JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/33171
REVIEW ARTICLE

An Evidence-based Systematic Review of Pleiotropic Potential Health Benefits of *Sorghum bicolor* Supplement: A Polyphenol-rich Derivative of the Leaf Sheaths of *Sorghum* Plant

Adaeze Adebesin[1], Adrian Itivere Omogbiya[2], Oluwafemi Gabriel Oluwole[3], Olajuwon Okubena[4*], Rita Onyekachukwu Asomadu[5], Michael O. S. Afolabi[6], Samira B. Lobo Makanjuola[7], Louis Chukwuemeka Ajonuma[8], Adedoyin O. Dosunmu[9], Ololade Otitoloju[4] and Solomon Umukoro[10]

[1]Department of Pharmacology and Therapeutics, College of Health Sciences, Olabisi Onabanjo University, Sagamu, Nigeria
[2]Department of Pharmacology, College of Health of Sciences, Delta State University, Abraka, Nigeria
[3]Department of Pathology, University of Cape Town, South Africa
[4]Health Forever Product Limited, Lagos, Nigeria; okubena@gmail.com
[5]Department of Biochemistry, University of Nigeria, Nsukka, Nigeria
[6]Department of Paediatrics and Community Medicine, University of Manitoba, Winnipeg, Canada
[7]Department of Pharmacology, Therapeutics and Toxicology, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria
[8]Department of Physiology, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria
[9]Department of Haematology and Blood Transfusion, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria
[10]Neuropharmacology Unit, Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Nigeria

Abstract

Globally, across different cultures, humans 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 have been strongly attributed to the presence of secondary metabolites, particularly polyphenols. The potential health benefits of the leaf sheaths of the West African variety of *Sorghum bicolor*-based Jobelyn Supplement (SBJS) have also been ascribed to its high contents of polyphenols. This systematic review seeks to synthetically harmonize findings from various experimental and clinical studies on the health benefits of SBJS in different disease conditions including arthritis, cancer, chronic viral infections, stroke, anaemia, and premature aging. A systematic search was conducted using three primary databases (PubMed, Europe PMC, and Cochrane Library), to identify published articles on therapeutic potentials of SBJS and ethnomedicinal surveys on the application of the West African variety of *S. bicolor* using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard. The inclusion criteria were experimental and clinical studies conducted on SBJS and West African variety of *S. bicolor*; while ethnomedicinal surveys were on the therapeutic uses of the West African variety of *S. bicolor* published in the English language. The review provides valuable information suggesting that SBJS possesses pleiotropic therapeutic potentials in diverse pathological conditions through mechanisms relating to antioxidant, anti-inflammatory, immunomodulatory, chemopreventive, and neuroprotective activities. The

*Author for correspondence

Article Received on: 28.02.2023 Revised on: 05.01.2024 Accepted on: 21.02.2024

review also showed that SBJS contains several bioactive substances with polyvalent pharmacological potentials including modulation of pathological mechanisms involved in the mediation of aging and age-related diseases, such as arthritis, stroke, memory loss and cancer as well as chronic viral infections. Taken together, these findings further suggest the need for more robust studies (including disease-specific clinical trial programs) in order to replicate and validate the prior insights gleaned from previous investigations on SBJS.

Keywords: Anti-aging, Antioxidant, Anti-inflammatory, Chemoprevention, Immunomodulation, Polyphenolic Constituents, *Sorghum bicolor*

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 that orchestrates 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 is also known to underpin the health-promoting benefits of the polyphenol-rich derivative of the leaf sheaths of the West African variety of *Sorghum bicolor*-Jobelyn supplement (SBJS). Indeed, SBJS 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 SBJS 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 SBJS 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, chemo-preventive, and immunomodulatory activities, to elicit more robust studies and clinical trials on SBJS concerning various associated medical conditions, are also discussed.

2. Study Design and Search Strategy

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), to identify and screen the published literature on SBJS and West African variety of *Sorghum bicolor*. The literature searches and analysis for selection and quality assessment were performed between June 1 and July 8, 2022. The inclusion criteria were reviews, experimental, clinical, and *in vitro* studies on SBJS and the West African variety of *Sorghum bicolor*, as well as ethnomedicinal surveys on the therapeutic use of the West African variety of *Sorghum bicolor* published in the English language. Articles describing the health benefits of polyphenols and their mechanisms of action were also included. The exclusion criteria were plant-based genome, and agricultural studies; studies that merely cite SBJS and *Sorghum bicolor*-related papers without being a primary study on them; clinical trials whose results have not been published; and studies/reviews/surveys that do not focus on SBJS or West African variety of *Sorghum bicolor.*

2.1 Data Extraction and Synthesis

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).

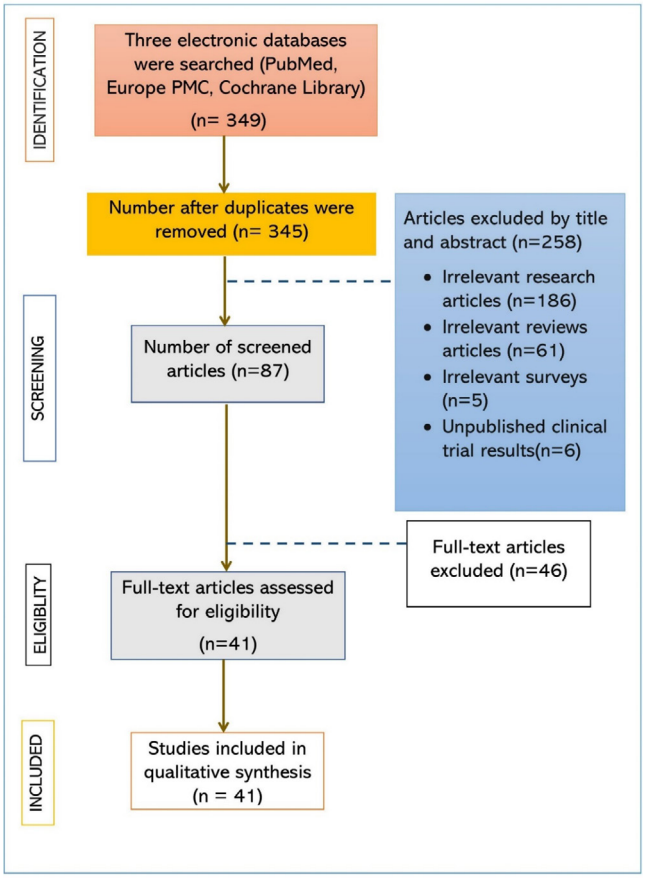


Figure 1. PRISMA flow diagram for literature search.

3. Search Results

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

4. 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 SBJS-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.

4.1 Source of SBJS

As depicted in Figure 2, SBJS is obtained from the polyphenol-rich leaf sheaths of the 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[4-15]. Accordingly, *S. bicolor* plant-based regimens have been used for well over a century in treating various ailments in traditional African medical settings[20,21]. Folklore medical practices have revealed that herbal concoctions of the root are used as an antimalarial, especially by natives of Southern Rhodesia, while the 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 portion of *S. bicolor* is known to exhibit better therapeutic effects against diverse diseases over those derived from other parts of the plant[14].

It is instructive to note that SBJS has an FDA (USA) *GRAS* certification with an organ systems tolerance profile[14,22,23]. It has also gained local and international recognition for the management 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 much-needed energy during periods of recovery from debilitating diseases[16]. There have been reports that SBB 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, enhance the body's defence mechanisms in response to stress and infections, and aid recovery from debilitating illnesses[16,17].

