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Sorghum (*sorghum bicolor* L.): Nutrients, Bioactive Compounds, and Potential Impact on Human Health

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**SORGHUM (*SORGHUM BICOLOR* L.): NUTRIENTS, BIOACTIVE COMPOUNDS,
AND POTENTIAL IMPACT ON HUMAN HEALTH**

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ABSTRACT

Sorghum is the fifth most produced cereal in the world and is a source of nutrients and bioactive compounds for the human diet. We summarize the recent findings concerning the nutrients and bioactive compounds of sorghum and its potential impact on human health, analyzing the limitations and positive points of the studies and proposing directions for future research. Sorghum is basically composed of starch, which is more slowly digested than that of other cereals, has low digestibility proteins and unsaturated lipids, and is a source of some minerals and vitamins. Furthermore, most sorghum varieties are rich in phenolic compounds, especially 3-deoxyanthocyanidins and tannins. The results obtained in vitro and in animals have shown that

phenolics compounds and fat soluble compounds (polycosanols) isolated from sorghum benefit the gut microbiota and parameters related to obesity, oxidative stress, inflammation, diabetes, dyslipidemia, cancer, and hypertension. The effects of whole sorghum and its fractions on human health need to be evaluated. In conclusion, sorghum is a source of nutrients and bioactive compounds, especially 3-deoxyanthocyanidins, tannins, and polycosanols, which beneficially modulate, in vitro and in animals, parameters related to noncommunicable diseases. Studies should be conducted to evaluate the effects of different processing on protein and starch digestibility of sorghum as well as on the profile and bioavailability of its bioactive compounds, especially 3-deoxyanthocyanidins and tannins. Furthermore, the benefits resulting from the interaction of bioactive compounds in sorghum and human microbiota should be studied.

Keywords: nutritional value; 3-deoxyanthocyanidins; tannins; noncommunicable diseases; oxidative stress; cancer

ABBREVIATIONS: ABCA1: ATP-binding cassette transporter A1; *COX-2*: cyclooxygenase-2; DP: degree of polymerization; GPx: glutathione peroxidase activity; HDL-c: high-density lipoprotein-cholesterol; HIF-1 α : hypoxia-inducible factor 1 α ; HMG-CoA: 3-hydroxy-3-methylglutaryl CoA; IGF-1R: insulin-like growth factor 1; IL-1 β : interleukin-1 β ; LDL-c: low-density lipoprotein-cholesterol; MUFA: monounsaturated fatty acids; NQO: NADH:quinone oxyreductase; NF- κ B: nuclear factor- κ B; PPAR- γ : peroxisome proliferator-activated receptor gamma; PUFA: polyunsaturated fatty acids; RES: reactive electrophilic species; RNS: reactive nitrogen species; ROS: reactive oxygen species; SOD: superoxide dismutase; TBARS:

thiobarbituric acid reactive substances; TNF- α : tumor necrosis factor- α ; VEGF: vascular endothelial growth factor.

1. INTRODUCTION

Sorghum (*Sorghum bicolor* L.) is a cereal of the family *Poaceae*, native to Africa, and was domesticated between 3,000 and 5,000 years ago (U.S. Grains Council, 2004). It is the fifth most produced cereal in the world, and is preceded by wheat, rice, maize, and barley (Food and Agricultural Organization, 2010). Around the world, there are over 7,000 varieties of sorghum (Kangama & Rumei, 2005).

The sorghum crop is extremely important in Asia, Africa, and other semi-arid regions of the world, where it is mainly used in human feeding (Afify, et al., 2011; Dillon, et al., 2007; Elkhailifa, et al., 2005). In Western countries such as the United States, Australia, and Brazil, sorghum is developed and cultivated primarily for animal feeding (Taleon, et al., 2012). However, due to its high nutritional and functional potential, several studies on sorghum for human consumption have been conducted in these countries (Ciacci, et al., 2007; Dykes, et al., 2005; Ferreira, et al., 2009; Maunder, 2005; Schober, et al., 2005; Taylor, J. R. N., et al.).

The sorghum grain has three distinct anatomical structures called the pericarp, endosperm, and germ. Some varieties have a fourth structure called the testa, located between the pericarp and the endosperm (Earp, et al., 2004). The proportion and chemical composition of sorghum's anatomical structures depend on the variety and growing conditions (Waniska & Rooney, 2000). Generally, the pericarp (outer coating) and the testa are composed of non-starch polysaccharides, phenolic compounds (3-deoxyanthocyanidins, tannins, and phenolic acids, among others), and carotenoids. The starch, proteins, B-complex vitamins, and minerals are located in the endosperm (storage tissue). The germ (embryo) is composed of lipids, fat-soluble

vitamins, B-complex vitamins, and minerals (Earp, et al., 2004; Food Security Department, 1999; Slavin, 2004; Waniska & Rooney, 2000).

Sorghum is an excellent source of bioactive compounds that can promote benefits to human health. The results of in vitro and animal studies have shown that compounds isolated from sorghum, mainly phenolics, promote beneficial changes in parameters related to noncommunicable diseases such as obesity, diabetes, dyslipidemia, cardiovascular disease, cancer, and hypertension (Awika, et al., 2009; Farrar, et al., 2008; Kamath, V., et al., 2007; Kim, J. & Park, 2012; Moraes, et al., 2012a; Muriu, et al., 2002; Shih, C.-H., et al., 2007; Woo, et al., 2012; Yang, L., et al., 2009).

Given the high beneficial potential of sorghum on human health and the absence of a critical review about the subject, we summarize the recent findings concerning the nutrients and bioactive compounds of sorghum and its potential to modulate parameters related to human health, analyzing the limitations and positive points of recent studies and proposing directions for future research.

2. METHODOLOGY

Original articles published between 2005 and 2013 in scientific indexing bases (PubMed, Biological Abstracts, CAB Abstracts, Food Science and Technology Abstracts, LILACS, Scielo, MEDLINE, and Science Direct) were researched. 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 chemical composition and nutritional value (starch, amylose, amylopectin, proteins, kafirins, dietary fibers, minerals, vitamins, mineral bioavailability, starch

digestibility, phenolic compounds, phenolic acids, tannins, flavonoids, 3-deoxyanthocyanidins, flavones, flavanones, sterols, polycosanols, stilbenes, antioxidant profile, phytates, protease inhibitors: trypsin, chymotrypsin and amylase, and lectins) and another group related to chronic noncommunicable diseases (obesity, weight loss, dyslipidemia, cardiovascular disease, cholesterol, triacylglycerol, high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), diabetes, fasting glucose, glycemic response, fasting insulin, insulinic response, cancer, oxidative stress, inflammation, interleukins, gut microbiota, and hypertension). The articles were screened and selected based on the title and abstract presented.

3. CHEMICAL COMPOSITION AND NUTRITIONAL VALUE

The chemical composition and nutritional value of whole sorghum are similar to rice, corn, and wheat. The energy value of 100g of sorghum grains varies between 296.1 and 356.0 kcal (Martino, et al., 2012; U.S. Department of Agriculture, 2012). The main components of sorghum are the polysaccharides (starch and non-starch), followed by proteins and lipids (Martino, et al., 2012; U.S. Department of Agriculture, 2012).

