhazmi et al. have found that *Sorghum bicolor* is one of the medicinal plants from which molecules with potential therapeutic use against viral diseases, such as COVID-19, have been extracted [103]. From a broader perspective, SBSJ is, therefore, a potential chemopreventive agent for modulating the immune function and controlling inflammatory reactions in the context of viral infections, such as HIV/AIDs and COVID-19. In fact, clinical studies have shown that it increased the CD4+ T-lymphocyte cellular count as well as bone marrow function, indicating a direct potential benefit in HIV/AIDS [15, 39].

3.8. Cancer chemopreventive potential of SBSJ

The bioactive constituents of SBSJ are known to inhibit cell proliferation in cancer cells through the stimulation of various apoptotic promoter genes, as well as down-regulating certain apoptotic inhibitor genes that are critical in carcinogenesis [104]. It is worth noting that cancer is a disease with multiple pathologies, though dysregulated or abnormal cell replication appears to be the primary underlying factor [105-106]. Cancer may ensue as a result of critical alterations in DNA at the site of some classes of genes that are important in regulating cell proliferation, cell death, and DNA repair, as well as tumour-suppressing genes [105-106]. Damage to DNA repair genes is a major predisposing factor leading to mutations in the genome, ultimately increasing the probability of neoplastic transformations [105-106]. Basically, cancer formation involves three major phases: Initiation, promotion, and progression (see Figure 5). The stage of initiation is a rapid, irreversible change in the genetic machinery of the target cell that primes it for subsequent neoplasm. This early phase of carcinogenesis is known to be due to exposure to mutagenic carcinogens, which interact with the DNA to form permanent heritable change(s) in the genome that are yet to be expressed phenotypically [105-106]. This suggests that initiation alone does not result in tumour formation; however, initiated cells

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display altered cellular characteristics, which may include altered responsiveness to the microenvironment and a proliferative advantage, relative to the surrounding normal cells [105-106].

The stage of promotion has been described as a reversible process in the life cycle of the cancer cell, which usually entails the conversion of initiated cells into active proliferation to a greater extent than normal cells [105-106]. An essential feature of tumour promotion is the creation of a mitogenic environment and enhancement of the possibility for further genetic damage [105-106]. It has been reasoned that polyphenols with multiple actions capable of targeting the various pathways that trigger the promotion of initiated/latent cells to active proliferations may retard tumour development [10, 107-108]. This suggests the importance of polyphenol-rich foods with chemopreventive capabilities. The final phase of cancer progression is characterized by the development of irreversible neoplasm, manifested as a rapid increase in tumour size, with the cells undergoing further mutations with invasive and metastatic potentials [105-106, 108]. Although the efficacy of phytochemicals might be limited in this last phase, there have been several claims of the effectiveness of dietary polyphenols against a variety of tumours. Epidemiological and animal studies have shown that phenolic compounds exhibit anti-cancer properties through multiple mechanisms related to antioxidant activity, induction of cell cycle arrest and apoptosis, and the promotion of tumour suppressor proteins [7, 10, 109].