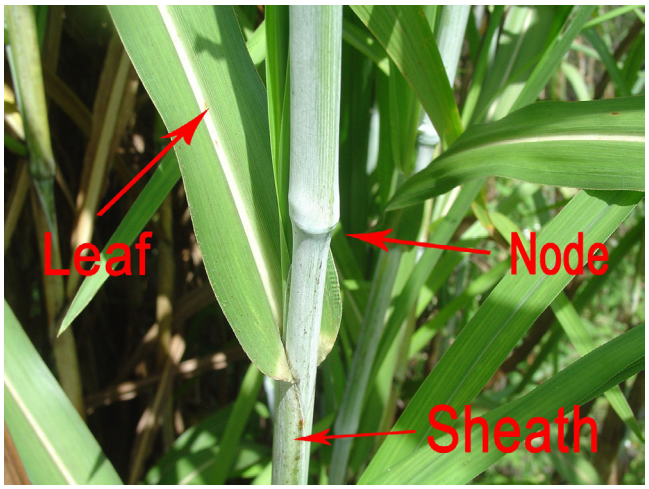


Figure 2. *Sorghum bicolor* plant with leaves, sheaths, and nodes.

4.2 Phytoactive Constituents and Nutritional Composition of SBJS

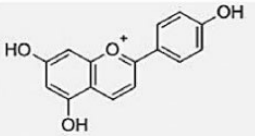
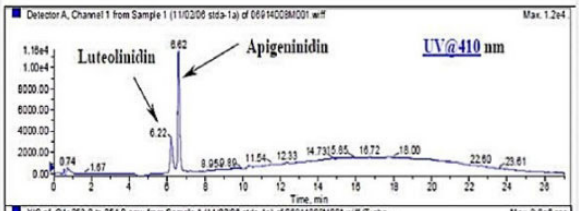
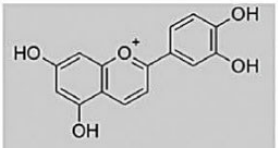
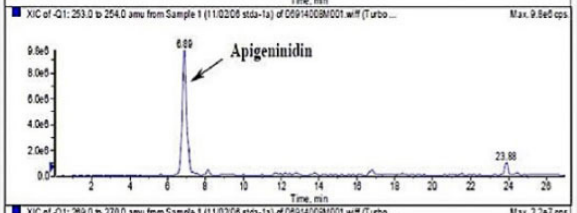
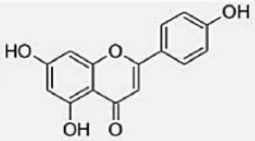
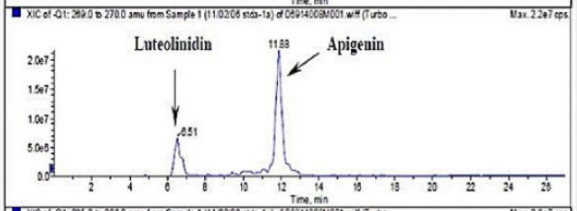
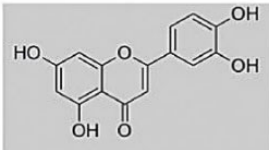
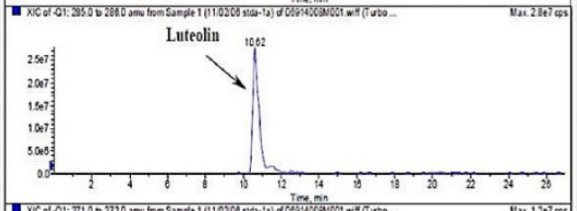
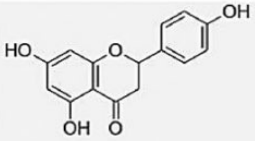
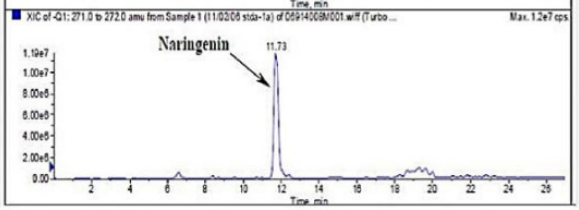
Some phytochemical studies have shown that SBJS contains diverse bioactive polyphenol-rich constituents, which can be broadly divided into phenolic acids and flavonoids. Polyphenols are the main secondary metabolites known to exhibit antioxidant, anti-inflammatory, immunomodulatory, and chemopreventive effects; the four key pillars of healthy living and wellness[9,25-27]. 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. It is interesting to note that these unique properties, among other scientific reasons, explain its inclusion into the Drug Dictionary of the National Cancer Institute, USA, where it was described as a substance rich in polyphenols and polyphenolic acids with the potential for antioxidant, anti-inflammatory, immunomodulatory, and chemopreventive capabilities[28]. Specifically, the capability to modulate the immune system by

increasing the activity of Natural Killer (NK) cells and the activation of macrophages was also ascribed to this *Sorghum*-based supplement[28].

High-performance liquid chromatography (HPLC)-UV spectral characterization studies have revealed that SBJS contains stabilized 3-deoxyanthocyanidin (apigenindin and luteolinidin), luteolin (flavone), and naringenin (flavone); see Table 1. Thus, flavonoids are the most bioactive polyphenolic compounds present in SBJS[15,17,29]. A literature survey indicated that luteolin, naringenin, and apigenin are the most-studied bioactive flavonoids present in SBJS, with diverse pharmacological activities including anti-inflammatory, antimutagenic, anticancer, immunomodulatory, antioxidant, and neuroprotective effects[17,27,30]. The richness of 3-deoxyanthocyanidin in this *Sorghum*-based supplement such as luteolinidin and apigeninidin has also been implicated in the induction of apoptosis and inhibition of cell proliferation in cancer cells through the stimulation of various apoptosis promoter genes and the downregulation of certain apoptosis inhibitor genes. In addition, due to their strong antioxidant nature, these compounds can scavenge free radicals and prevent tissue damage[17].

Besides, SBJS is also 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

Table 1. Phytochemical constituents of leaf sheaths of *Sorghum bicolor*, Jobelyn®. It is reprinted/adapted with permission from Makanjuola *et al*

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

neuronal communication[31]. It is also rich in various vitamins, including vitamin $B_{12,}$ niacin, and riboflavin. 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. Omega-3 and -6 fatty acids, for example, have been recognized as active promoters of anti-inflammation, anti-apoptosis, and modulation of neurotransmitter 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 SBJS.

4.3 Potential Therapeutic Indications of SBJS in Anaemic Conditions

The ability of SBJS to boost haemoglobin (Hb) content and to cause rapid stimulation of the production of Red Blood Cells (RBCs) has been reported in literature[15,19,24]. 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 B_{12} deficiency, and bone marrow tumours[36]. However, factors responsible for the 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 B_{12} 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 SBJS 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]. Pre-clinical studies have shown that SBJS 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 was reported that SBJS increased RBC count, Hb content, and PCV in women with pre-operative anaemic conditions without inducing significant changes in the white blood cell and platelet counts[41]. Indeed, the prophylactic importance of its use in anaemia has been well documented[40,42,43].

The high concentration of iron in SBJS may be one of the ways through 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, might also act to protect RBCs from lysis in pathological conditions. Interestingly, it has also been found to protect RBCs against lysis induced by hyposaline, suggesting the presence of phytochemicals with a cytoprotective 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, its efficacy in anaemic conditions may be related to the combined capacity to boost Hb production and reduce oxidative stress in RBCs. Nevertheless, more studies are necessary to elucidate the exact mechanism(s) underlying its capacity to boost RBC and Hb production in anaemic conditions (Table 2).