3.1. Polysaccharides

The content and composition of starch, the main polysaccharide of sorghum, are influenced by the genetic characteristics and growing conditions of the grain (Hill, et al., 2012). In some varieties, starch ranges between 32.1 and 72.5 g/100g and is composed mainly of amylopectin (81.0-96.5%) and amylose (3.5-19.0%) (Shegro, et al., 2012; Udachan, et al., 2012). The proportion of amylose and amylopectin affects the rheological proprieties (gelatinization, retrogradation, and gelling) and digestibility of the sorghum starch (Sang, et al., 2008; Singh, H., et al., 2010).

Sorghum has the lowest starch digestibility among cereals due to the strong association between the starch granules and proteins and tannins (Barros, et al., 2012; Mkandawire, et al., 2013; Rooney & Pflugfelder, 1986). Overall most of the starch granules are slowly digestible (30.0-66.2%) and the remainder is rapidly digestible (15.3-26.6%) or resistant (16.7-43.2%) (Mkandawire, et al., 2013; Sang, et al., 2008). The non-starch polysaccharides of sorghum (6.0 to 15.0 g/100g) include insoluble fibers (75.0-90.0%), mainly arabinoxylans, and soluble fibers (10.0-25.0%) (Martino, et al., 2012; Taylor, J. R. N. & Emmambux, 2010; U.S. Department of Agriculture, 2012).

3.2. Proteins

Sorghum proteins are classified as prolamins and non prolamins. Prolamins correspond on average to 79% (77-82%) of the total proteins (7 to 15g/100g) and the remainder is albumins, globulins, and glutelins (Afify, et al., 2012b; Belton, et al., 2006; Martino, et al., 2012; U.S. Department of Agriculture, 2012). The kafirins are the major prolamins of the sorghum and comprise three major classes: α -kafirins (66-84%), β -kafirins (8-13%) and γ -kafirins (9-21%) (Belton, et al., 2006; Mokrane, et al., 2010). Sorghum kafirins are stored in the endoplasmic reticulum in spherical protein bodies. The β and γ -kafirins are located in the peripheral protein bodies region while α and δ -kafirins are encapsulated in the inner region (Wu, Yongrui, et al., 2013). This conformation determines the digestibility of sorghum proteins.

Overall, the digestibility of sorghum proteins, especially after cooked, is lower than cereals like wheat and maize (Afify, et al., 2012b; Duodu, et al., 2003; Mokrane, et al., 2010; Moraes, et al., 2012b). The kafirins of sorghum are resistant to peptidase due to the formation of intramolecular disulfide bonds; this is the main cause of the low digestibility (Belton, et al.,

2006). However, in varieties rich in tannins, the complexation of the kafirins with this phenolic compound can reduce the protein digestibility up to 50% (Taylor, J., et al., 2007). Furthermore, other exogenous factors (interaction of the proteins with non-protein components such as starch, non-starch polysaccharides, phytic acid, and lipids) and endogenous factors (nature and organization of proteins inside the grain) contribute to this low digestibility (Belton, et al., 2006; da Silva, et al., 2011a; Duodu, et al., 2002; Duodu, et al., 2003; Ezeogu, et al., 2008; Ezeogu, et al., 2005).

Despite the reduction in protein digestibility of sorghum after cooking in wet heat, processing such as fermentation and germination may increase the digestibility up to 2 times (Afify, et al., 2012b; Correia, et al., 2008; ELKhier & Abd-ALRaheem, 2011; Pranoto, et al.; Wedad, et al., 2008). However, major recent efforts to improve the protein digestibility of sorghum aim to reduce the amount of kafirins, especially β and γ forms, and to increase the glutenins and albumins (da Silva, et al., 2011b; Goodall, et al., 2012; Kumar, et al., 2012; Taylor, J. & Taylor, 2011; Wu, Yongrui, et al., 2013). The genetically modified varieties have in vitro digestibility from 23 to 102% higher than control varieties (da Silva, et al., 2011a; Kumar, et al., 2012; Taylor, J. & Taylor, 2011).

The α -kafirins are the last proteins to be digested in the intestine and, because of their high abundance, the indigestibility reduces their nutritive value (Wu, Yongrui, et al., 2013). The β and γ -kafirins are rich in cysteine, which forms disulfide bonds, and are therefore assumed to block the accessibility of α -kafirins to hydrolytic enzymes (Duodu, et al., 2003; Wong, et al., 2009). Thus, the higher digestibility in modified varieties can be attributed to increased enzyme susceptibility of the major storage protein, α -kafirin, because of changes in protein body

morphology as well as to a reduction of the formation of disulfide bonds between β and γ -kafirins (Henley, et al., 2010; Kumar, et al., 2012; Mehlo, et al., 2013; Oria, et al., 2000).

Generally, sorghum proteins are rich in glutamic acid and nonpolar amino acids (proline, leucine, and alanine) and have lysine as the main limiting amino acid (De Mesa-Stonestreet, et al., 2010; Mokrane, et al., 2010; Moraes, et al., 2012b). In addition, they may be deficient in 5 other essential amino acids (methionine, cysteine, isoleucine, valine, and threonine) (Moraes, et al., 2012b). However, varieties obtained through breeding programs have 52-115% more lysine than conventional varieties (da Silva, et al., 2011b; Henley, et al., 2010; Kumar, et al., 2012; Taylor, J. & Taylor, 2011). Improved lysine contents were attributed to decreased levels of kafirin proteins and increased levels of lysine-rich, non-kafirin proteins in the grain endosperm (Shewry, 2007).

Unlike the major prolamins of wheat (gliadin), rye (secalin), and barley (hordein), the kafirins do not trigger an allergic response or an autoimmune reaction in humans (De Mesa-Stonestreet, et al., 2010). In addition to the qualitative evidence based on the type of proteins found in sorghum, there is genetic evidence that it has characteristics that do not allow the expression of toxic peptides related to gliadin (Pontieri, et al., 2013). Thus, sorghum is an effectively safe cereal for consumption by people with celiac disease.

3.3. Lipids

Sorghum has a reduced lipid content (1.24 to 3.07 g/100g), which is mainly composed of unsaturated fatty acids (83-88%) (Afify, et al., 2012a; Martino, et al., 2012; U.S. Department of Agriculture, 2012). In most of the varieties of sorghum the polyunsaturated fatty acids (PUFA) are higher than monounsaturated fatty acids (MUFA) (Afify, et al., 2012a; Hadbaoui, et al.,

2010; Mehmood, et al., 2008). The major fatty acids of sorghum are linoleic (45.6-51.1%), oleic (32.2-42.0%), palmitic (12.4-16.0%), and linolenic acids (1.4-2.8%) (Afify, et al., 2012a; Hadbaoui, et al., 2010; Mehmood, et al., 2008).

