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Review Article

# Potential Benefits of Sorghum [*sorghum bicolor* (l.) Moench] on Human Health: A Review

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**Abstract:** *Introduction*: From a nutritional perspective, sorghum is very important with respect to healthy and nutrition. Its higher proportion of slowly digestible and resistant starch components compared with other staple cereal crops. Furthermore, Sorghum is a source of some minerals, proteins (kafirins that have high degrees of polymerization, extensive disulfide bridges, strong interaction with tannins and starch makes proteins resistant to enzymatic digestion in the digestive tract) lipids, vitamins and phenolic compounds. Possessing diverse phytochemical content particularly in the bran layer (six times higher than the whole grain) and other beneficial compounds makes it more important and represents a promising opportunity to be exploited as a functional food or food ingredient and to reduce risk of non-communicable chronic diseases. *Objective*: To review literatures on potential health benefits of sorghum grain and understanding detailed phenolic extracts with respect to health. *Method*: original, adequate and recent articles on the same field were researched and conduct a comprehensive review on this topic. Thus, extraction and isolation of these compounds from sorghum is another option to fully exploit their application potential. In addition, some relevant scientific papers published in previous years were included. The article search was performed by matching the terms sorghum and *Sorghum bicolor* L. with a group of terms related to phenolic composition and nutritional value. The articles were screened and selected based on the title and abstract presented. *Result*: results of several articles showed that some sorghum varieties (black and brown sorghums) are rich in phenolic compounds, especially 3-deoxyanthocyanidins and condensed tannins which will show a lot of promise for utilization of sorghum with regard to human health in near future and sorghum may also be used as promising natural multifunctional additives in broad food processing. The studies demonstrated *in vitro* and in animals have shown that phenolic compounds and fat soluble polycosanols isolated from sorghum can benefit in different parameters. Sorghum phenolic compounds may also be used in medicinal products such as creams and cosmetics due to their pharmacological and antimicrobial properties. But the effects of whole sorghum and its fractions on human health need to be evaluated especially, preventive and therapeutic effects of sorghum whole grain and its fractions on human health, including gene and protein expression. *Conclusion*: Sorghum is an excellent source of bioactive compounds that can promote benefits to human health. In recent times, genetic engineering and breeding tools provide promising prospects to develop sorghum with desirable nutritional and phenolic profile, while maintaining good agronomic performance and yield, and this could be a fruitful area for further research. Investigations through mutagenesis-assisted breeding revealed that biosynthesis of phenolic compounds can be enhanced in sorghum.

**Keywords:** *in vitro*, Antioxidant Activity, Cardiovascular Diseases, Diabetes, Cancer, Inflammation, Oxidative Stress, Dyslipidemia and Obesity

## 1. Introduction

Sorghum grain comprises three main parts including bran layer (pericarp and testa), endosperm and the germ [1, 2]. Non starch polysaccharides such as phenolic acids, flavonoids, condensed tannins and some vitamins such as carotenoids were mainly found in pericarp and testa of sorghum. Starch, proteins, some vitamins (vitamin B complex) and minerals

were mainly found in the endosperm. The germ fraction is mainly composed of lipids and proteins. Vitamin B complex, fat-soluble vitamins and minerals were also found in the germ fraction of sorghum [1-3]. However, because of its high phytochemical content, sorghum bran has attracted the most interest than other parts. Sorghum also has a big potential, given its agronomic properties, as well as the emerging evidence on the biological belongingness of the phytochemicals present in the grain which has a great positive impact on human health. But the potential benefits to human health associated with the consumption of compounds isolated from sorghum, and especially the whole grain, are still unknown. However, the results of *in vitro* and animal studies have been shown promises that various phytochemicals including tannins, phenolic acids, anthocyanins, phytosterols and policosanols beneficially regulate the gut micro biota and parameters related to non-communicable diseases such as obesity, diabetes (Type-2), dyslipidemia, cardiovascular disease, cancer, and hypertension [4-6]. Alongside its agronomic advantages, sorghum contains a diverse range of important bioactive phenolic compounds [7, 8]. Nearly all classes of phenolic compounds such as simple phenolic acids, flavonoids and tannins are the most abundant and diverse compared to other major cereal crops [8]. Thus, unique phenolic profile makes sorghum potentially beneficial to human health. Sorghum phenolic compounds can be used in manufacturing of creams and cosmetics because of their pharmacological and antimicrobial treatments. Currently, healthy and plant-based foods were highly preferred by consumers' hence change in demand. Therefore, sorghum has huge potential for exploitation and development into healthy and functional foods and food additives. Efforts have been made in recent times to use sorghum whole grain or ingredients to make new foods such as sorghum grain tea, as well as adding sorghum into foods, such as breads and meat products, to advance food quality and health benefits [9-11]. Beside its agronomic importance, sorghum grain is gluten free, high in resistant starch and is a rich source of nutrients, prolamin (such as kafirins) and non-prolamin (such as globulins, glutelins, and albumin) storage proteins and lipids. Most importantly, Kafirins are the principal form of protein storage in sorghum grain and account for 70% of the total protein in sorghum whole grain and have low digestibility. Sorghum kafirins have high degrees of polymerization and extensive disulfide bridges that are resistant to enzymatic digestion in the digestive tract; their strong interaction with tannins and starch also hinders the protein digestion [12-14]. Despite the high levels and diversity of phytochemicals in sorghum, research on this crop as a source of valuable health promoting compounds lags behind other commodities such as fruits and vegetables. The main mechanisms of action of the compounds isolated from sorghum on parameters related to non-communicable diseases, as found in results of *in vitro* and animal studies were discussed by many scholars in detail. However, utilization of sorghum fractions in foods to improve nutritional and phenolic profile with respect to human health is very limited. Further investigation is required to better understand the preventive and therapeutic effects of sorghum whole grain. Thus, the objectives of this review were: (a) To review literatures on potential human health benefits of sorghum grain. (b) To asses and understanding detailed phenolic profiles about sorghum germplasm. (c) To discuss about the different extracts of sorghum grain with respect to health.