4.4 Potential Benefits of SBJS in Arthritic Conditions

There have been claims that SBJS is helpful in the management of arthritic pain and other inflammatory conditions[17,43]. 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[48-50]. 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 in 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 triggers 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, several polyphenol-rich medicinal plants are being investigated as new medicines for the treatment of arthritis-related pains[57,58]. In this regard, SBJS has been extensively studied in various *in vitro* and *in vivo* models of inflammation[17,43,48]. In a carrageenan model of acute inflammation, SBJS was shown to potentially 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 attenuation of acute inflammation in humans[59]. In another study, SBJS was evaluated in the granuloma air pouch model of sub-acute inflammation. This model has been shown to closely mimic the pathology of arthritic disorders, based on the patterns 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 model; is based on the 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, SBJS was reported to decrease the volume of inflammatory exudates, and WBC count, and positively modulated the altered fluid concentrations of biomarkers of oxidative stress in rats. More importantly, histological studies revealed that it also protected the pouch tissue of the rats subjected to carrageenan-induced granulomatous inflammation[43]. These findings further provide experimental evidence supporting its potential in chronic inflammatory diseases such as arthritis. This observation has also been validated by the finding that SBJS 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 SBJS has been evaluated using the 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 is known to be related to the release of haemoglobin from RBCs exposed to hyposaline, and the prevention of RBC lysis has been described as a biochemical index for the evaluation of compounds with anti-inflammatory property[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 SBJS exhibited membrane-stabilizing activity lend credence to its possession of anti-inflammatory effect and probable beneficial effect in combating inflammatory diseases. Furthermore, Benson *et al.*,[17] also evaluated its *in vitro* anti-inflammatory effect on cultured polymorphonuclear cells and reported that it showed anti-inflammatory activity through mechanisms relating to suppression of leukocyte migration and antioxidation. They further reported that its antioxidant protective capacity was significantly higher than that reported for various cereal grains and vegetables[17]. This *Sorghum*-based supplement was also shown to exhibit 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 it also contained polyphenol-rich phytomolecules, such as luteolin, naringenin, and apigenin, which have been established as potent antioxidant and anti-inflammatory compounds[17]. Similarly, findings from the *in vitro* studies of Mankanjuola *et al.*,[29] have also revealed that 7-methoxyflavone-apigeninidin and apigenin constituents of this *Sorghum*-based supplement exhibited inhibitory activity against PG-E2 expression

and COX-2 enzyme activity, further suggesting its role in inflammatory disorders (Table 2).

4.5 Potential Use of SBJS for Stroke Disorders

There is some evidence in the literature that has established that the polyphenol-rich phytomoieties found in SBJS exhibited a wide range of neuroprotective effects against certain brain conditions, including stroke. It has been suggested that its protective effect against ischemic stroke might be related to several mechanisms, including inhibition of NF-kB signalling pathway[67-69]. It is worth noting that ischemic stroke is a fatal disease caused by sudden obstruction of cerebral blood flow and subsequent neuronal cell death[67,70,71]. Occlusion of the carotid artery and the attendant 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 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. Bioactive compounds of plant origin with potent antioxidant and anti-inflammatory activities are believed to hold promise for the development of therapeutic strategies[67,68,78,79].

Indeed, several studies have shown that various phytochemicals can target the multiple pathways involved in the pathophysiology of stroke, including oxidative stress, inflammation, and apoptotic cell death. 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]. The effect of SBJS has been experimentally evaluated against ischemic stroke using the occlusion of the bilateral common carotid artery by a group of scientists at the University of Ibadan, Nigeria[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 SBJS[16]. In addition, it also mitigated the biochemical changes relating to increases in oxidative biomarkers and depletion of antioxidant defence molecules in the brains of the rats subjected to the ischemic stroke[16]. 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 were reduced by SBJS[16]. The neuroprotective effect of this *Sorghum*-based supplement is another major finding obtained from this 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 SBJS 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 to establish its clinical efficacy in stroke (Table 2).

4.6 Anti-aging Potential of SBJS

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 age-related diseases, as well as increased vulnerability to death. 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. Indeed, food supplements with antioxidant-boosting capacity have been gaining attention for the prevention and treatment of chronic conditions linked to Reactive Oxygen Species (ROS), as they have relevant properties related to age-related and chronic syndromes[78,86-88].

The probable anti-aging potentials of SBJS lie in its antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective effects in experimental models[22,43,89]. Studies have shown that its polyphenolic constituents such as apigenin and luteolin exhibit anti-aging activity through neuroprotective mechanisms relating to anti-inflammatory, antioxidant, and anti-apoptosis effects[78,82,90]. Interestingly, the first concrete evidence regarding its anti-aging effect 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, the aging of the skin[91]. Specifically, SBJS was shown to be more effective than vitamin C and ferulic acid in inhibiting collagenase and elastase, suggesting its capability to promote skin health[15]. Also, its potential in age-related diseases, such as Alzheimer's disease, has been investigated in a scopolamine-induced amnesia model[92]. The study revealed that it also attenuated amnesia produced by scopolamine through its neuronal antioxidant protective mechanisms[92]. A more recent study using *Drosophila melanogaster* showed that the supplement extended the lifespan and improved motor function of the flies, through augmentation of the antioxidant status[93]. In addition, it also extended the lifespan of *D. melanogaster* exposed to lipopolysaccharide (LPS)[92]. In another study, SBJS was 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 its potential in promoting cellular survival and longevity (Table 2).

4.7 Potential of SBJS in Chronic Viral Infections

The probable beneficial effects of SBJS 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 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 SBJS[15,17,42] are strongly indicative of its anti-viral potential against HIV/AIDs and COVID-19. Pre-clinical studies have shown that SBJS 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 by HIV infection[17,95,100]. Specifically, Benson *et al.*,[17] have shown that SBJS causes several folds increase 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]. It was also reported to exert an immunomodulatory effect 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 it increased interferon-alpha (IFN-α) levels by 12-fold[17], further suggesting 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 SBJS - has been reported to show 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 leaf sheaths of *Sorghum bicolor* - the principal source of SBJS - 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.*,[103] have reported that *S. bicolor* is one of the medicinal plants from which molecules with potential benefit against viral diseases, such as COVID-19, have been extracted[103]. From a broader perspective, SBJS is therefore, a potential chemo-preventive agent for modulating the immune function and controlling inflammatory reactions in the context of viral infections, such as HIV/AIDs and COVID-19. Clinical studies have shown that it increased the CD4+ T-lymphocyte cellular count as well as bone marrow function, indicating a potential benefit in HIV/AIDS[15,39] (Table 2).

4.8 Cancer Chemopreventive Potential of SBJS

The bioactive constituents of SBJS 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 of 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]. Cancer formation involves three major phases: initiation, promotion, and progression (Figure 3). 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 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 proliferation 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 at 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 relating to antioxidant activity, induction of cell cycle arrest and apoptosis, and the promotion of tumour suppressor proteins[7,10,109].

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

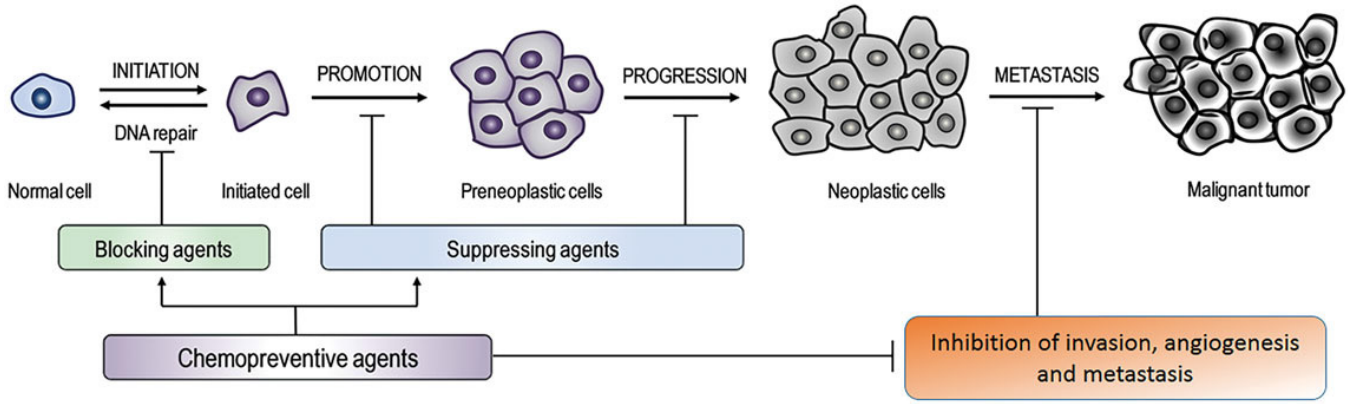


Figure 3. Phases of Carcinogenesis: Initiation, promotion, progression, and metastasis reprinted/adapted from Siddiqui *et al*[108].