3.4. Minerals and vitamins

Sorghum is a source of minerals (phosphorus, potassium, and zinc) whose content varies according to the place of cultivation (Table 1) (Martino, et al., 2012; Shegro, et al., 2012; Silva, et al., 2012; U.S. Department of Agriculture, 2012). The bioavailability of most minerals of sorghum is still little known. However, it is known that zinc availability varies between 9.7% and 17.1% and iron availability ranges from 6.6% to 15.7% (Afify, et al., 2011; Kruger, et al., 2013). Studies have been conducted in order to increase the content and bioavailability of iron and zinc through biofortification, fortification, and genetic improvement of sorghum (Ashok Kumar, et al., 2013; Kruger, et al., 2013; Tripathi, et al., 2010; Tripathi & Platel, 2013).

Information on the content of vitamins in sorghum is scarce. However, it is worth noting that it is a source of some B-complex vitamins (thiamine, riboflavin, and pyridoxine) and fat-soluble vitamins (D, E, and K) (Cardoso, et al., 2014; Martino, et al., 2012; Ochanda, et al., 2010; U.S. Department of Agriculture, 2012).

4. BIOACTIVE COMPOUNDS

4.1. Phenolic compounds and their bioavailability

The phenolic compounds are the main bioactive compounds of sorghum and are present in all varieties of this cereal (Dykes & Rooney, 2006). Almost all classes of phenolics are found in sorghum (Awika & Rooney, 2004; Dykes, et al., 2005); however, the classes of phenolic acids, tannins, and flavonoids are major.

The profile and content of phenolic compounds in sorghum are more diverse and higher than those observed in wheat, barley, rice, maize, rye, and oats (Ragaei, et al., 2006). Sorghum varieties resistant to biotic and abiotic stresses were found to have on average higher contents of proanthocyanidins, 3-deoxyanthocyanidins, and flavan-4-ols than susceptible varieties (Dicko, et al., 2005).

The bioavailability of phenolic compounds after dietary intake has been a topic of increasing research in recent years (Crozier, et al., 2010; Faria, et al., 2013; Hole, et al., 2012; Prior & Wu, 2006; Yang, M., et al., 2011). However, the results obtained in humans are scarce and controversial. In addition, information about the bioavailability of phenolic compounds of sorghum, including tannins and 3-deoxyanthocyanidins, is not available yet.

The main difficulty in analyzing the bioavailability of phenolic compounds is the absence of standardized methods capable of identifying their metabolites. For example, the analysis of phenolic compounds in urine provides a more realistic bioavailability but does not include the possibility that their metabolites were sequestered by body tissues (Crozier, et al., 2010). This limitation underestimates the bioavailability of phenolic compounds in food.

Different factors affect the bioavailability of phenolic compounds in humans, including environmental factors, food processing, food matrix, and interaction with other compounds and polyphenols (D'Archivio, et al., 2010; Fernandes, et al., *In press*). There is a need for extensive investigation about the alterations of phenolic compounds by the gastrointestinal tract and their subsequent absorption and metabolism, including distribution in tissues (D'Archivio, et al., 2010; Lafay & Gil-Izquierdo, 2008). Studies have shown that catabolites of phenolic compounds

not absorbed in the small intestine pass into the large intestine where they can affect the colon microbiota (Crozier, et al., 2010; Faria, et al., 2013).

Knowledge of the bioavailability of phenolic compounds in sorghum, including dietary factors able to modulate it, is essential for analysis of their functional potential in humans and, in the long term, for the implementation of therapeutic measures for health professionals.

4.1.1. Phenolic acids

The phenolic acids are classified as hydroxybenzoic acid derivatives and hydroxycinnamic acid derivatives (Figure 1). These acids exhibit high antioxidant activity in vitro and thus may promote benefits to human health (Kamath, V. G., et al., 2004).

The content of phenolic acids in some sorghum varieties ranged between 135.5 and 479.40 $\mu\text{g/g}$ (Afify, et al., 2012c; Chiremba, et al., 2012), with major amounts of the protocatechuic (150.3 to 178.2 $\mu\text{g/g}$) and ferulic (120.5 to 173.5 $\mu\text{g/g}$) acids and small amounts of the p-coumaric (41.9 to 71.9 $\mu\text{g/g}$), syringic (15.7 to 17.5 $\mu\text{g/g}$), vanillic (15.4 to 23.4 $\mu\text{g/g}$), gallic (14.8 to 21.5 $\mu\text{g/g}$), caffeic (13.6 to 20.8 $\mu\text{g/g}$), cinnamic (9.8 to 15.0 $\mu\text{g/g}$), and p-hydroxybenzoic (6.1 to 16.4 $\mu\text{g/g}$) acids (Afify, et al., 2012c; Svensson, et al., 2010).

The phenolic acids in wines, fruits, and vegetables have a good bioavailability. In these matrices, the majority of phenolic acids are free or as conjugated forms that can be hydrolyzed in the upper intestinal tract (Hole, et al., 2012). On the other hand, phenolic acids in cereals, including in sorghum, are mostly bound to arabinoxylans chains or lignin (Abdel-Aal, et al., 2012; Dykes & Rooney, 2006; Hole, et al., 2012). These bound phenolic acids are not hydrolyzed by human digestive enzymes that decrease their bioavailability, but are fermented by the microbiota of the colon (Hole, et al., 2012; Saura-Calixto, 2010).

Knowledge about techniques for improving the bioavailability of phenolic acids in sorghum is incipient. The microorganisms and processing of grains can play a key role in improving this bioavailability. The study results demonstrated that cereal fermentation with specific probiotic strains and cooking processes can significantly increase the content-free phenolic acids (Hole, et al., 2012; Lafay & Gil-Izquierdo, 2008; N'Dri, et al., 2013; Saura-Calixto, 2010), thereby improving their bioavailability. The effects of other types of processing on the profile of phenolic acids in sorghum need to be studied.

4.1.2. Tannins (*proanthocyanidins*)

Tannins, secondary metabolites found in many plant species, are phenolic compounds that often act as a defense mechanism against pathogens and predators (Kaufman, et al., 2013). Overall, these compounds are absent in other major cereals, such as rice, wheat, and maize, but are present in sorghum varieties that have pigmented testa (Awika, 2003; Dykes & Rooney, 2006; Wu, Yuye, et al., 2012). The presence and content of condensed tannins in sorghum are controlled by the genes *S* and *Tannin1*, among others (Hahn, D. H. & Rooney, L. W., 1986; Wu, Yuye, et al., 2012).

The tannins in sorghum vary as to the type, content, and distribution of the individual oligomers and polymers. They are classified as type I (no significant levels), type II (tannins that are extractable only in acidified methanol) and type III (tannins that are extractable in methanol and acidified methanol) (Hahn, D. & Rooney, L., 1986; Price, et al., 1978). Almost all of the tannins in sorghum are condensed and constituted by oligomers or polymers of catechins (flavan-3-ols and/or flavan-3,4-diols) (Awika & Rooney, 2004; Wu, Yuye, et al., 2012). In general, most

sorghum tannins have a high molecular weight and a degree of polymerization (DP) higher than 10 (69-81%) (Awika, et al., 2003).

The content of tannins in sorghum varies between 0.2 and 48.0 mg/g and is highest in sorghum with black testa (Afify, et al., 2012c; Awika, et al., 2003; Dykes, et al., 2013; Martínez, et al., 2009; Schons, et al., 2011). However, this content, as well as the activity of tannins in sorghum, can be affected by the season (Mkandawire, et al., 2013). Therefore, the effect of the environment on tannins should be considered during the selection and breeding of tannin containing sorghum genotypes when the aim is to achieve health benefits (Mkandawire, et al., 2013).