## 2. Methodology

Original, adequate and recent articles on the same field were researched and conduct a comprehensive review on this topic. Thus, extraction and isolation of phenolic compounds from sorghum is another option to fully exploit their application potential. In addition, some relevant scientific papers published in previous years were included. The article search was performed by matching the terms sorghum and *Sorghum bicolor* L. with a group of terms related to phenolic composition and nutritional value. The articles were screened and selected based on the title and abstract presented.

## 3. Potential Health Benefits and Phenolic Profiles of Sorghum

### 3.1. Antioxidant Activity

Oxidative stress is the source of various chronic diseases such as non-communicable diseases and make happened by free radical and antioxidant imbalances [15, 16]. The antioxidant activity of sorghum phenolic compounds seems to play a crucial role in the health advancement and disease prevention associated with sorghum consumption. Various methods have been used to measure the antioxidant activity of natural compounds, and these methods are almost exclusively based on the colorimetric methods using *in vitro* assays. The functional benefits from sorghum are attributed to the phenolic compounds and are most evident when extracts from black or red sorghum were used [17, 5]. The phenolic compounds extracted from sorghum grain exhibit the highest antioxidant activity among cereal grains of wheat, rice, and corn, and are also comparable to common fruits and vegetables [18-21]. Now a day's there are a number of methods that are widely used *in vitro* to estimate sorghum antioxidant activity these are; Oxygen radical absorbance capacity (ORAC), ferric reducing antioxidant power, and 2, 2'_ azino-bis3-ethylbenzothiazoline-6-sulphonic acid (ABTS) and 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging methods. However, it is important to note that the *in vitro* antioxidant activity does not accurately, or does not at all, reflect the actual antioxidant capacity or health benefits *in vivo*, because it does not account for the physiological conditions such as pH, temperature, bioavailability, and metabolism [22, 23]. Biological systems are far more intricate than the simple *in vitro* assays used, and antioxidants may function through several steps and mechanisms [24]. The best approach to examine the antioxidant activity may involve animal or human subjects, but this is more expensive,