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 SBJS exhibited anticancer potential through the modulation of immune cells in *in vitro* models. This echoes the description by the National Cancer Institute of SBJS 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 SBJS are necessary, the existing information suggests its valuable benefits as a supplement for cancer prevention (Table 2).

4.9 Potential of SBJS as Adaptogen

The routine use of SBJS in an adaptogenic-like fashion for the relief of feelings of intense stress and to restore much-needed energy during periods of recovery from debilitating diseases represents another major reason for its routine use[16,20,24]. 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 - 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 were 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, 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 conditions[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 concerning tolerance to mental exhaustion and enhanced attention[117].

Extensive reviews have documented the ability of adaptogenic substances to activate the protective mechanisms of cells, 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 inflammatory 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*[8].

The first concrete experimental evidence of the potential adaptogenic-like activity of SBJS was based on its reported ability to bring about relief concerning feelings of intense stress and as an energizer in the context of general body weakness[16,20,24]. Its adaptogenic potential has also been demonstrated in Unpredictable Chronic Mild Stress (UCMS) through neuroprotective mechanisms relating to the suppression of oxidative stress and pro-inflammatory cytokines[120]. It is worthy

of note to understand that UCMS mimics how humans encounter multiple stressors daily, 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 the UCMS model, SBJS attenuated the loss of neuronal cells in the Cornu Ammonis 3 (CA3) of the hippocampus, 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 SBJS to reduce corticosterone further suggests that it has an adaptogenic-like property[120]. The possibility of this supplement 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 was also reported that SBJS protected RBCs against hyposaline-induced haemolysis[43], suggesting cytoprotection and increased cellular resistance to stress. Notably, the recent finding that it increased the survival rate and prolonged the lifespan of flies exposed to LPS further reinforced its potential adaptogenic-like property[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 the elucidation of the neurobiological mechanisms of stress and age-related disorders. The capability of this *Sorghum*-based supplement 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. These sets of reports are suggestive of its capability to mitigate stress in healthy individuals (Table 2).

4.10 Future Perspectives and Direction for Further Studies

This systematic review provides evidence-based information on the health benefits of SBJS associated with its well-known anti-oxidative, anti-inflammatory, immunomodulatory, chemopreventive and neuroprotective activities. Nevertheless, there is still a need for more robust experimental studies to understand the exact molecular mechanisms of action of SBJS 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

Table 2. Major pharmacological activities of SBJS

Sl. No.	Major pharmacological effect of SBJS	References
1.	Boost blood volume in moderate to severe anaemic conditions	20,40,41
2.	Demonstrated *in vitro* and *in vivo* anti-inflammatory activity, and immune-modulating effect	17,43,29
3.	Reduces neurological deficits and pro-inflammatory cytokines, and NF-κB signalling pathway in rats with ischemic stroke	16
4.	Exhibited neuroprotective effect in alcoholic rats via alterations in GFAP and NF protein expressions	22
5.	Anti-tumour, antiviral and immune-modulating properties	17,40,113
6.	Attenuated inflammatory responses and neurobehavioural deficits in complete Freund-adjuvant-induced arthritis in mice	48
7.	Reduces neuronal degeneration via modulation of p53 and ɤ-Enolase protein expressions in the prefrontal cortex of rats exposed to ethanol	87
8.	Demonstrated anti-amnesic effect in rodents through its antioxidant property	90
9.	Demonstrated antidepressant-like properties in mice	121
10.	Exhibited adaptogenic property in the unpredictable chronic mild stress model	120
11.	Extended the life span and improves motor function in *Drosophila melanogaste* via augmentation of antioxidant status	91

whether this supplement can continue to be used as a standalone supplement, or if some of its components may be isolated and clinically matched with specific pathological conditions. It is also important to identify other possible components. For instance, while SBJS is prepared from the leaf sheaths of *S. bicolor,* a 2 kD, the cationic, amphipathic, and virucidal peptide has been isolated from *Sorghum* seeds, which binds and masks essential viral envelope proteins[123-125]. As such, it is important to determine whether the same protein is present in *Sorghum's* leaf sheaths and, if so, to evaluate its concentration and investigate what contributory role (in terms of antagonistic or synergistic activities) the peptide may play in the potential health benefits of SBJS.

Finally, the limited clinical studies on SBJS underscore the need to clinically evaluate its therapeutic potential 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[126] in mainstream medical practice.

5. Conclusion

This systematic review provides updated information on experimental and clinical studies on the health benefits of SBJS, a unique herbal supplement derived from the polyphenols-rich leaf sheaths of *Sorghum* plant in diverse pathological conditions including arthritis, stroke and cancer. The findings that it also increased the activity of natural killer cells and up-regulated the expression of chemokines; and also inhibited the release of pro-inflammatory cytokines suggest that it might be useful in infectious diseases such as HIV/AIDS and COVID-19. Some clinical studies have also shown its therapeutic potential in the management of moderate to severe anaemia in patients with HIV/AIDs and sickle cell disease. This review also documented experimental evidence, which suggests that it has adaptogenic-like properties through multiple mechanisms relating to the suppression of oxidative and inflammatory pathways. These findings may perhaps support its usefulness in the relief of feelings of intense stress and weakness experienced during periods of debilitating illnesses.

6. References

1. Cragg GM, Newman DJ. Natural products drug discovery in the next millennium. Pharmaceutical Biol. 2001; 39:8-17. https://doi.org/10.1076/phbi.39.s1.8.0009 PMid:21554167
2. Soejarto DD. Biodiversity prospecting and benefit-sharing: Perspectives from the field. J Ethnopharmacol. 1996; 51:1-15. https://doi.org/10.1016/0378-8741(95) 01345-8 PMid:9213606
3. Balandrin MF, Kinghorn AD, Farnsworth NR. Plant-derived natural products in drug discovery and development: An overview. In: Kinghorn AD, Balandrin MF editors. Human Medicinal Agents from Plants. Washington DC American Chemical Society; 1993. p. 2-12. https://doi.org/10.1021/bk-1993-0534.ch001
4. Ellis JM, Reddy P. Effects of Panax ginseng on quality of life. Ann Pharmacother. 2002; 36(3):75-79. https://doi.org/10.1345/aph.1A245 PMid:11895046
5. Josey ES, Tackett RL. St. John's wort: A new alternative for depression? Int J Clin Pharm. 1999; 37:111-19.
6. Aschwanden C. Herbs for health but how safe are they? Bulletin of the World Health Organization. 2001; 79:691-2.
7. Chen X, Shen J, Xu J, Herald T, Smolensky D, Perumal R, *et al.* Sorghum phenolic compounds are associated with cell growth inhibition through cell cycle arrest and apoptosis in human hepatocarcinoma and colorectal adenocarcinoma cells. Foods. 2021; 10(5). https://doi.org/10.3390/foods10050993 PMid:34062914 PMCid:PMC8147257
8. Panossian AG, Efferth T, Shikov AN, Pozharitskaya ON, Kuchta K, Mukherjee PK, *et al.* Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related disease. Med Res Rev. 2021; 41:630-703. https://doi.org/10.1002/med.21743 PMid:33103257 PMCid:PMC7756641
9. Espitia-Hernández P, Mónica L, González C, Ascacio-Valdés JA, Dávila-Medina D, Flores-Naveda A, *et al.* Sorghum (*Sorghum bicolor* L.) as a potential source of bioactive substances and their biological properties. Crit Rev Food Sci. 2002; 62:2269-80. https://doi.org/10.1080/10408398.2020.1852389 PMid:33280412
10. Cox S, Noronha L, Herald T, Bean S, Lee SH, Perumal R, *et al.* Evaluation of ethanol-based extraction conditions of Sorghum bran bioactive compounds with downstream anti-proliferative properties in human cancer cells.