The tannins reduced the availability of minerals, proteins, and starch of the sorghum (Al-Mamary, et al., 2001; Barros, et al., 2012; Taylor, J., et al., 2007). This reduction correlates not only with the content of tannins in the grain, but also with DP (Kaufman, et al., 2013; Mkandawire, et al., 2013). It is attributed mainly to the tannins with higher molecular weight or more complex tannin structures (DP > 10) (Barros, et al., 2013; Mkandawire, et al., 2013; Osman, 2004). Polymeric tannins, for example, are the major contributors to resistant starch formation due to their stronger interaction with starch, especially amylose (Barros, et al., 2013).

Despite the anti-nutritional effect, tannins are 15–30 times more effective than simple phenolics in radical scavenging ability (Hagerman, et al., 1998). Thus, tannins have been extensively studied for health-promoting capabilities (Beecher, 2004). The functional benefits of sorghum are attributed mainly to oligomers, which have been extensively studied (Beecher, 2004). The oligomers of tannins in foods contribute up to 19% of the antioxidant capacity of the diet and promote benefits to human health due to immunomodulatory, anticancer, antioxidant,

antirradical, anti-inflammatory, vasodilatory, cardioprotective, anti-thrombotic, and anti-UV actions (Dixon, et al., 2005; Floegel, et al., 2010; Sharma, S. D., et al., 2007; Waniska & Rooney, 2000).

The oligomeric and polymeric proanthocyanidins are not absorbed by animals and humans (Crozier, et al., 2010; Serrano, et al., 2009). But minor quantities of dimers of B1 and B2 procyanidins are detected in human plasma (Donovan, et al., 2007; Holt, et al., 2002). However, so far, it is unclear whether this low bioavailability is also observed in tannins in sorghum. Most tannins in foods pass unaltered to the large intestine where part of them are catabolized by the colonic microbiota yielding a diversity of phenolic acids (Selma, et al., 2009). The biological effects of tannins are generally attributed to their more readily absorbed colonic breakdown products, the phenolic acids, although there is a lack of detailed study in this area (Crozier, et al., 2010).

As to phenolic acids, processing can improve the digestibility of tannins in sorghum. The processing of grain sorghum in dry heat (95 °C for 20 min and 121 °C for 30 minutes) can depolymerize the condensed tannins in sorghum (Barros, et al., 2012), which can increase their bioavailability. The thermal processing can be a strategy to increase the bioavailability of tannins with a minimum reduction in the content of these compounds. Thus, the functional potential of sorghum rich in tannins can be maintained or even increased. Furthermore, the nutritional value of the grain may increase due to higher digestibility of starch and proteins resulting from the reduction of polymeric tannins. The depolymerization of tannins through other types of processing needs to be studied.

4.1.3. *Flavonoids*

Most flavonoids of the sorghum are located in the outer layers of the grain. Thus, differences in the color and thickness of the pericarp and presence of the testa influence the concentration and profile of flavonoids (Awika, et al., 2005; Dykes, et al., 2009). In turn, the physical characteristics of the sorghum are determined by genetic and environmental factors (Taleon, et al., 2012).

Three classes of flavonoids are in large quantities in sorghum: anthocyanins, flavones, and flavanones. Sorghum anthocyanins belong to the class of 3-deoxyanthocyanidins and correspond up to 79% of the flavonoids' content (Dykes & Rooney, 2006; Shih, C.-H., et al., 2007; Taleon, et al., 2012). They have a differentiated structure due to the absence of a hydroxyl group at position C-3 and therefore they are more stable than other anthocyanins (Awika, 2008; Awika & Rooney, 2004; Dykes, et al., 2009; Shih, C.-H., et al., 2007).

The main 3-deoxyanthocyanidins of the sorghum are non-methoxylated forms (luteolinidin and apigeninidin) (Awika, et al., 2004) (Figure 2). However, small quantities of methoxylated 3-deoxyanthocyanidins (5-methoxy-luteolinidin, 7-methoxy-luteolinidin, and 7-methoxy-apigeninidin) are observed in the sorghum as well as methoxylated 3-deoxyanthocyanins (5-methoxy-luteolinidin 5-glucoside, 5-methoxy-luteolinidin 7-glucoside, 7-methoxy-luteolinidin 5-glucoside, and 7-methoxy-apigeninidin 5-glucoside) and other non-methoxylated 3-deoxyanthocyanins (apigeninidin 5-glucoside and luteolinidin 5-glucoside) (Cardoso, et al., 2014; Taleon, et al., 2012; Wu, X. & Prior, 2005; Yang, L., et al., 2009). The content of sorghum 3-deoxyanthocyanidins correlates with its color and antioxidant activity (Awika & Rooney, 2004). Varieties with pericarp and black testa have 3 to 4 times more total 3-

deoxyanthocyanidins (5.4 to 6.1 mg/g) than red and brown varieties (1.6 to 2.8 mg/g) (Awika, et al., 2004).

The total flavones of the sorghum vary from 0 to 386 $\mu\text{g/g}$ (on average, 87 $\mu\text{g/g}$), with a prevalence of aglycone forms of luteolin and apigenin (Dykes, et al., 2011; Dykes, et al., 2009). The main flavanones of sorghum are the aglycone forms of eriodictyol and naringenin (Dykes, et al., 2011; Dykes, et al., 2009). The smallest contents are found in white varieties and the largest contents are observed in those with lemon-yellow pericarp (474 to 1780 $\mu\text{g/g}$) (Dykes, et al., 2011).

Information about the bioavailability of the 3-deoxyanthocyanidins, flavones, and flavanones in sorghum is not available in the literature so far. In other foods, including cereals, flavones and flavanones are highly available and are rapidly absorbed and excreted (Crozier, et al., 2009; Donovan, et al., 2007). The aglycone of flavones and flavanones, the forms most prevalent in sorghum, are rapidly absorbed (Spencer & Crozier, 2012; Urpi-Sarda, et al., 2012).

The bioavailability of anthocyanins in foods is relatively low compared to flavones and flavanones (Yang, M., et al., 2011) and is influenced by the nature of the sugar and also the structure of the anthocyanidin aglycone (Wu, X., et al., 2005). Unlike flavonoids, where glycosides are hydrolyzed, anthocyanin glycosides are rapidly and efficiently absorbed in the small intestine (Fernandes, et al.; Prior & Wu, 2006). This fact indicates that the main aglycone forms present in sorghum can have low bioavailability.

The anthocyanins in foods appear to be rapidly absorbed and eliminated, reaching only low maximal concentrations in plasma and urine (Fernandes, et al.). In studies with animals and humans, the quantities of anthocyanins excreted in urine were less than 0.1% of intake (Crozier,

et al., 2010; McGhie, et al., 2003; Prior & Wu, 2006; Wu, X., et al., 2005). Although anthocyanin bioavailability in foods appears low, it could have been underestimated due to the fact that some major metabolites have been ignored or not analyzed due to analytical limitations (Manach, et al., 2005). The difficulty in overcoming those analytical problems may contribute significantly to the low bioavailability of anthocyanins (Fernandes, et al.).