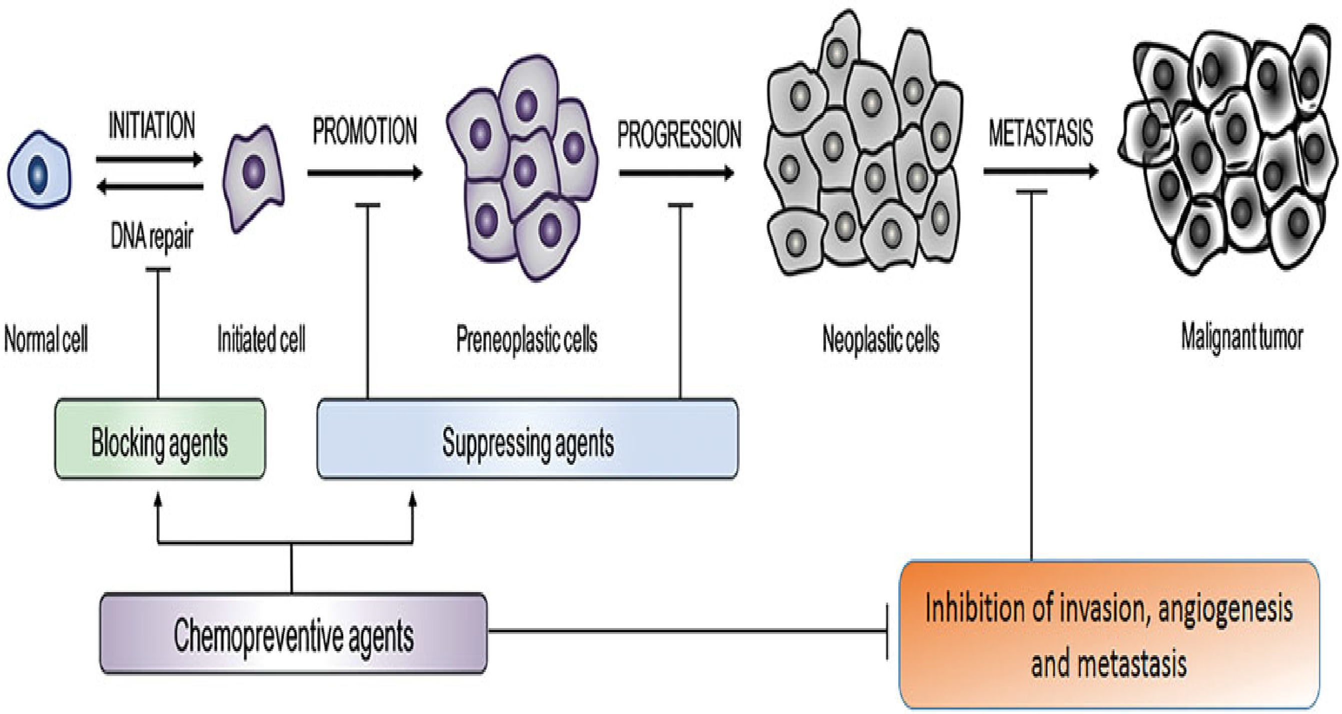

Figure 5. Carcinogenesis phases: initiation, promotion, progression, and metastasis [108].

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Epidemiological studies have also reported that sorghum consumption is correlated with a low incidence of oesophageal cancer in various parts of the world [10, 109-111]. Park et al. [112] have reported that the metastasis of breast cancer to the lungs was blocked by sorghum extracts in an immune-deficient mouse metastasis model. *In vitro* studies of sorghum extracts on several cancer cells have revealed induction of cell apoptosis, inhibition of cell proliferation, and promotion of the expression of cell cycle regulators [13, 18, 104, 107]. The effects of phenolic extracts from 13 sorghum accessions on cancer cell growth on both hepatocarcinoma HepG2 and colorectal adenocarcinoma Caco2 cell lines have recently been investigated [7]. It was concluded that the phenolic extracts of various sorghum accessions inhibited HepG2 or Caco-2 cancer cell growth in a dose- and time-dependent manner, through cytostatic and apoptotic mechanisms [7].The anticancer properties of sorghum extracts have been ascribed partly to the high content of 3-deoxyanthocyanidins [13]. Moreover, Makanjuola et al. [113] have reported that the 7-methoxyflavone-apigeninidin and apigenin constituents of SBSJ exhibited anticancer potential through the modulation of immune cells in *in vitro* models. This echoes the description by the National Cancer Institute of SBSJ as the richest source of 3-deoxyanthocyanidins; indeed, it has the highest contents of various polyphenolic compounds among food plants, with high capability for chemoprevention and inhibition of cell proliferation [28]. Although more studies on the potential anticancer efficacy of JB are necessary, the existing information suggests its valuable benefits as a supplement for cancer prevention.