Heliyon. 2019; 5. https://doi.org/10.1016/j.heliyon.2019.e01589 PMid:31111105 PMCid:PMC6512580
11. Duthie GG, Duthie SJ, Kyle JAM. Plant polyphenols in cancer and heart disease: Implications as nutritional antioxidant. Nutr Res Rev. 2000; 13:79-106. https://doi.org/10.1079/095442200108729016 PMid: 19087434
12. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients. 2018; 10. https://doi.org/10.3390/nu10111618 PMid:30400131 PMCid:PMC6266803
13. Devi PS, Saravanakumar M, Mohandas S. Identification of 3-deoxyanthocyanins from red Sorghum (*Sorghum bicolor*) bran and its biological properties. Afr J Pure Appl Chem. 2011; 5:181-93.
14. Adebayo AH, Yakubu OF, Egbung GE, Williams OI, Okubena O. Sub-acute toxicological effects of Jobelyn on pregnant albino rats. American Inst Phy. 2018; 1954. https://doi.org/10.1063/1.5033398
15. Okubena O, Makanjuola S, Ajonuma LC, Dosunmu A, Umukoro S, Erah PO. The West African *Sorghum bicolor* leaf sheath extract Jobelyn® and its diverse therapeutic potentials. MOJ Drug Des Dev Ther. 2018; 2:1-10.
16. Umukoro S, Oghwere EE, Ben-Azu B, Owoeye O, Ajayi AM, Omorogbe O, *et al.* Jobelyn® ameliorates neurological deficits in rats with ischemic stroke through inhibition of release of pro-inflammatory cytokines and NF-κB signaling pathway. Pathophysio. 2018; 26(1):77-88. https://doi.org/10.1016/j.pathophys.2018.10.002 PMid:30413288
17. Benson KF, Beaman JL, Ou B, Okubena A, Okubena O, Jensen GS. West African *Sorghum bicolor* leaf sheaths have anti-inflammatory and immune-modulating properties *in vitro*. J Med Food. 2013; 16:230-8. https://doi.org/10.1089/jmf.2012.0214 Mid:23289787 PMCid:PMC3598435
18. Woo HJ, Oh LT, Lee JY, Jun DY, Seu MC, Woo KS, *et al.* Apigeninidin induces apoptosis through activation of Bak and Bax and subsequent mediation of mitochondrial damage in human promyelocytic leukemia HL-60 cells. Process Biochem. 2012; 47:1861-71. https://doi.org/10.1016/j.procbio.2012.06.012
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Br Med J. 2021; 372. https://doi.org/10.1136/bmj.n71
20. Okochi VI, Okpuzor J, Okubena MO, Awoyemi AK. The influence of African herbal formular on the haematological parameters of trypanosome infected rats. Afr J Biotechnol. 2003; 2:312-16. https://doi.org/10.5897/AJB2003.000-1064
21. Awika JM, Rooney LW. Sorghum phytochemicals and their potential impact on human health. Phytochem. 2000; 65:1199-221. https://doi.org/10.1016/j.phytochem.2004.04.001 PMid:15184005
22. Oyinbo CA, Dare WN, Avwioro OG, Igbigbi PS. Neuroprotective effect of Jobelyn in the hippocampus of alcoholic rat is mediated in part by alterations in GFAP and NF protein expressions. Adv Biol Sci Res. 2015; 9:305-17.
23. Eniojukan JF, Aina BA. Toxicological profiles of commercial herbal preparation, Jobelyn. Int J Health Res. 2009; 2:369-74. https://doi.org/10.4314/ijhr.v2i4.55438
24. Erah PO, Asonye CC, Okhamafe AO. Response of Trypanosomabrucei-induced anaemia to a commercial herbal preparation. Afr J Biotech. 2003; 2:307-11. https://doi.org/10.5897/AJB2003.000-1063
25. Nnaji M. How an African-made dietary supplement promises to revolutionize medical treatment. The African Courier [Internet]. 2016. [cited 2022 Sep 23]. Available from: https://www.theafricancourier.de/news/africa/jobelyn-how-a-nigerian-made-drug-promises-to-mix-up-things-in-medical-treatment/
26. Paraiso IL, Revel JS, Stevens JF. Potential use of polyphenols in the battle against COVID-19. Curr Opin Food Sci. 2020; 32:149-55. https://doi.org/10.1016/j.cofs.2020.08.004 PMid:32923374 PMCid:PMC7480644
27. Xu H, Wang E, Chen J, Xiao J, Wan M. Neuroprotective phytochemicals in experimental ischemic stroke: Mechanisms and potential clinical applications. Oxid Med Cell Longev. 2021. https://doi.org/10.1155/2021/6687386 PMid:34007405 PMCid:PMC8102108
28. Drug Dictionary of National Cancer Institute, USA. *Sorghum bicolor* supplement [Internet]. n.d. [cited 2023 Feb 12]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/sorghum-bicolor-supplement
29. Makanjuola SBL, Ogundaini AO, Ajonuma LC, Dosunmu A. Apigenin and apigeninidin isolates from the *Sorghum bicolor* leaf targets inflammation via cyclooxygenase-2 and prostaglandin-E2 blockade. Clin Transplant. 2018; 21:1487-95. https://doi.org/10.1111/1756-185X.13355 PMid:30146750
30. Kim J, Fann DY, Seet RC, Jo DG, Mattson MP, Arumugam TV. Phytochemicals in ischemic stroke. Neuromolecular Med. 2016; 18:283-305. https://doi.org/10.1007/s12017-016-8403-0 PMid:27193940
31. Shayganfard M. Are essential trace elements effective in modulation of mental disorders? Update and perspectives. Biol Trace Elem Res. 2022; 200:1032-59. https://doi.org/10.1007/s12011-021-02733-y PMid:33904124
32. Roth W, Mohamadzadeh M. Vitamin B12 and gut-brain homeostasis in the pathophysiology of ischemic stroke. eBio Medicine. 2021; 73. https://doi.org/10.1016/j.ebiom.2021.103676 PMid:34749301 PMCid:PMC8586745
33. Tamura J, Kubota K, Murakami B, Sawamura M, Matsushima T, Tamura T, *et al.* Immunomodulation by vitamin B12: Augmentation of CD8+ T lymphocytes

and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immunol. 2001; 116:28-32. https://doi.org/10.1046/j.1365-2249.1999.00870.x PMid:10209501 PMCid:PMC1905232