Between 60 and 90% of the anthocyanins may disappear from the gastrointestinal tract within 4 h after a meal (Prior & Wu, 2006). What happens to the bulk of the anthocyanins that disappear is not clear. Degradation accounts for a part of this disappearance, but differs for the various aglycones and may be modified further by the nature of the aglycone glycosylation, which further complicates our understanding of this process (Prior & Wu, 2006). Special attention is given to the contribution of the gastric mucosa to anthocyanin absorption as the result of the high content of intact anthocyanins (20–25%) detected in plasma few minutes after intake (Fernandes, et al.).

The contribution of intestinal tissue and the microbiota impact on absorption and anthocyanin bioavailability is also highlighted (Faria, et al., 2013; Fernandes, et al.). It has been suggested that this is likely due to the spontaneous degradation under physiological conditions or following microbial metabolism (Fernandes, et al.; Woodward, et al., 2009). In fact, colonic microbiota hydrolyzes glycosides into aglycones and degrades them to simple phenolic acids (Fernandes, et al.), which can be further fermented in the colon (Williamson & Clifford, 2010).

4.1.4. Stilbenes

Stilbenes are a small family of phenolic compounds derived from the phenylpropanoid pathway that have numerous implications in plant disease resistance and human health (Chong,

et al., 2009). The total content of stilbenes correlates with the color of the grain and is present in smaller quantities in white varieties. White sorghum contains traces of trans-piceid (up to 0.1 mg/kg) and trans-resveratrol is absent while in red sorghum, these two classes are present (Bröhan, et al., 2011).

4.2. Polycosanols and phytosterols

Polycosanols and phytosterols are associated with the lipid fraction of the sorghum (Leguizamón, et al., 2009; Wang, et al., 2008; Zbasnik, et al., 2009). Thus, these compounds have been studied mainly in lipids extracted from dry sorghum obtained after alcohol production.

One of the main components of the long-chained lipids extracted from sorghum grain kernels are polycosanols (33.4–44%) (Hwang, Keum Taek, et al., 2005; Hwang, Keum T, et al., 2004). Sorghum can be a major source of polycosanols that have physiological benefits. Total polycosanols content in unpolished sorghum grain was 74.5 mg/100g in the dry kernel while the content in the polished grain was 9.8 mg/100g in the dry kernel (Hwang, Keum Taek, et al., 2005; Hwang, Keum T, et al., 2004).

The content of sorghum phytosterols (4.13 to 24.45 µg/g, dry weight basis) is affected by growing conditions (Chung, et al., 2013). Sorghum grains are a relatively rich source of phytosterols when compared with fruits, vegetables, and other cereal grains commonly found in the food supply. Of the more than 200 sterols in vegetables, 3 have been identified in sorghum (sitosterol: 44.8 to 48.2%; campesterol: 26.1 to 38.0% and stigmasterol: 17.3% to 25.6%) (Delgado-Zamarreño, et al., 2009; Leguizamón, et al., 2009; Singh, V., et al., 2003; Wang, et al., 2007; Ye, et al., 2010).

4.3. Phytochemicals with anti-nutritional activity

Like other cereals, sorghum has phytochemicals with anti-nutritional activity. Phytates are major anti-nutritional compounds identified in sorghum (Abdel-Rahman & Osman, 2011; Afify, et al., 2011; Schons, et al., 2011). In addition, some varieties have protease inhibitors (trypsin, chymotrypsin, and amylase) and lectins (Abdel-Rahman & Osman, 2011; Neucere, 1982; Raimi, et al., 2012). These phytochemicals decrease the digestibility of proteins and carbohydrates, and mineral bioavailability.

5. POTENCIAL IMPACT OF SORGHUM ON THE HUMAN HEALTH

The potential functional benefits to human health associated with the consumption of compounds isolated from sorghum, and especially the whole grain, are still unknown. The results of in vitro and animal studies have shown that phenolics or fat soluble compounds isolated from sorghum beneficially modulate the gut microbiota and parameters related to noncommunicable diseases such as obesity, diabetes, dyslipidemia, cardiovascular disease, cancer, and hypertension (Tables 2 and 3). The main mechanisms of action of the compounds isolated from sorghum on parameters related to noncommunicable diseases, as found in results of in vitro and animal studies, are presented in Figure 3.

5.1. Oxidative stress

The chronic and excessive production of free radicals is crucial in the development of noncommunicable diseases (Hotamisligil, 2006; Lee, S., et al., 2011). The activity of components isolated from sorghum against oxidative stress has been demonstrated in vitro (Table 2). These functional benefits are attributed to the phenolic compounds and are most

evident when extracts from black or red sorghum were used (Burdette, et al., 2010; Moraes, et al., 2012a).

Phenolic compounds isolated from sorghum regulate the expression of phase II enzymes (Awika, et al., 2009; González-Montilla, et al., 2012; Yang, L., et al., 2009). These enzymes modulate the defense system against oxidative stress by continuously converting highly reactive electrophilic species (RES) into non-toxic and excretable metabolites (González-Montilla, et al., 2012; Takabe, et al., 2006).

The main effect of sorghum on phase II enzymes is to increase the NADH:quinone oxyreductase (NQO) activity (Figure 3). This effect is attributed to sorghum 3-deoxyanthocyanidins and depends on their profile but not on the content (Awika, et al., 2009; Lewis, 2008; Suganyadevia, et al., 2011b; Yang, L., et al., 2009). Recent studies demonstrated that apigeninidin and luteolinidin did not show any significant NQO inducer activity (Awika, et al., 2009; Yang, L., et al., 2009). On the other hand, their 7-methoxylated forms were strong NQO inducers (Awika, et al., 2009; Yang, L., et al., 2009).

Varieties of black sorghum may exert greater effects on NQO due to the rich profile and high content of 3-deoxyanthocyanidins (Awika, et al., 2009; Lewis, 2008; Suganyadevia, et al., 2011b; Yang, L., et al., 2009). However, sorghum varieties with different pericarp color can also induce the activity of NQO. For example, white sorghum (KARI-Mtama), which has low levels of pigments, extractable phenolics, and antioxidant capacity, has relatively strong NQO inducers (Awika, et al., 2009; Yang, L., et al., 2009). This fact demonstrated that sorghum is a source of other phytochemicals, pigmented or not, that might act synergistically with 3-deoxyanthocyanidins and produce high inducer activity. Conversely, sorghum tannins have a

very poor ability to induce NQO and can inhibit the NQO activity caused by other phenolic compounds (Awika, et al., 2009).

The effects of sorghum on the oxidative stress *in vivo* are little known (Table 3). The superoxide dismutase activity (SOD) increased in normolipidemic rats fed with black sorghum bran (rich in 3-deoxyanthocyanidins) (Lewis, 2008). This increase 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 suppressed the glutathione peroxidase activity (GPx) (Lewis, 2008). 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 (Moraes, et al., 2012a). The absence of significant changes in the SOD activity (Moraes, et al., 2012a) 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 Moraes, et al. (2012a) had lower concentrations of thiobarbituric acid reactive substances (TBARS) in their livers. This reduction suggested that whole sorghum inhibited the RES and that it can reduce oxidative stress through other mechanisms not evaluated in this study, 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 also may have contributed to these results.