3.9. SBSJ as an adaptogen

The routine use of SBSJ in an adaptogenic fashion for the relief of feelings of intense stress and to restore the much-needed energy during periods of recovery from debilitating diseases represents another major reason for its use [16, 19, 24]. It is important to note that the response to both biotic (pathogens) and abiotic (physical and psychosocial factors) stressors induces adaptive responses; however, when stress persists and becomes intense, the adaptive mechanisms of the organism become deficient, resulting in the pathogenesis of several human diseases [114-116]. The breakdown in adaptive responses, which signals organ pathologies and immune dysfunctions, was coined by Hans Selye as general adaptation syndrome [8, 117-118], who reasoned that human illnesses stemmed from ineffective adaptation [118]. The notion of general adaptation syndrome led to the search during the second World War by Russian scientists for substances—later called adaptogens—

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of plant origin that could be used to enhance the capability for physical and mental work, and which can help individuals to survive in challenging situations involving intense/prolonged stress [117, 119].

Adaptogens were initially defined as substances that enhance the "state of non-specific resistance" to stress; a physiological condition that is linked with dysregulation of the neuroendocrine–immune system [117, 119]. More recently, adaptogens have been defined as a category of herbal medicinal and nutritional products promoting the adaptability, resilience, and survival of living organisms in stressful situations [8]. Thus, adaptogens are meant to stimulate the intrinsic adaptive mechanisms of the organism, in order to help it survive in situations of intense/prolonged stress [117]. The most striking features of adaptogens include the capability to mount resistance against varied stressors, such as physical, chemical, biological (pathogens), and psychological noxious factors, thus exerting beneficial healthy effects independent of the nature of the pathological state [117, 119]. However, in clinical settings, adaptogens are generally reputed for their ability to exert an anti-fatigue effect, increasing mental work capacity against a background of stress and fatigue, particularly with respect to tolerance to mental exhaustion and enhanced attention [117].

Extensive reviews have documented the ability of adaptogenic substances to activate the protective mechanisms of cells, in order to promote increased survival rates in both *in vitro* and *in vivo* models [8, 117]. Adaptogens have been reported to effectively prevent and treat stress-related and aging disorders, such as chronic fatigue, memory impairment, depression, anxiety, sleep disturbance, diabetes, heart diseases, chronic inflammation and autoimmune diseases, infections, and cancer [8]. Based on the polyvalent pharmacological actions of adaptogens, it has been proposed that the normal paradigm of "one drug for one disease: does not correctly apply to them [8]. Plants with known adaptogenic actions include *Panax ginseng*, *Withania somnifera* (L.) Dunal, *Glycyrrhiza glabra* L., *Asparagus racemosus* Willd., *Ocimum sanctum* L., *Piper longum* L., *Tinospora cordifolia* (Thunb.) Miers, *Emblica officinalis* Gaertn., *Rhodiola rosea* L., *Schisandra chinensis* (Turcz.) Baill., and *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. [8].

The first concrete experimental evidence of the potential adaptogenic activity of SBSJ was based on its reported ability of bringing about relief with respect to feelings of intense stress and as an energizer in the context of debilitating disease [16, 19, 24]. Its adaptogenic potential has also been demonstrated in unpredictable chronic mild stress (UCMS), as it attenuated memory deficits induced by UCMS through