34. Djuricic L, Calder PC. Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: An update for 2021. Nutrients. 2021; 13. https://doi.org/10.3390/nu13072421 PMid:34371930 PMCid:PMC8308533
35. Tantipaiboonwong P, Chaiwangyen W, Suttajit M, Kangwan N, Kaowinn S, Khanaree C, *et al*. Molecular mechanism of antioxidant and anti-inflammatory effects of omega-3 fatty acids in perilla seed oil and rosmarinic acid rich fraction extracted from perilla seed meal on TNF-α induced A549 lung adenocarcinoma cells. Molecules. 2021; 26. https://doi.org/10.3390/molecules26226757 PMid:34833849 PMCid:PMC8622939
36. Janz TG, Johnson RL, Scott D, Rubenstein SD. Anemia in the emergency department: Evaluation and treatment. Emerg Med. Pract. 2013; 15:1-15.
37. van Hensbroek MB, Jonker F, Bates L. Severe acquired anaemia in Africa: New concepts. Br J Haematol. 2011; 154:690-95. https://doi.org/10.1111/j.1365-2141.2011.08761.x PMid:21707575
38. West CE. Strategies to control nutritional anaemia. Am J Clin Nutr. 1996; 64:789-90. https://doi.org/10.1093/ajcn/64.5.789 PMid:8901803
39. Low MS, Speedy J, Styles CE, De-Regil LM, Pasricha SR. Daily iron supplementation for improving anaemia, iron status and health in menstruating women. Cochrane Database Syst Rev. 2016; 4. https://doi.org/10.1002/14651858.CD009747.pub2 PMid:27087396
40. Ayuba GI, Jensen GS, Benson KF, Okubena AM, Okubena O. Clinical efficacy of a West African *Sorghum bicolor*-based traditional herbal preparation Jobelyn shows increased hemoglobin and CD4+ T-lymphocyte counts in HIV-positive patients. J Altern Complement Med. 2014; 20(1):53-6. https://doi.org/10.1089/acm.2013.0125 PMid:24283768 PMCid:PMC3904510
41. Tayo AO, Dosunmu AO, Akinola IO, Adewunmi A, Oloyede OA, Akinbami AA, *et al*. Makanjuola SBL. An open-label, randomized, parallel-group comparative study of the efficacy of *Sorghum bicolor* extract in preoperative anemia. Nutrition. 2007; 33:113-17. https://doi.org/10.1016/j.nut.2016.05.005 PMid:27461168
42. Archer N, Galacteros F, Brugnara C. Clinical trials update in sickle cell anaemia. Am J Hematol. 2015; 90:934-50. https://doi.org/10.1002/ajh.24116 PMid:26178236 PMCid:PMC5752136
43. Umukoro S, Oluwole OG, Eduviere AT, Omogbiya IA, Ajayi AM. Jobelyn exhibited anti-inflammatory, antioxidant, and membrane-stabilizing activities in experimental models. J Basic Clin Physiol Pharmacol. 2015; 26:501-8. https://doi.org/10.1515/jbcpp-2014-0113 PMid:26020554
44. Barodka VM, Nagababu E, Mohanty JG, Nyhan D, Berkowitz DE, Rifkind JM, *et al*. New insights provided by a comparison of impaired deformability with erythrocyte oxidative stress for sickle cell disease. Blood Cell Mol Dis. 2013. https://doi.org/10.1016/j.bcmd.2013.10.004 PMid:24246527
45. Nagababu E, Mohanty JG, Bhamidipaty S, Ostera GR, Rifkind JM. Role of the membrane in the formation of heme degradation products in red blood cells. Life Sci. 2010; 86:133-8. https://doi.org/10.1016/j.lfs.2009.11.015 PMid:19958781 PMCid:PMC2819203
46. Wang C, Zennadi R. The role of RBC oxidative stress in sickle cell disease: From the molecular basis to pathologic implications. Antioxidants. 2021; 10. https://doi.org/10.3390/antiox10101608 PMid:34679742 PMCid:PMC8533084
47. Mohanty JG, Nagababu E, Rifkind JM. Red blood cell oxidative stress impairs oxygen delivery and induces red blood cell aging. Front Physiol. 2014. https://doi.org/10.3389/fphys.2014.00084 PMCid:PMC3937982
48. Omorogbe O, Ajayi AM, Ben-Azu B, Oghwere EE, Adebesin A, Aderibigbe AO, *et al*. Jobelyn® attenuates inflammatory responses and neuro behavioural deficits associated with complete Freund-adjuvant-induced arthritis in mice. Biomed Pharmacother. 2018; 98:585-93. https://doi.org/10.1016/j.biopha.2017.12.098 PMid:29288974
49. Choy E. Understanding the dynamics: Pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology. 2012; 51:3-11. https://doi.org/10.1093/rheumatology/kes113 PMid:22718924
50. García-González A, Gaxiola-Robles R, Zenteno-Savín T. Oxidative stress in patients with rheumatoid arthritis. Rev Invest Clin. 2015; 67:46-53.
51. Muller-Ladner U, Pap T, Gay RE, Neidhart M, Gay S. Mechanisms of disease: The molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheum. 2005; 1:102-10. https://doi.org/10.1038/ncprheum0047 PMid:16932639
52. Hernández-Hernández V, Ferraz-Amaro I, Díaz-González F. Influence of disease activity on the physical activity of rheumatoid arthritis patients. Rheumatology. 2014; 53:722-31. https://doi.org/10.1093/rheumatology/ket422 PMid:24369410
53. Hitchon, CA, El-Gabalawy HS. Oxidation in rheumatoid arthritis. Arthritis Res Ther. 2004; 6:265-78. https://doi.org/10.1186/ar1447 PMid:15535839 PMCid:PMC1064874
54. Winrow VR, Winyard PG, Morris CJ, Blake DR. Free radicals in inflammation: second messengers and mediators of tissue destruction. Br Med Bull. 1993;

49:506-22. https://doi.org/10.1093/oxfordjournals.bmb.a072627 PMid:8221019
55. Jones A, Al-Janabi M, Solanki K, Snack PR, Greenwood A, Doyle D, Britton KM, Huskisson E. *In vivo* leukocyte migration in arthritis. Arthritis Rheumatol. 1991; 34:270-5. https://doi.org/10.1002/art.1780340304 PMid:2003853
56. Yudoh K, Karasawa R, Masuko K, Kato T. Water-soluble fullerene (C60) inhibits the development of arthritis in the rat model of arthritis. Int J Nanomedicine. 2009; 4:217-25. https://doi.org/10.2147/IJN.S7653 PMid:19918368 PMCid:PMC2775692
57. Rangan U, Bulkley GB. Prospects for treatment of free radical-mediated tissue injury. Br Med Bull. 1993; 49:700-18. https://doi.org/10.1093/oxfordjournals.bmb.a072641 PMid:8221033
58. Frech TM, Clegg DO. The utility of nutraceuticals in the treatment of osteoarthritis. Curr Rheumatol Rep. 2007; 9:25-30. https://doi.org/10.1007/s11926-007-0018-x PMid:17437663
59. Winter CA, Risley EA, Nuss GW. Carrageenan induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. Proc Soc Exp Biol Med. 1962; 111:544-7. https://doi.org/10.3181/00379727-111-27849 PMid:1400 1233
60. Benitz KF, Hall LM. The carregeenin-induced abscess, a new test for anti-inflammatory activity of steroids and non-steroids. Arch Int Pharmacodyn Ther. 1969; 144:185-95.
61. Boris A, Stevenson RH. The effects of some non-steroidal anti-inflammatory agents on carrageenin-induced exudate formation. Arch Int Pharmacodyn Ther. 1965; 153:205-9.
62. Pearson CM, Wood FD. Studies of polyarthritis and other lesions induced in rats by injection of mycobacterial adjuvant. General clinical and pathological characteristics and some modifying factor. Arthritis Rheumatol. 1969; 2:440-59. https://doi.org/10.1002/1529-0131(195910)2:5<440::AID-ART1780020510>3.0.CO;2-N
63. Newbould BB. Chemotherapy of arthritis induced in rats by mycobaterial adjuvant. Br J Pharmacol Chemother. 1963; 21:127-36. https://doi.org/10.1111/j.1476-5381.1963.tb01508.x PMid:14066137 PMCid:PMC1703866
64. ShindeUA, Phadke AS, Nair AM, Mungantiwar AA, Dikshit VJ, Saraf MN. Membrane stabilizing activity: a possible mechanism of action for the anti-inflammatory activity of Cedrusdeodara wood oil. Fitoterapia. 1999; 70:251-7. https://doi.org/10.1016/S0367-326X(99)00030-1
65. Gadamsetty G, Maru S, Sarada NC. Antioxidant and anti-inflammatory activities of the methanolic leaf extract of traditionally used medicinal plant *Mimusops elengi* L. J Pharm Sci. 2013; 5:125-30.
66. Anrather J, Iadecola JC. Inflammation and stroke: An overview. Neurotherapeutics. 2016; 13:661-70. https://doi.org/10.1007/s13311-016-0483-x PMid:27730544 PMCid:PMC5081118
67. Boslett J, Hemann C, Zhao YJ, Lee H, Zweier JL. Luteolinidin protects the postischemic heart through CD38 inhibition with preservation of NAD(P)(H). J Pharmacol Exp Ther. 2017; 36:99-108. https://doi.org/10.1124/jpet.116.239459 PMid:28108596 PMCid:PMC5363772
68. Doyle KP, Simon RP, Stenzel-Poore MP. Mechanisms of ischemic brain damage. Neuropharmacology. 2008; 55:310. https://doi.org/10.1016/j.neuropharm.2008.01.005 PMid:18308346 PMCid:PMC2603601
69. Lipton P. Ischemic cell death in brain neurons. Physiol Rev. 1999; 79:1431-568. https://doi.org/10.1152/physrev.1999.79.4.1431 PMid:10508238
70. Adeloye D. An estimate of the Incidence and prevalence of stroke in Africa: A systematic review and meta-analysis. PLoS One. 2014; 9. https://doi.org/10.1371/journal.pone.0100724 PMid:24967899 PMCid:PMC4072632
71. Ramsey LE, Siegel JS, Lang CE, Strube M, Shulman GL, Corbetta M. Behavioural clusters and predictors of performance during recovery from stroke. Nat Hum Behav. 2017; 1. https://doi.org/10.1038/s41562-016-0038 PMid:28713861 PMCid:PMC5508212
72. Feigin VL, Norrving B, George MG, Foltz JL. Prevention of stroke: A strategic global imperative. Nat Rev Neurol. 2016; 12:501-12. https://doi.org/10.1038/nrneurol.2016.107 PMid:27448185 PMCid:PMC8114177
73. Edward CJ. Ischemic Stroke: An acute onset syndrome. Neurol. 2017; 17:1-16.
74. Petrovic-Djergovic D, Goonewardena SN, Pinsky DJ. Inflammatory disequilibrium in stroke. Circ Res. 2016; 119:142-58. https://doi.org/10.1161/CIRCRESAHA.116.308022 PMid:27340273 PMCid:PMC5138050
75. Zhang H, Gao W, Qian T, Tang J, Li J. Transcription factor changes following long term cerebral ischemia/reperfusion injury. Neural Regen Res. 2013; 8.
76. Meccariello B, D'Angelo S. Impact of polyphenolic-food on longevity: An elixir of life. An Overview. Antioxidants. 2021; 10. https://doi.org/10.3390/antiox10040507 PMid:33805092 PMCid:PMC8064059
77. Chen Y, Jui-Sheng W, Yang S, Huang C, Chang C, Sun GY, Lin T. Stroke, angiogenesis and phytochemicals. Front Biosci. 2012; S4:599-610. https://doi.org/10.2741/s287 PMid:22202079
78. Simret B, Litrus L, Soriano L, Monbureau M, To LK, Braithwaite SP, *et al*. A Pharmacological screening approach for discovery of neuroprotective compounds in ischemic stroke. PLoS One. 2013; 8. https://doi.org/10.1371/journal.pone.0069233 PMid:23874920 PMCid:PMC3715457
79. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153:1194-217.