5.2. Cancer

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 (Sharma, S., et al., 2010; Shih, P.-H., et al., 2007). 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 (Takabe, et al., 2006).

The benefits of sorghum on phase II enzymes cited in the previous section, especially on NQO reductase, demonstrate its chemoprevention (Table 2 and Figure 3). However, it is not possible to infer its effects in humans due to the lack of studies. There is epidemiological evidence that corroborates its potential to prevent cancer in humans. The substitution of sorghum by corn as a staple food of the diet increased the incidence of esophageal cancer in black South Africans (Isaacson, 2005). The mechanisms by which sorghum reduced the risk of esophageal cancer in humans are still unknown.

Elimination of tumors in early stages is considered an integral part of anticancer effects. The results of the study have demonstrated that phenolic compounds from sorghum, especially 3-deoxyanthocyanidins, act directly against cancer cells due to the increase of the apoptosis and inhibition of the growth and metastasis of cancer cells of skin melanoma, colon, esophagus, liver, breast, and bone marrow (Awika, et al., 2009; Hwang, J.-M., et al., 2013; Park, Jin Hee, et al., 2012; Shih, C.-H., et al., 2007; Suganyadevia, et al., 2011a; Woo, et al., 2012; Yang, L., et al., 2009). Sorghum 3-deoxyanthocyanidins are more cytotoxic to cancer cells than the respective analogous anthocyanidins present in other foods (cyanidin and pelargonidin) (Shih, C.-H., et al.,

2007). In addition to 3-deoxyanthocyanidins, apoptosis of the colon cancer cells resulted from estrogenic activity of the flavones of sorghum (Yang, L., et al., 2012).

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 activity), and inhibition of anti-apoptotic factors (Bcl2 gene, anti-apoptotic Bcl2 proteins, mitochondrial cytochrome C, and apoptosis-inducing factor) (Park, Jin Hee, et al., 2012; Suganyadevia, et al., 2011b, 2013; Woo, et al., 2012; Yang, L., et al., 2012). 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-1 α - hypoxia-inducible factor 1 α) (Park, Jin Hee, et al., 2012; Suganyadevia, et al., 2011a; Woo, et al., 2012). All of these events can inhibit cellular DNA synthesis, as was recently observed in skin melanoma cells (Hwang, J.-M., et al., 2013).

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 (Huang, et al., 2009). However, sorghum tannins still need to be better studied. In an recent study, sumac sorghum bran extract rich in tannins inhibited human aromatase (CYP19) activity in vitro more strongly than black sorghum bran extract rich in 3-deoxyanthocyanidins (Hargrove, et al., 2011). This suggests that the tannins found in sumac sorghum are more potent inhibitors than the 3-deoxyanthocyanidins found in

black sorghum, inhibiting and precipitating aromatase (Hargrove, et al., 2011). This enzyme is key to the synthesis of estrogen and is an important target for chemotherapy of breast cancer dependent on this hormone (Dowsett, et al., 2010).

The anticancer effects of sorghum *in vivo* have been little studied (Table 3). 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 (Park, Jin Hee, et al., 2012). 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 (Lewis, 2008). Furthermore, sorghum rich in tannins increased the colonocytes apoptosis.

5.3. Obesity and inflammation

Obesity is a pandemic that correlates with various noncommunicable diseases. The results of the studies demonstrate that sorghum rich in tannins reduces weight gain in animals (rats, pigs, rabbits, and poultry) (Al-Mamary, et al., 2001; Muriu, et al., 2002). 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 complexation of this compound to sorghum starch that helps lower caloric intake. Starch is the major component of cereals and the main source of calories in cereal products (Margareta Leeman, et al., 2006). A recent study demonstrated that polymeric tannins from sorghum can naturally modify starch by interacting strongly with amylose forming resistant starch (Barros, et al., 2013). Resistant starch cannot be digested in the small intestine and thus reaches the large intestine, delivering the health benefits of dietary fiber (Fuentes-Zaragoza, et al., 2010).

Furthermore, sorghum tannins can inhibit starch digestion by inhibiting saccharase and amylase enzymes (Mkandawire, et al., 2013; Nyamambi, et al., 2000; Osman, 2004).

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) (Ali, et al., 2009; Barros, et al., 2013; Frazier, et al., 2010; Nyamambi, et al., 2000; Osman, 2004; Rahman & Osman, 2011; Taylor, J., et al., 2007). 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 (Medugu, et al., 2010). Despite the evidence in animals, it is unknown whether sorghum (rich in tannins or not) modulates human weight. It is highlighted that the high consumption of sorghum rich in tannins can reduce the bioavailability of iron and zinc (Towo, et al., 2006).

Obesity is characterized by a chronic low-grade inflammation (Gregor & Hotamisligil, 2011). Until recently, the role of fat itself in the development of the obesity and its consequences was considered to be a passive one and adipocytes were considered to be little more than storage cells for fat (Greenberg & Obin, 2006; Gregor & Hotamisligil, 2011). 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 (Greenberg & Obin, 2006). 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 (Gregor & Hotamisligil, 2011).

In an *in vitro* study, the extracts of sorghum rich in 3-deoxyanthocyanidins inhibited the secretion of interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α) and nitric oxide by human mononuclear cells activated with bacterial lipopolysaccharide (Burdette, et al., 2010) (Figure 3). These effects were not observed in varieties with tannins. However, in another study, sorghums rich in tannins were more effective than those rich in 3-deoxyanthocyanidins in inhibiting hyaluronidase, an important enzyme associated with inflammation (Bralley, et al., 2008). The greater inhibitory effect of tannins can be attributed to their ability to complex the enzymes (competitive inhibition). However, in this study the tannins inhibited hyaluronidase through a competitive binding (Bralley, et al., 2008) and this indicates that the tannins bind to binding sites of this enzyme.

The evaluation *in vivo* of the anti-inflammatory effects of sorghum is still incipient but the results are promising. The addition of whole red grains without tannins or its lipid fraction to a hyperlipidemic diet reduced the expression of TNF- α in rats (Moraes, et al., 2012a; Park, Ji Heon, et al., 2012). 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 (Park, Ji Heon, et al., 2012). However, the sorghum extract of sorghum rich in tannins reduced the formation of edema in rats via the down-regulation of cyclooxygenase-2 (COX-2) expression, resulting in lower vascular permeability and edema with infiltration of neutrophils (Burdette, et al., 2010; Shim, et al., 2013). 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.

5.4. Dyslipidemia

In vitro and animal studies have shown that the lipidic and phenolic fractions from sorghum modulate parameters related to dyslipidemia and the risk of cardiovascular disease. These benefits result from the action of phytosterols, polycosanols, and phenolic compounds, which may modulate absorption, excretion, and synthesis of cholesterol.