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neuroprotective mechanisms relating to the suppression of oxidative stress and pro-inflammatory cytokines [120]. UCMS is known to mimic the ways in which humans encounter multiple stressors on a daily basis, and is generally accepted as the most suitable model for elucidation of the pathological mechanisms of chronic stress-induced organ pathologies and immune dysfunctions. In a UCMS model, SBSJ also attenuated loss of neuronal cells in the Cornu Ammonis 3 (CA3) of the hippocampus (see Figure 6), suggesting a neuroprotective effect [120]. Moreover, it also reduced serum corticosterone concentrations [120], a major biomarker of chronic stress response. It is well-known that cortisol-induced activation of oxidative stress and inflammatory pathways is the primary culprit involved in the mediation of stress-related pathologies [8]. Indeed, an elevated concentration of cortisol serves as a key biomarker of intense stress. Substances with adaptogenic activity have been shown to reduce serum concentrations of corticosterone [8]. Thus, the ability of SBSJ to reduce corticosterone is an important finding from the study of Umukoro et al. [120]. The possibility of SBSJ behaving like an adaptogen is also based on findings that it attenuated depression-like symptoms in mice subjected to stressful situations (i.e., forced swimming exercise and tail suspension protocols) [121]. In an *in vitro* stress model, it has also been reported that SBSJ protected RBCs against hyposaline-induced haemolysis [43], suggesting cyto-protection and increased cellular resistance to stress. Notably, the recent finding that SBSJ increased the survival rate and prolonged the lifespan of LPS-exposed *Drosophila melanogaster* reinforces its potential adaptogenic-like properties [93]. This is in agreement with previous reports linking adaptogens to increased lifespan and stress resistance in *C. elegans* [122]; another model organism widely used for elucidation of the neurobiological mechanisms of stress and age-related disorders. The capability of SBSJ to combat stress in various models may be related to the presence of minerals, vitamins, and phytochemicals that can modulate the key mediators of stress response and immune defence mechanisms in response to stressors. Thus, it may be concluded that its routine use by healthy individuals to mitigate stress and prevent age-related diseases may to be justified.

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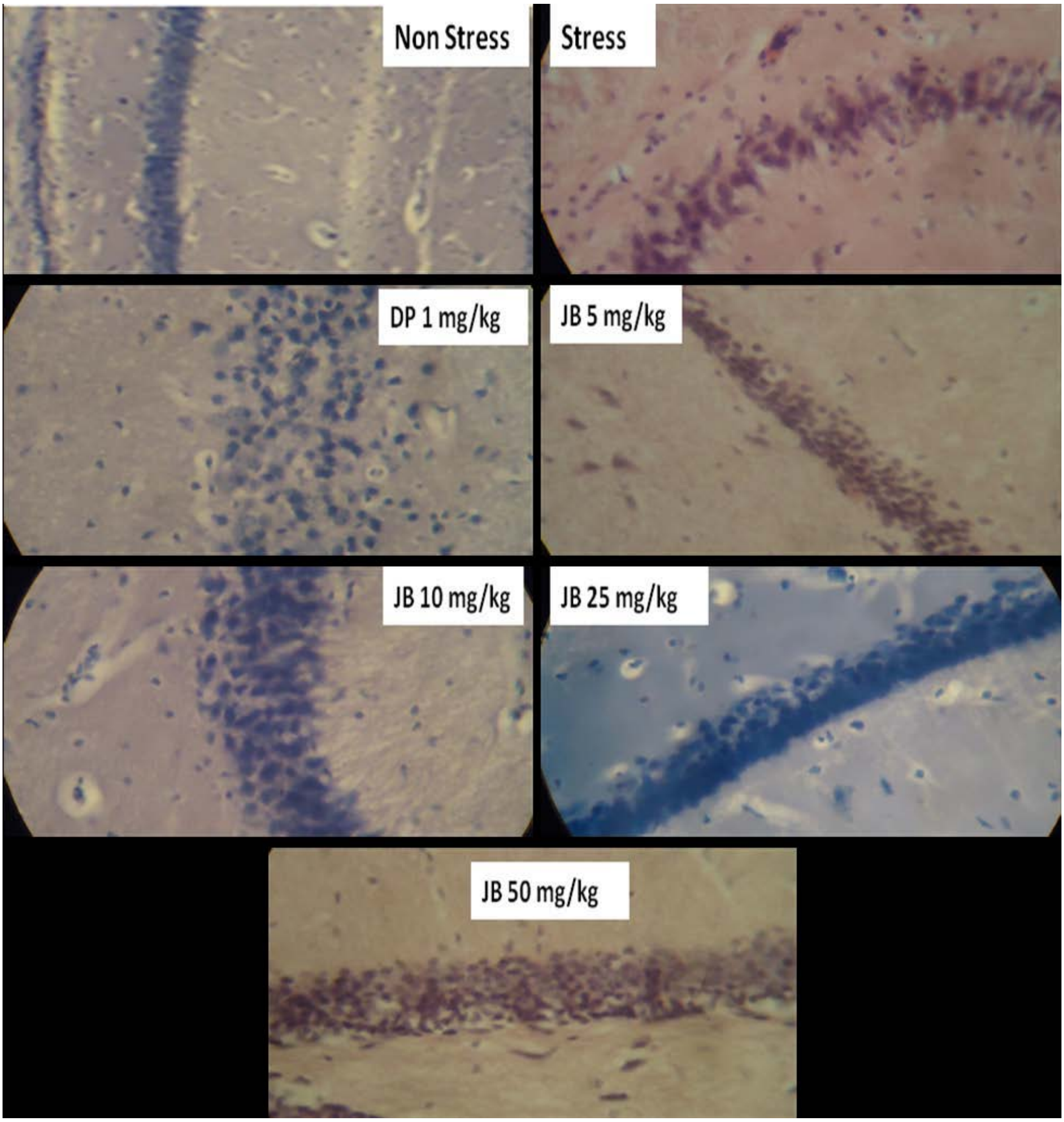