https://doi.org/10.1016/j.cell.2013.05.039 PMid:23746838 PMCid:PMC3836174

80. de Almeida AJO, Ribeiro TP, de Medeiros IA. Aging: Molecular pathways and implications on the cardiovascular system. Oxid Med Cell Longev. 2017. https://doi.org/10.1155/2017/7941563 PMid:28874954 PMCid:PMC5569936
81. Riera CE, Merkwirth C, Filho CDDM, Dillin A. Signaling networks determining life span. Annu. Rev Biochem. 2018; 85:35-64. https://doi.org/10.1146/annurev-biochem-060815-014451 PMid:27294438
82. Harman D. Aging: A theory based on free radical and radiation chemistry. J Gerontol. 1996; 11:298-300. https://doi.org/10.1093/geronj/11.3.298 PMid:13332224
83. Jarrett SG, Boulton ME. Consequences of oxidative stress in age-related macular degeneration. Mol Aspects Med. 2012; 33:399-417. https://doi.org/10.1016/j.mam.2012.03.009 PMid:22510306 PMCid:PMC3392472
84. Sachdeva V, Roy A, Bharadvaja N. Current prospects of nutraceuticals: A review. Curr Pharm Biotechnol. 2010; 21:884-96. https://doi.org/10.2174/1389201021666200130113441 PMid:32000642
85. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly) phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal. 2013; 18:1818-92. https://doi.org/10.1089/ars.2012.4581 PMid:22794138 PMCid:PMC3619154
86. Cory H, Passarelli S, Szeto J, Tamez M, Mattei J. The role of polyphenols in human health and food systems: A mini-review. Front Nutr. 2018; 5:87. https://doi.org/10.3389/fnut.2018.00087 PMid:30298133 PMCid:PMC6160559
87. Oyinbo CA, Igbigbi PS, Avwioro OG. Jobelyn supplement lowered neuronal degeneration: Significance of altered p53 and ɤ-Enolase protein expressions in prefrontal cortex of rat exposed to ethanol. Ann Neurosci. 2016; 23:139-48. https://doi.org/10.1159/000449179 PMid:27721582 PMCid:PMC5043160
88. Leri M, Scuto M, Ontario ML, Calabrese V, Calabrese EJ, Bucciantini M, Stefani M. Healthy effects of plant polyphenols: Molecular mechanism. Int J Mol Sci. 2020; 21. https://doi.org/10.3390/ijms21041250 PMid:32070025 PMCid:PMC7072974
89. Thring T, Hili P, Naughton D. Anti-collagenase, anti-elastase and anti-oxidant activities of extracts from 21 plants. BMC Complement Med Ther. 2009; 9. https://doi.org/10.1186/1472-6882-9-27 PMid:19653897 PMCid:PMC2728709
90. Umukoro S, Ugbomah A, Aderibigbe A, Omogbiya A. Antioxidant property of Jobelyn® as the possible mechanism underlying its anti-amnesic effect in rodents. Basic Clin Neurosci. 2013; 4:42-9.
91. John R, Abolaji AO, Adedara AO, Ajayi AM, Aderibigbe AO, Umukoro S. Jobelyn® extends the life span and improves motor function in *Drosophila melanogaster* exposed to lipopolysaccharide via augmentation of antioxidant status. Metab Brain Dis. 2022; 37:1031-40. https://doi.org/10.1007/s11011-022-00919-4 PMid:35156155
92. Chun TW, Fauci AS. HIV reservoirs: pathogenesis and obstacles to viral eradication and cure. AIDS. 2012; 26(10):1261-8. https://doi.org/10.1097/QAD.0b013e328353f3f1 PMid:22472858
93. Naif H. Pathogenesis of HIV infection. Infect Dis Rep. 2013; 6. https://doi.org/10.4081/idr.2013.s1.e6 PMid:24470970 PMCid:PMC3892619
94. Yazdanpanah F, Hamblin MR, Rezaei N. The immune system and COVID-19: Friend or foe? Life Sci. 2020; 256. https://doi.org/10.1016/j.lfs.2020.117900 PMid:32502542 PMCid:PMC7266583
95. Goc A. Phenolic compounds disrupt spike-mediated receptor-binding and entry of SARS-CoV-2 pseudo-virions. PLoS One. 2021; 16. https://doi.org/10.1371/journal.pone.0253489 PMid:34138966 PMCid:PMC8211150
96. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, *et al*. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Life Sci. 2020; 63:457-60. https://doi.org/10.1007/s11427-020-1637-5 PMid:32009228 PMCid:PMC7089049
97. Verma S, Twilley D, Esmear T, Oosthuizen CB, Reid AM, Nel M, Lall N. Anti-SARS-CoV natural products with the potential to inhibit SARS-CoV-2 (COVID-19). Front Pharmacol. 2020; 11. https://doi.org/10.3389/fphar.2020.561334 PMid:33101023 PMCid:PMC7546787
98. Alkhatib G, Bombardier C, Broder CC, Feng Y, Kennedy PE, Murphy PM, *et al*. CC CKR5: A RANTES, MIP-1alpha, IP-1beta receptor as a fusion cofactor for macrophage-tropic HIV. Science. 1996; 272:1955-8. https://doi.org/10.1126/science.272.5270.1955 PMid:8658171
99. Scagnolari C, D'Amore A, Palombi F, Criscuolo E, Frasca F, Pierangeli A, *et al*. Naringenin is a powerful inhibitor of SARS-CoV- 2 infection *in vitro*. Pharmacol Res. 2021; 163. https://doi.org/10.1016/j.phrs.2020.105255 PMid:33096221 PMCid:PMC7574776
100. Lawal LO, Olufade II, Rafiu BO, Aremu AO. Ethnobotanical survey of plants used for treating cough associated with respiratory conditions in Ede South local government area of Osun State, Nigeria. Plants. 2020; 9. https://doi.org/10.3390/plants9050647 PMid:32443771 PMCid:PMC7286022
101. Alhazmi HA, Najmi A, Javed SA, Sultana S, Al Bratty M, Makeen HA, *et al*. Medicinal plants and isolated molecules demonstrating immunomodulation activity as potential alternative therapies for viral diseases including COVID-1.