time-consuming, and perhaps risky. The antioxidant activity was measured by effective, relatively fast, methods that take into account the biological system, and more accurately reflects the antioxidant activity [24]. In recent times, [24] applied this method to investigate the cellular antioxidant activity in sorghum-incorporated Chinese steamed bread, and showed that incorporation of sorghum in the bread significantly increased the cellular antioxidant activity. However, the "actual" antioxidant activity of sorghum phenolic compounds still requires further investigation. The antioxidant activity is strongly related to the total phenolic contents, particularly the condensed tannin content in sorghum [19]. Sorghums with condensed tannins (black and brown sorghums) have consistently demonstrated high antioxidant activity *in vitro*, especially in the bran where the phenolics are concentrated [25, 26]. For example, a brown sorghum (Sumac SU99) bran showed the highest *in vitro* antioxidant activity (ORAC=3,124 μmol TE/g, ABTS=768 μmol TE/g and DPPH=716 μmol TE/g) among sorghum grain or bran and higher than most of fruits and vegetables known to have high antioxidant activities including blueberry (ORAC=842 μmol TE/g), strawberry (ORAC=402 μmol TE/g) and broccoli (ORAC=173 μmol TE/g) [19, 21]. Apart from the direct antioxidant effects, phenolic compounds isolated from sorghum have been shown to regulate the expression of phase II enzymes (endogenous detoxifying enzymes) that are able to converting the harmful reactive oxygen or nitrogen species (highly reactive electrophilic species) into nontoxic and execrable compounds, and thus indirectly enhances the body defense against oxidative stress [4, 27, 6]. The chief inducing effect of phenolic compounds, particularly, 3-deoxyanthocyanidins on phase II enzymes is very strong so as to increase the NADH: quinone oxyreductase (NQO) activity. Sorghum extracts that were supposed to be rich in 3-deoxyanthocyanidin standards and 3-deoxyanthocyanidin significantly upsurge the NQO activity in some cancer cells [4, 27 6], but the effect has not been reported in their anthocyanin analogs. Recent studies confirmed that apigeninidin and luteolinidin did not show any significant NQO inducer activity rather more cytotoxic [4, 6]. On the other hand, the Methoxylated substitution at the C-5 and C-7 positions can significantly enhance the inducing effect on the NQO activity. For example, 7-methoxyapigeninidin and 5, 7-dimethoxyapigeninidin, forms were strong NQO inducers [4, 6]. The inducing capacity of 3-deoxyanthocyanidins on the phase II enzyme varies greatly with their structure and substitution. Varieties of black and red sorghum may put forth larger effects on NQO due to the rich profile and high content of 3-deoxyanthocyanidins [4, 28, 29, 6]. However, sorghum varieties with pericarp color white (KARI-Mtama) and low 3-deoxyanthocyanidin content have also been reported to show significant inducing effects on the NQO [4, 6]. This fact verified that sorghum is a source of other phytochemicals, pigmented or not, that might act synergistically with 3-deoxyanthocyanidins and produce high inducer activity, thus, play an important role in combating oxidative stress. Contrariwise, sorghum tannins have a very poor ability to

induce NQO and can inhibit the NQO activity caused by other phenolic compounds [4]. The effects of sorghum condensed tannins on the oxidative stress *in vivo* are little known but may be directly linked to the antioxidant activity *in vitro* [25 30]. This is because condensed tannins believed to be not absorbed by the body and also react with other molecules to form complexes; they may act as free radical "sinks," especially in the gastrointestinal tract, against the oxidative stress [3]. The superoxide dismutase activity (SOD) increased in normolipidemic rats fed with black sorghum bran (rich in 3-deoxyanthocyanidins) [28].This escalation appears to be strictly related to the action of 3-deoxyanthocyanidins present in the bran. Furthermore, white (rich in phenolic acids), brown (rich in tannins) or black (rich in 3-deoxyanthocyanidins) sorghum brans inhibited the glutathione peroxidase activity (GPx) [28]. However, in the single animal study done so far using whole grains, normolipidemic rats that consumed different sorghum varieties (white, brown rich in tannin, and red without tannin) showed no change in the SOD activity [5]. The absence of significant changes in the SOD activity [5] may reflect the lower content of bioactive compounds in whole sorghum grain compared with the bran. Thus, the amount of bioactive compounds consumed by the rats treated with whole grain may have been lower than those fed sorghum bran. On the other hand, the normolipidemic animals fed with whole red sorghum evaluated by [3] had lower concentrations of thiobarbituric acid reactive substances (TBARS) in their livers. This reduction suggested that whole sorghum suppressed the reactive electrophilic species (RES) and that it can reduce oxidative stress through different mechanisms including the increase of other antioxidant enzymes (i.e., catalase, GPx and SOD) and total antioxidant capacity. Furthermore, the under or overexpression of genes and proteins related to the oxidative system may also have been contributed to these changes.

### 3.2. Cancer Deterrence

Most cancers originate from DNA damage caused by carcinogens (toxics, mutagenic, and carcinogenic agents) that make up reactive intermediates, such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and other reactive electrophilic metabolites [32, 33]. The carcinogen rate in humans is strongly dependent on the activity of the phase I (cytochrome P-450) and II of the enzyme systems, which also removed endogenous and environmental carcinogens [34]. The benefits of sorghum on phase II enzymes as stated in the previous section, especially on NQO reductase, reveal its chemoprevention. However, it is impossible to conclude its striking effects in humans due to the lack of studies. There is epidemiological evidence that validates sorghum's potential to prevent cancer. Furthermore, 3-deoxyanthocyanidins and 3-deoxyanthocyanidin-rich sorghum extracts were more effective in the fight against the growth of various cancer cells, including colon, hepatoma, esophageal, intestinal, epithelial, leukemia, breast, and stomach cancer cells; these compounds act directly against cancer by persuading cell apoptosis and hindering the