Figure 6. Effects of SBSJ (JB) and donepezil (DP) on representative stained sections of CA3 of mice brains exposed to unpredictable chronic mild stress; H&E, 400× [120].

4. Conclusion

In this review, we highlighted key reports focused on the multi-faceted pharmacological activities of SBSJ. We found that SBSJ includes bioactive substances with polyvalent biological effects, including the modulation of pathological mechanisms involved in the mediation of aging and age-related diseases, such as stroke, memory loss, cancer, and arthritis. The findings that SBSJ increased the cell counts of natural killer cells, IFN-α, and CD4; up-regulated the expression of chemokines; and inhibited pro-inflammatory cytokines suggest that it may be useful in infectious diseases such as HIV/AIDS and COVID-19. Some pre-clinical and clinical studies have also shown the therapeutic potential of Jobelyn in the management of moderate to severe anaemia in patients with HIV/AIDs and sickle cell disease. Taken together, the available evidence suggests that SBSJ likely exhibits adaptogenic-like properties through multiple mechanisms related to the suppression of oxidative and inflammatory pathways, providing it the ability to relieve the feelings of intense stress and weakness experienced during periods of debilitating illness.

There is an urgent need for further experimental studies in order to understand the exact molecular mechanisms of action of SBSJ and how some of its components may act synergistically and/or antagonistically, either when used alone or in combination with food or other drugs. Insights gained from such studies will determine whether SBSJ can continue to be used as a standalone supplement, or if some of its components may need to be isolated and clinically matched with specific pathological conditions. It is also important to identify other possible components; for instance, while SBSJ is made from the leaf sheaths of *S. bicolor*, a 2 kD, cationic, amphipathic, and virucidal peptide has been isolated from Sorghum seeds which binds and masks essential viral envelope proteins [123-124]. As such, it is important to determine whether the same protein occurs in the leaf sheaths and, if so, to evaluate the concentration and investigate what contributory role the peptide plays in the antiviral action of SBSJ. Finally, the limited clinical studies on SBSJ underscore the need to clinically evaluate its therapeutic potentials in specific disease conditions, including arthritis, cancer, chronic viral infections, and stroke, through rigorous clinical trials. This is especially important in a developing African context, where the high cost of conventional therapies hinders drug compliance and contributes to disease-related morbidity and mortality. The results from such clinical trials are necessary, as they are expected to provide the evidential strength that researchers need to significantly reduce some of the barriers to the clinical adoption of validated indigenous phytomedicines [121] in mainstream medical practice.

Author Contributions: Conceptualization and data gathering O.O., S.U., and O.G.O; Validation O.O., OGO., M.O.S.A, S.B.L.M., A.D.D., and L.C.A.; Writing—original draft preparation O.O., S.U., O.G.O., M.O.S.A., A.I.O., and A.A.; Writing—review and editing: S.U., RIO., O.G.O., M.O.S.A, S.B.L.M., A.D.D., and L.C.A. All authors have read and approved the submission of the manuscript.

Funding: This research did not receive external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest
The authors declare no conflict of interest.

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