The supplementation of the diet with sorghum lipids reduced the hepatic and plasma cholesterol of normolipidemic hamsters (Carr, et al., 2005; Hoi, et al., 2009) (Table 2). The phytosterols are one of the major bioactive compounds from sorghum lipid fraction able to inhibit the cholesterol absorption (Figure 3). Studies demonstrated that phytosterols isolated from other foods inhibited cholesterol absorption in humans, leading to increased fecal excretion and reduced plasma LDL-c concentration (Amiot, et al., 2011, 2013). These compounds reduce the amount of cholesterol captured in the gut enterocytes by inhibiting its incorporation into micelles, thereby lowering cholesterol absorption (Jesch & Carr, 2006).

The lipid fraction may also affect cholesterol absorption by altering the gut microbiota (Martínez, et al., 2009). 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, and reduced the family *Coriobacteriaceae* (mainly yet unclassified phylotypes) and non-HDL-c (Martínez, et al., 2009). 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 (Martínez, et al., 2009). 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 (Cho, et al., 2000). 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 receptor activity (Marinangeli, et al., 2010).

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 normolipidemic hamsters (Hoi, et al., 2009). 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) (Hoi, et al., 2009). 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 7 α -hydroxylase) (Hoi, et al., 2009). 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. The results of recent studies have demonstrated that the oral intake of freeze-dried extracts of phenolic compounds of sorghum (50 to 600 mg/kg for 14 days) also reduced the plasma concentration of cholesterol and triacylglycerol in rats (Chung, et al., 2011a; Chung, et al., 2011b; Kim, J. & Park, 2012). These functional benefits vary according to the sorghum variety and type of solvent used during preparation of the extracts (Chung, et al., 2011a; Chung, et al., 2011b).

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 (Cho, et al., 2000).

5.5. Diabetes

Recent results indicate that sorghum fractions modulate the glucose metabolism in animals due to the action of the phenolic compounds (Table 2 and 3). However, it is not known whether the components isolated from sorghum and especially the whole grain are beneficial to humans. In studies with mice, the intake of extracts of sorghum phenolic compounds reduced the

area under the curve of glucose and glycaemia (Chung, et al., 2011a; Kim, J. & Park, 2012; Park, Ji Heon, et al., 2012). 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 glibenclamide, an antidiabetic medication used in the control group (Chung, et al., 2011a; Kim, J. & Park, 2012).

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 (Figure 3). 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 (Kim, J.-S., et al., 2011). Thus, the decrease in the rate of glucose digestion through inhibition of enzymes may be the first action mechanism of sorghum on human metabolism.

Study results 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 mice that received extracts of phenolic compounds (Chung, et al., 2011a). 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 antidiabetic effects in mice fed with a hiperlipidic diet through a mechanism that

increased adiponectin and decreased TNF- α via overexpression of PPAR- γ , leading to improved insulin sensitivity (Park, Ji Heon, et al., 2012).

Furthermore, 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 (Kim, J. & Park, 2012). However, sorghum extract had no significant effect on glucose uptake by skeletal muscle determined by GLUT4 translocation and Akt phosphorylation (Kim, J. & Park, 2012). It is not known whether sorghum exerts 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% (Farrar, et al., 2008). 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- $\kappa\beta$ (NF- $\kappa\beta$) (Yamagishi, 2011).

Despite numerous in vitro evidence about the potential of bioactive compounds from sorghum to modulate parameters related to diabetes, only one published study to date evaluated the effects of whole sorghum. However, in this study, normolipidemic rats that ingested from 1 to 5% of whole sorghum added to a hyperlipidemic diet showed no changes in blood glucose, glycated proteins, and triacylglycerol (Moraes, et al., 2012a). The absence of significant changes in the study cited above may have resulted from a consumption of bioactive compounds less than

those obtained in in vivo studies that used sorghum fractions. Therefore, these results indicate that consumption of whole sorghum may not promote significant changes in a short period of time during consumption of a nutritionally unbalanced diet. It is remarkable that the results do not refute the possibility that sorghum can promote preventive and therapeutic effects on other markers not analyzed in this study, including gene expression and conjugated protein to balanced and unbalanced diets.

5.6. Hypertension

Recently there is an indication in the scientific literature that sorghum can reduce blood pressure (Table 2). In this study, an isolate of sorghum α -kafirins inhibited in competitive and non-competitive ways the activity of the angiotensin I converting enzyme (Kamath, V., et al., 2007).

5.7. Gut microbiota

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 (Clemente, et al., 2012; Laparra & Sanz, 2010). 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 microbiota environment and, consequently, human metabolism or could act at the membrane border inducing signal transduction pathways (Fernandes, et al.). The probable effects of bioactive compounds sorghum on the gut microbiota are unknown. It is important to analyze these effects during interventions in humans.

There is scientific evidence that unabsorbed phenolic compounds and their metabolites contribute to the maintenance of gut health by the modulation of the gut microbial balance through the stimulation of the growth of beneficial bacteria and the inhibition of pathogen bacteria, exerting prebiotic-like effects (Cardona, et al., 2013; Clemente, et al., 2012; Larrosa, et al., 2009; Requena, et al., 2010). 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 microbiota (Requena, et al., 2010). Furthermore, sorghum has resistant starch and dietary fiber, which can modify gut microbiota (Martínez, et al., 2010; Scott, et al., 2008).

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 microbiota (Cardona, et al., 2013; Requena, et al., 2010). 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* (Dolara, et al., 2005; Duarte, et al., 2006; Hidalgo, et al., 2012; Lee, H. C., et al., 2006; Tzounis, et al., 2011). The effects of sorghum, including varieties rich in tannins and 3-deoxyanthocyanidins, on gut microbiota are a field still to be explored. To date only one study has evaluated the relationship between bioactive compounds in sorghum in the gut microbiota of hamsters (Martínez, et al., 2009).

6. FINAL CONSIDERATIONS

Sorghum has a high nutritional value and is basically composed of starch, which is more slowly digested than that of other cereals, low digestibility proteins (mainly kafirins), unsaturated lipids, and is a source of some minerals (phosphorus, potassium, and zinc) and some B-complex vitamins (thiamine, riboflavin, and pyridoxine) and fat-soluble vitamins (D, E, and K). Furthermore, some varieties, especially the red, brown, and black colors, have a high content of phenolic compounds, especially 3-deoxyanthocyanidins and tannins, which are beneficial to human health.

The results of in vitro studies have demonstrated that compounds isolated from sorghum, particularly 3-deoxyanthocyanidins, tannins, and lipids, play a strong modulatory effect on gut microbiota and processes related to noncommunicable diseases (obesity, diabetes, dyslipidemia, cardiovascular disease, cancer, and hypertension). However, knowledge about the sorghum-specific bioactive compounds that promote these functional benefits is incipient.

Studies are needed to determine the preventive and therapeutic effects of sorghum whole grain and its fractions on human health, including gene and protein expression. It should be noted that the response of the human organism to these compounds may be dependent on their bioavailability. Thus, evaluating the bioavailability of sorghum's bioactive compounds is essential to determining the benefits of sorghum grains and bioactive compounds on human health.

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.

7. ACKNOWLEDGEMENT

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TABLES

Table 1: Average content of minerals (mg/100g) in sorghum grown in Brazil, United States and Ethiopia.