proliferation and metastasis of cancer cells [4, 35, 36, 33, 37]. The substitution of sorghum by corn as a staple food of the diet increased the incidence of esophageal cancer in black South Africans [38]. The mechanisms by which sorghum reduced the risk of esophageal cancer in humans are still unknown. Elimination of tumors in early stages is considered as an integral part of anticancer effects. Sorghum 3-deoxyanthocyanidins are more cytotoxic to cancer cells than the respective analogous anthocyanidins present in other foods (cyanidin and pelargonidin) [33]. In addition to 3-deoxyanthocyanidins, apoptosis of the colon cancer cells resulted from estrogenic activity of the flavones of sorghum [39]. The mechanisms by which sorghum's phenolic compounds induce *in vitro* apoptosis included the overexpression of genes and apoptotic proteins (BAX e BAK proteins and p53 gene expression), increase in enzymes' activity (caspase-9 and caspase-3 activityy), and inhibition of anti-apoptotic factors (Bcl2 gene, anti-apoptotic Bcl2 proteins, mitochondrial cytochrome C, and apoptosis-inducing factor) [40, 37]. Moreover, the sorghum phenolics inhibit the growth and metastasis of cancer cells by reducing the phosphorylation of STAT5 and STAT3, and the expression or the release of insulin-like growth factor 1 (IGF-1R) and vascular endothelial growth factor (VEGF) and increasing cell cycle inhibitors (expression of cyclin D, cyclin E, and pRb; Brk, p53, and HIF-1α - hypoxia-inducible factor 1α) [40, 41]. All of these events can inhibit cellular DNA synthesis, as was recently observed in skin melanoma cells [42]. Furthermore, in addition to 3-deoxyanthocyanidins, sorghum has tannins that may have anticancer activity. Studies have shown that tannins isolated from other foods affect regulatory enzymes, blocking signal transduction pathways and inducing apoptosis; thus, they have attracted wide attention for cancer treatment [43]. However, sorghum tannins still need to be better studied. In a recent study, sumac (SU99) sorghum bran extract rich in tannins inhibited human aromatase (CYP19) activity *in vitro* more strongly than tannin-free black sorghum bran extract, rich in 3-deoxyanthocyanidins [44]. This suggests that the tannins found in sumac (SU99) sorghum are more potent inhibitors than the 3-deoxyanthocyanidins found in black sorghum, inhibiting and precipitating aromatase [44]. This enzyme is a key to the synthesis of estrogen and is an important target for chemotherapy of breast cancer dependent on this hormone [45]. The anticancer effects of sorghum *in vivo* have been little studied. Recently, cellular growth and metastasis in breast cancer cells (MDA-MB 231 and MCF-7) in rats were reduced after the application of subcutaneously methanolic extract of sorghum rich in phenolic compounds [40]. Sorghum tannins have been shown to inhibit aromatase (an enzyme that is involved in breast cancer) and thus prevent the formation of undesirable cancer growth stimulus [44, 43]. Tannins extracted from sorghum were also reported to be more effective against the growth of colon cancer cells than tannins from grape seed. The results of the single study that evaluated the anticancer effects of sorghum showed that whole grains of the black and brown varieties (rich in 3-deoxyanthocyanidins and tannins, respectively) reduced the number of aberrant crypts of mice [28]. Furthermore, sorghum rich in tannins increased the colonocytes apoptosis.