Front Immunol. 2021; 12. https://doi.org/10.3389/fimmu.2021.637553 PMid:34054806 PMCid:PMC8155592
102. Devi PS, Kumar MS, Das SM. Evaluation of antiproliferative activity of red Sorghum bran anthocyanin on a human breast cancer cell line (mcf-7). Int J Breast Cancer. 2011. https://doi.org/10.4061/2011/891481 PMid:22312562 PMCid:PMC3262581
103. Pitot HC. The molecular biology of carcinogenesis. Cancer. 1993; 72:962-70. https://doi.org/10.1002/1097-0142(19930801)72:3+<962::AID-CNCR2820721303>3.0.CO;2-H PMid:8334671
104. Oliveira PA, Colaço A, Chaves R, Guedes-Pinto H, Luis F, De-La-Cru P, Lopes C. Chemical carcinogenesis. An Acad Bras Cienc. 2007; 79:593-616. https://doi.org/10.1590/S0001-37652007000400004 PMid:18066431
105. Smolensky D, Rhodes D, McVey DS, Fawver Z, Perumal R, Herald T, *et al.* High-polyphenol Sorghum bran extract inhibits cancer cell growth through ROS induction, cell cycle arrest, and apoptosis. J Med Food. 2018; 21:990-8. https://doi.org/10.1089/jmf.2018.0008 PMid:29733262
106. Siddiqui LA, Sanna V, Ahmad N, Sechi M, Mukhtar H. Resveratrol nano formulation for cancer prevention and therapy. Ann N Y Acad Sci. 2015; 134:20-31. https://doi.org/10.1111/nyas.12811 PMid:26109073
107. Xu S, Shen Y, Xu J, Qi G, Chen G, Wang G, *et al.* Antioxidant and anticancer effects in human hepatocarcinoma (HepG2) cells of papain-hydrolyzed Sorghum kafirin hydrolysate. J Funct Foods. 2019; 58:374-82. https://doi.org/10.1016/j.jff.2019.05.016
108. Van Rensburg SJ. Epidemiologic and dietary evidence for a specific nutritional predisposition to esophageal cancer. J Natl Cancer Inst. 1981; 67:243-51.
109. Isaacson C. The change of the staple diet of black South Africans from Sorghum to maize (corn) is the cause of the epidemic of squamous carcinoma of the oesophagus. Med Hypotheses. 2005; 64:658-60. https://doi.org/10.1016/j.mehy.2004.09.019 PMid:15617883
110. Park JH, Darvin P, Lim EJ, Joung YH, Hong DY, Park EU, *et al. Hwanggeumchal* Sorghum induces cell cycle arrest, and suppresses tumor growth and metastasis through Jak2/STAT pathways in breast cancer xenografts. PLoS ONE. 2012; 7. https://doi.org/10.1371/journal.pone.0040531 PMid:22792362 PMCid:PMC3391253
111. Makanjuola SBL, Dosunmu D, Ajonuma L, Ogundaini A, Okubena O. Newly isolated compounds from West African Sorghum *bicolor* leaf sheaths Jobelyn® show potential in cancer immunosurveillance. J Cancer Res Ther. 2016; 4:31-7. https://doi.org/10.14312/2052-4994.2016-6
112. deKloet ER, Joels M, Holsboer F. Stress and the brain: From adaptation to disease. Nat Rev Neurosci. 2005; 6:463-75. https://doi.org/10.1038/nrn1683 PMid:15891777
113. McEwen BS, Biron CA, Brunson KW, Bulloch K, Chambers WH, Dhabhar FS, *et al.* The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions. Brain Res Rev. 1997; 23:79-133. https://doi.org/10.1016/S0165-0173(96)00012-4 PMid:9063588
114. McEwen BS, Gray JD, Nasca C. Recognizing resilience: Learning from the effects of stress on the brain. Neurobiol Stress. 2015; 1:1-11. https://doi.org/10.1016/j.ynstr.2014.09.001 PMid:25506601 PMCid:PMC4260341
115. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. Curr Clin Pharmacol. 2009; 4:198-219. https://doi.org/10.2174/157488409789375311 PMid:19500070
116. Selye H. The general adaptation syndrome and disease of adaptation. J Clin Endocrinol Metab. 1946; 6:117-230. https://doi.org/10.1210/jcem-6-2-117 PMid:21025115
117. Brekhman II, Dardymov IV. New substances of plant origin which increase nonspecific resistance. Annu Rev Pharmacol Toxicol. 1968; 8:419-30. https://doi.org/10.1146/annurev.pa.09.040169.002223 PMid:4892434
118. Umukoro S, Omorogbe O, Aluko OM, Eduviere TA, Owoeye O, Oluwole OG. Jobelyn, a Sorghum-based nutritional supplement attenuates unpredictable chronic mild stress-induced memory deficits in mice. Behav Brain Sci. 2015; 5:586-97. https://doi.org/10.4236/jbbs.2015.513056
119. Umukoro S, Eduviere AT, Aladeokin AC, Olugbemide A. Antidepressant-like property of Jobelynan African unique herbal formulation in mice. Drug Res. 2014; 64:146-50. https://doi.org/10.1055/s-0033-1354366 PMid:24002928
120. Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA. Plant adaptogens increase lifespan and stress resistance in C. elegans. Biogerontology. 2009; 10:27-42. https://doi.org/10.1007/s10522-008-9151-9 PMid:18536978
121. Simnadis TG, Tapsell LC, Beck EJ. Effect of sorghum consumption on health outcomes: A systematic review. Nutr Rev. 2016; 74:690-707. https://doi.org/10.1093/nutrit/nuw036 PMid:27694643
122. Boas LC, Campos ML, Berlanda EL, de CarvalhoNeves N, Franco OL. Antiviral peptides as promising therapeutic drug. Cell Mol Life Sci. 2019; 76. https://doi.org/10.1007/s00018-019-03138-w PMid:31101936 PMCid:PMC7079787
123. Mammari N, Krier Y, Albert Q, Devocelle M, Varbanov M. Plant-derived antimicrobial peptides as potential antiviral agents in systemic viral infections. Pharmaceuticals. 2021; 14(8):774. https://doi.org/10.3390/ph14080774 PMid:34451871 PMCid:PMC8400714
124. Afolabi MO. Resolving the identity dilemmas of Western healthcare in Africa: Towards ethical and pragmatic

approaches. Culture and Dialogue. 2020; 8:147-65. https://doi.org/10.1163/24683949-12340080

125. Mammari N, Krier Y, Albert Q, Devocelle M, Varbanov M. Plant-derived antimicrobial peptides as potential antiviral agents in systemic viral infections. Pharmaceuticals. 2021; 14(8):774. https://doi.org/10.3390/ph14080774 PMid:34451871 PMCid:PMC8400714
126. 126. Afolabi MO. Resolving the identity dilemmas of Western healthcare in Africa: Towards ethical and pragmatic approaches. Culture and Dialogue. 2020; 8:147-65. https://doi.org/10.1163/24683949-12340080