### 3.3. Obesity and Inflammation Preventions

Obesity is wide-ranging that draws parallel with various non-communicable diseases. In addition, long-term oxidative stress can lead to chronic inflammation and consequently can result in various chronic diseases. The results of the studies demonstrate that sorghum rich in tannins reduces weight gain in animals (rats, pigs, rabbits, and poultry) [46, 47]. The lower weight gain is undesirable in animals for slaughter, but can provide benefits against obesity in humans. The lower weight gain in animals fed with sorghum rich in tannins results in part from the higher complexation of this compound to sorghum starch that helps lower caloric intake as the higher molecular weight of tannin, the stronger the interaction with starch [48]. It is also produce a low glycemic response that is desirable for people with obesity and diabetes [49]. A recent study showed that healthy people who consumed biscuits made of sorghum whole grain reported higher satiety and lower hunger ratings than wheat biscuits [50]. Starch is the major component of cereals and the main source of calories in cereal products [51]. Another study demonstrated that condensed tannins from sorghum can naturally modify starch by interacting strongly with amylose forming resistant starch [52]. Resistant starch cannot be digested in the small intestine and thus touches the large intestine, delivering the health benefits of dietary fiber [53]. Furthermore, polymeric tannins from sorghum can inhibit starch digestion by inhibiting saccharase and amylase enzymes [54, 55]. Another important factor that may also have contributed to this lower weight gain was the complexation of tannins with proteins as well as digestive enzyme inhibition (trypsin, chymotrypsin, and lipases) [56-59]. Proteins rich in proline bind more sorghum tannins than other proteins. In addition, a protein containing more proline repeats will bind more tannin than one with fewer such repeats [60]. Despite the evidence in animals, it is unknown whether sorghum (rich in tannins or not) modulates human weight. It is tinted that the high consumption of sorghum with polymeric tannins can reduce the bioavailability of iron and zinc [61]. Obesity is characterized by a chronic low-grade inflammation [62]. Up to now, the role of fat itself in the development of obesity and its consequences was considered to be a passive one and adipocytes were regarded as little more than storage cells for fat [63, 62]. However, it is known that adipocytes and obesity play an important role on inflammatory mediators that signal this process. The discovery that obesity itself results in an inflammatory state in metabolic tissues opened a research field that examines the inflammatory mechanisms in obesity [63]. This remarkable understanding allows a more clear definition of the role that adipocytes play in health and in obesity and how inflammatory mediators act as signaling molecules in this process [62]. During inflammation, a number of pro-inflammatory compounds such as interleukin (IL), cyclooxygenase (COX)-2, tumor necrosis factor (TNF)-α, and prostaglandin E2 (PG-E2) are generated (Shim, *et al.,* 2013). Many phenolic compounds for example phenolic acids,

such as gallic acid and ferulic acids, from sorghum were reported to suppress the COX- 2 enzyme, and ferulic acid has been shown to inhibit the production of TNF-$\alpha$ [64]. Flavone apigenin and luteolin inhibits the production of COX-2, hence, suppressed the transcription factor (nuclear factor kappa B) that activates the production of these pro-inflammatory compounds [64-67]. Collectively, several phenolic compounds extracted from sorghum grain have been proven to inhibit the production of pro-inflammatory compounds [64, 66, 68, 69]. In an *in vitro* study, the extracts of sorghum rich in 3-deoxyanthocyanidins shown to inhibit the secretion of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and nitric oxide by human mononuclear cells activated with bacterial lipopolysaccharide [64, 69]. 3-Deoxyanthocyanidins have also been shown to suppress the production of COX-2 and PG-E2 [68]. Moreover, the crude phenolic extract from black sorghum bran, has demonstrated strong inhibitory effects against COX-2, IL-1*β*, and TNF-*α* pro-inflammatory activity, and the effect is similar to the anti-inflammatory drug indomethacin [64, 69]. Mice with inflammatory triggered ear edema treated with the phenolic extract from black and red sorghum bran demonstrated significant reduction of ear edema via the down regulation of cyclooxygenase-2 (COX-2) expression, resulting in lower vascular permeability and edema with infiltration of neutrophils [64, 69]. In addition, recent studies have shown that the combination of flavone apigenin and flavonol quercetin, as well as the apigenin-rich extract from sorghum and quercetin-rich extract from cowpea, has a strong synergistic anti-inflammatory effect by enhancing their bioavailability through the suppression of the phase II metabolism and ATP binding cassette membrane transporter function in cellular models [65, 70]. It is believed that the C2=C3 conjugation structure of apigenin and quercetin may play an important role in enhancing the anti-inflammatory effect [70]. Recently, a study showed that the introduction of sorghum whole grain biscuits in the human (overweight adults) diet significantly reduced the pro-inflammatory compounds IL-1*β*, IL-6, IL-8, and TNF-*α* over 12 weeks [50]. In general, all sorghum varieties, regardless of pericarp color and condensed tannin content, demonstrated a significant inhibitory effect against hyaluronidase activity [71]. Furthermore, sorghums rich in tannins were more effective than those rich in 3-deoxyanthocyanidins in inhibiting hyaluronidase, an important enzyme associated with joint inflammation [71]. The greater inhibitory effect of tannins can be attributed to their ability to complex the enzymes (competitive inhibition). The evaluation *in vivo* of the anti-inflammatory effects of sorghum is still incipient but *in vitro* and animal study attempts among different scholars were promising. The addition of whole red grains without tannins or its lipid fraction to a hyperlipidemic diet reduced the expression of TNF-α in rat [5; 40]. The functional benefits in humans due to the consumption of whole sorghum and its fractions are still unknown, but they may result in part from the increased expression of adiponectin, which inhibits this inflammatory marker [40]. Thus, the results of *in vitro* and animal studies suggest that the anti-inflammatory effects of

sorghum stem from its action on enzymes while 3-deoxyanthocyanidins act mainly on cytokines.

### 3.4. Dyslipidemia and Cardiovascular Disease Prevention

*In vitro* and animal studies have been shown that the lipidic and phenolic fractions from sorghum control parameters related to dyslipidemia and the risk of cardiovascular disease. These assistances resulted from the action of phytosterols, polycosanols, and phenolic compounds, which may regulate absorption, excretion, and synthesis of cholesterol. Recent studies have shown that the administration of sorghum oral intake of freeze-dried phenolic extracts (50 to 600 mg/kg for 14 days) significantly lowered the plasma cholesterol and triacylglycerol levels in hyper lipidemic rats [72-74]. The supplementation of the diet with sorghum lipids reduced the hepatic and plasma cholesterol of normo lipidemic hamsters [75, 76]. Studies demonstrated that phytosterols isolated from other foods inhibited cholesterol absorption in humans, leading to increased fecal excretion and reduced plasma LDL-c concentration [77]. These compounds reduce the amount of cholesterol captured in the gut enterocytes by inhibiting its incorporation into micelles, thereby lowering cholesterol absorption and thus, impacts cholesterol balance [78]. The lipid fraction may also affect cholesterol absorption by altering the gut microbiota [79]. The addition of sorghum lipid fraction to the diet of hamsters increased the *Bifidobacterium spp* (mainly a phylotype related to *B. animalis*) and HDL-c (high density lipoprotein-cholesterol) and reduced the family *Coriobacteriaceae* (mainly yet unclassified phylotypes) and non-HDL-c [79]. The correlation between the family *Coriobacteriaceae* and both non-HDL-c and cholesterol absorption suggest that this family could have a negative impact on cholesterol homeostasis by increasing cholesterol absorption. On the other hand, *Bifidobacterium* correlated with HDL-c and had no association with cholesterol absorption [79]. The mechanisms by which these bacteria affect cholesterol metabolism remain an important field of future research. In addition to affecting the absorption of exogenous cholesterol, the sorghum lipidic fraction affects the synthesis and excretion of endogenous cholesterol. In one of the first *in vitro* studies about this subject, the sorghum lipid fraction inhibited in a dose-dependent manner the 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase activity, a key enzyme in cholesterol synthesis [80]. However, the ability to reduce the *in vivo* cholesterol synthesis through HMG-CoA reductase requires further investigation. The polycosanols are one of the compounds present in the sorghum lipid fraction that can reduce the HMG-CoA reductase activity. These compounds, isolated from other food matrices, decrease the activity of this enzyme as well as increase the LDL-c (low density lipoprotein-cholesterol) receptor activity [81]. Sorghum lipid fraction promotes the excretion of gut neutral sterols (i.e., cholesterol and its metabolites) and thus decreased the concentration of plasma cholesterol in normo lipidemic hamsters [76]. It is not yet known whether sorghum bioactive compounds, including polycosanols and phytosterols, affect cholesterol metabolism through

mechanisms similar to those proposed for compounds isolated from other plants. Therefore, possible metabolic pathways affected by the sorghum lipid fraction, including the expression of genes and proteins, are not still understood and poorly studied. A single study published to date evaluated the effects of the sorghum lipid fraction on the molecular level of cholesterol metabolism in hamsters. This study observed the overexpression of a gene related to the synthesis of HDL-c (ABCA1 - ATP-binding cassette transporter A1) [76]. However, no changes were observed in the expression of genes related to cholesterol absorption (Niemann-Pick C1 like 1); cholesterol synthesis; (sterol regulatory element binding protein-2 and HMG-CoA reductase); and excretion of LDL-c and endogenous cholesterol (scavenger receptor class B type 1, low density lipoprotein receptor, cholesterol 7ahydroxylase) [76]. This lack of effect can indicate that the intervention time used in the study (4 weeks) was not enough to cause changes in these genes. In addition to the lipid fraction, sorghum phenolic compounds also affect the metabolism of cholesterol. However, the mechanisms involved in these functional benefits have not been elucidated. These functional benefits vary according to the sorghum variety and type of solvent used during preparation of the extracts [72, 73]. Knowledge about the effects of whole sorghum on the lipid profile and the risk for developing cardiovascular disease in animals is incipient and in humans is nonexistent. In a study on mice, the addition of 30% whole sorghum to the diet increased the fecal excretion of bile acid and plasma HDL-c [80].

### 3.5. Anti-Diabetic Activity

Contemporary studies have been indicated that sorghum fractions control the glucose metabolism in animals due to the action of the phenolic compounds. Additionally, the low starch and protein digestibility makes sorghum a promising food source for people with obesity and diabetes. However, it is not known whether the components isolated from sorghum and especially the whole grain are beneficial to humans. In studies with rats, the intake of extracts of sorghum phenolic compounds significantly decrease the plasma glucose and glycema concentration [72, 74, 40]. Due to its strong effect on plasma glucose and insulin, the studies in animals have shown that phenolic extracts of sorghum exhibited a hypoglycemic effect similar to glibenclamida, an anti-diabetic medication used in the control group [72, 74]. The phenolic extract was also reported to increase the serum insulin concentration in these rats [73]. Sorghum phenolics may play a role in insulin regulation and act as an adjuvant in diabetic treatment [72]. Moreover, consumption of muffins with the incorporation of sorghum has been shown to influence the blood glucose and insulin levels, and improve the glycemic response in healthy people [82]. The anti-diabetic activity of sorghum may be partially attributed to the condensed tannins. A study has shown that the tannin-rich extract from brown sorghum bran exhibits inhibitory activities against porcine pancreatic $\alpha$-amylase at low concentrations [44]. More recently [44] have demonstrated that the crude extract from type III tannin sorghum had powerful inhibitory activities against yeast $\alpha$-glucosidase, which was about 20,000 times stronger than acarbose, although acarbose was better at inhibiting the porcine pancreatic $\alpha$-amylase. The mechanisms by which sorghum phenolic compounds act involve metabolic pathways before and after absorption of carbohydrates that can contribute to the prevention and treatment of glycemic disorders in humans. It was recently demonstrated that these extracts inhibited *in vitro* activity of the enzymes *B. stearothermophilus* α-glucosidase as well as human pancreatic and salivary α-amylase [84]. Thus, the inhibition of digestive enzymes, to prevent glucose digestion, may be the first step (action) in anti-diabetic mechanism of sorghum phenolic compounds on human [83]. Study attempts suggest that phenolic compounds may also affect insulin-dependent pathways, including concentrations and sensitivity of this hormone in humans. The increase in insulin concentration was observed in diabetic rats that received extracts of phenolic compounds [72]. This increase indicates better functioning of the β cells and it has clinical relevance, especially for Type 2 diabetics, whose insulin synthesis is decreased. Furthermore, oral administration of the sorghum phenolic extracts can prevent and act as an adjuvant factor in the treatment of diabetes through an improvement in insulin sensitivity. This hypothesis is based on the fact that the extract of phenolic compounds from sorghum have induced anti-diabetic effects in rats fed with a hyper lipidic diet through a mechanism that increased adiponectin and decreased TNF-α (TNF-α: tumor necrosis factor-α) via overexpression of PPAR-γ (peroxisome proliferator-activated receptor gamma); leading to improved insulin sensitivity [40]. Moreover, it is suggested that phenolic compounds reduce blood glucose concentration by inhibiting hepatic gluconeogenesis due to the down expression of the PEPCK and p38 genes and overexpression of the AMPK gene [74]. However, sorghum extract had insignificant effect on glucose uptake by skeletal muscle determined by GLUT4 translocation and Akt phosphorylation [74]. It is unknown whether sorghum put forth an effect on protein expression during glucose hepatic production and glucose uptake by skeletal muscle. In addition to acting in basic processes of diabetes, the ethanolic extracts obtained from sorghum bran rich in phenolic compounds and with high antioxidant activity inhibit the glycation of proteins up to 60% [85]. However, sorghum bran extract with low antioxidant activity and content of phenolic compounds, as well as bran of rice, oats, and wheat, did not inhibit this process. The glycation products are associated with diabetes and insulin resistance and may increase the formation of reactive oxygen species and the activation of the nuclear factor-κβ (NF- κβ) [86].

### 3.6. Lowering Hypertension

In recent times there is an indication in the scientific literature that sorghum can reduce blood pressure. Very few studies refute the possibility that, an isolate of sorghum α-kafirins inhibited the activity of the angiotensin I converting enzyme in competitive and non-competitive ways [87].

### 3.7. Functional Promotion of Gut Micro Biota and Colonic Health

The human gut is populated by an array of bacterial species, which develop important metabolic and immune functions, with a marked effect on the nutritional and health status of the host [88, 89]. The functional benefits of phenolic compounds of foods on human health may result from direct action of the absorbed bioactive compounds (and their metabolites) or indirect effects mediated by non-absorbed compounds that modify the micro biota environment and, consequently, human metabolism or could act at the membrane border inducing signal transduction pathways (Fernandes, *et al.,*). Studies have demonstrated that 3-deoxyanthocyanidins are effective against a range of fungi and bacteria *in vitro* [90, 91], However, the probable effects of sorghum bioactive compounds on the gut micro biota are unknown. It is important to analyze these effects during interventions in humans. Most of the condensed tannins remain undamaged before reaching the lower gastrointestinal tract where they are partially broken down by intestinal micro flora in to a variety of absorbable phenolic acids, promoting gut and human health [92, 93]. There is scientific evidence that unabsorbed phenolic compounds and their metabolites contribute to the maintenance of gut health by the regulation of the gut microbial balance through the stimulation of the growth of beneficial bacteria and the inhibition of pathogen bacteria, exerting prebiotic-like effects [88, 94-96]. Among the compounds, tannins are of special interest due to their high abundance and because, even though they are not absorbed in the large intestine, they are metabolized by the colonic micro biota [96]. Furthermore, sorghum has resistant starch and dietary fiber, which can modify gut microbiota [79, 97]. Although a great range of health-promoting activities of dietary phenolic compounds has been widely investigated, further scientific investigation is still needed in relation to their effect on modulation of gut micro biota [94, 96]. Several studies demonstrated the effects of phenolic compounds from foods, including tannins and anthocyanins, on gut microbiota increasing the *Bifidobacterium spp* and *Lactobacillus spp* and decreasing the *Bacteroides spp*, *Clostridium spp*, *Propionibacterium spp*, *Salmonella typhimurium,* *Streptococcus mutans,* and *Escherichia Coli* [98]. The effects of sorghum, including varieties rich in tannins and 3-deoxyanthocyanidins, on gut micro biota are a field still to be explored. To date only one study has evaluated the relationship between bioactive compounds in sorghum in the gut micro biota of hamsters [79].

## 4. Conclusion and Future Prospects

Despite its big potential, given its agronomic properties and nutritional potential, sorghum has high concentrations and a wide variety of phenolic compounds that may not often be found in other cereal grains. Phenolic compounds in the bran layer differ in extractability, composition and concentration among sorghum varieties and genotypes.

However, play a strong modulatory effect on gut micro biota and parameters related to non-communicable diseases (obesity, diabetes, dyslipidemia, cardiovascular disease, cancer, and hypertension). Moreover, most of the evidences obtained are based on *in vitro* and animal studies, and more *in vivo* and possibly clinical studies are needed to confirm these health benefits, as well as the interactions between the bioactive compounds and the mechanisms involved. Many researches have been demonstrated to investigate the phenolic profile in sorghum, most of them are focusing on the total contents i.e. total phenolic, flavonoids, or condensed tannin contents by using colorimetric methods, rather than the individual phenolic. The profile of bioactive compounds has been shown to be a determinant factor of the functional potential of sorghum varieties. In this context, the selection of varieties of sorghum and practical optimization should be performed to ensure the accumulation of bioactive components that will maximize the benefits of sorghum in humans. Furthermore, the behavior assessment of bioactive compounds in different processing conditions is essential to define the manner of use in which sorghum promotes maximum benefits to human health. Thus, evaluating the bioavailability of sorghum's bioactive compounds is essential to determining the benefits of sorghum grains and bioactive compounds on human health. Further work is required to better understand the preventive and therapeutic effects of sorghum whole grain and its fractions on human health, including gene and protein expression. The modern genetic engineering and breeding tools provide exciting opportunities to develop sorghum with desirable nutritional and phenolic profile while maintaining good agronomic performance and yield, and this could be a fruitful area for further research. It has been shown that through mutagenesis-assisted breeding, the biosynthesis of phenolic compounds can be enhanced in sorghum. A sorghum mutagenesis variant, RED for GREEN, which can significantly increase the 3-deoxyanthocyanidins, condensed tannins, and total phenolic contents in sorghum leaf, has been identified [99]. Advances have also been made in breeding sorghum (germplasms ATx3363 and BTx3363) with high levels of 3-deoxyanthocyanidins in the grain pericarp and with satisfying grain yield [100]. Notwithstanding the health-promoting benefits, the use of sorghum has deteriorated in the regions where sorghum has been traditionally used as the main staple food as people shift to a more yielding and cash oriented crops.

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