Minerals	Brazil ¹ (n = 8)	United States ² (n = 1)	Ethiopia ³ (n = 31)
Calcium	10.7	28.00	31.13
Iron	1.64	4.40	6.14
Potassium	-	350.00	188.80
Manganese	0.06	-	1.58
Sodium	nd	6.00	23.00
Potassium	217.87	287.00	289.34
Zinc	1.65	-	2.42
Magnesium	102.77	-	116.8
Copper	0.51	-	-
Sulfur	79.20	-	-
Aluminum	nd	-	-
Cadmium	nd	-	-
Chrome	nd	-	-
Lead	nd	-	-

¹ Martino, et al. (2012); ² U.S. Department of Agriculture (2012); ³ Shegro, et al. (2012); nd: not detected, -: not analyzed.

Table 2: Description of the *in vitro* studies about the effects of the fractions isolated from sorghum on parameters related to chronic noncommunicable diseases.

Related pathology	Cell type (if any)	Sorghum fraction used and preparation form	Main results	References
Diabetes	Not applied	Extract of Sumac sorghum bran rich in 3-deoxyanthocyanidins and high antioxidant activity (10% bran diluted in ethanol 50%)	↓ Glycation of proteins in approximately 60%	Farrar, et al. (2008)
	Not applied	Extracts of five sorghum varieties (10% grain diluted in ethanol 70%)	↓ Activity of α -glucosidase of <i>B. stearothermophilus</i> ↓ Activity of human pancreatic and salivary α -amylases.	Kim, J.-S., et al. (2011)
Inflammation and cancer	Not applied	Extracts of bran of sorghum varieties rich in tannins and 3-deoxyanthocyanidins (10% bran diluted in ethanol 50%)	↓ Hyaluronidase activity	Bralley, et al. (2008)
	Skin sarcoma cells (Hs 63.T) LPS-induced	Extracts of sorghum rich in phenolic compounds (5% sorghum diluted in methanol)	↓ Nitric oxide, IL-6, TNF- α ↓ DNA synthesis	Hwang, J.-M., et al. (2013)
	LPS-induced peripheral blood mononuclear cells	Extracts of white, bronze, red and black sorghum (8.3% to 25% bran diluted in ethanol)	↓ IL-1 β and TNF- α in blood mononuclear cells (black sorghum rich in 3-deoxyanthocyanidins)	Burdette, et al. (2010)
	Hepatoma (Hepal1c1c7)	Extracts of red and black sorghum rich in	↑ NQO activity in Hepal1c1c7 cells	Yang, L., et al. (2009)

	and colon cancer (HT-29) cells	3-deoxyanthocyanidins	↓ Proliferation of HT 29 cells	
	Cancer cells of esophagus (OE33) and colon (HT-29)	Extracts of 8 varieties of sorghum (with or without tannins)	↑ NQO activity (black and white varieties without tannins) ↓ Cell proliferation (black and white varieties without tannins)	Awika, et al. (2009)
	Hepatoma cells (Hepa1c1c7 cell)	Extract of black sorghum rich in 3-deoxyanthocyanidins (10% bran diluted in methanol 80%)	↑ NQO activity	González-Montilla, et al. (2012)
Cancer	Leukemia cells (HL-60)	Extract of sorghum rich in 3-deoxyanthocyanidins	↑ Cell apoptosis	Shih, C.-H., et al. (2007)
	Breast cancer cells (MCF-7)	Extract of red sorghum rich in 3-deoxyanthocyanidins (5% sorghum diluted in methanol HCl 1%)	↑ Cell apoptosis	Suganyadevia, et al. (2011a)
	Not applied	Extracts of sorghum rich in 3-deoxyanthocyanidins or tannins	↑ Human aromatase activity	(Hargrove, et al., 2011)
	Cancer cells of colon (HT 29) and liver (HEP G2)	Extract of red sorghum bran rich in 3-deoxyanthocyanidins (5% sorghum diluted in methanol HCl 1%)	↓ Cell proliferation	Suganyadevia, et al. (2011b)
	Leukemia cells (HL-60)	Extract of red sorghum bran rich in 3-	↑ Activation of BAK and BAX, release of mitochondrial	Woo, et al. (2012)

		deoxyanthocyanidins	cytochrome C and apoptosis-inducing factor into the cytoplasm, and activation of caspase-9 and caspase-3 ↑ Cell apoptosis	
	Breast cancer cells (MDA-MB 231 and MCF-7)	Extract of phenolic compounds of sorghum	↓ Phosphorylation of STAT5 and STAT3, and the expression or release of insulin-like growth factor 1 and VEGF proteins ↑ Expression of cyclin D, cyclin E, and pRb; Brk, p53, and hypoxia-inducible factor 1 α	Park, Jin Hee, et al. (2012)
	Malignant cells of colonocytes	Extracts of white (rich in flavones), red and black sorghum (rich in 3-deoxyanthocyanidins)	↑ Luciferase and caspase-3 activity	Yang, L., et al. (2012)
	Breast cancer cells (MCF-7)	Extract of red sorghum bran rich in 3-deoxyanthocyanidins	↑ p53 gene expression ↓ Bcl-2 gene expression ↓ Cell proliferation	Suganyadevia, et al. (2013)
Hypertension	Not applied	Hydrolyzed proteins (α -kafirins) of sorghum	↓ Angiotensin I converting enzyme activity	Kamath, V., et al. (2007)

Table 3: Description of the *in vivo* studies about the effects of the isolated fractions from sorghum on parameters related to chronic noncommunicable diseases.

Related pathology	Animal	Fraction and doses used	Duration of the study	Observed effects (effective treatment)	References
Obesity	Male New Zealand white rabbits	Low or high tannin sorghum added to the diet (60% of the diet)	4 weeks	↓ Weight gain, feed conversion ratio, and activities of the α -amylase, trypsin and lipase (high tannin sorghum) ↑ Food consumption, fecal nitrogen excretion (high tannin sorghum)	Al-Mamary, et al. (2001)
	Male New Zealand white rabbits	White or black (high tannin) sorghum grain (approximately 35%) added to the diet	5 weeks	↓ Weight gain (high tannin sorghum)	Muriu, et al. (2002)
Dyslipidemia and cardiovascular risk	Mice	30% of whole sorghum (30%) added to the diet	4 weeks	↑ Fecal excretion of bile acid and plasma HDL-c	Cho, et al. (2000)
	Hamster	Sorghum lipids (0.5, 1.0 and 5.0%) added to the diet	4 weeks	↓ Non-HDL cholesterol in plasma, esterified cholesterol and cholesterol absorption in liver (0.5 to 5.0%)	Carr, et al. (2005)

			<p>≡ Plasma HDL-c, phospholipids and free cholesterol in liver (0.5 to 5.0%);</p> <p>↑ Hepatic triacylglycerol (5%) and fecal excretion of sterols (cholesterol) (0.5 to 5.0%)</p>	
Hamster	Sorghum lipids (0.5, 1.0 and 5.0%) added to the diet	4 weeks	<p>↓ Non-HDL cholesterol in plasma, free and esterified cholesterol in liver;</p> <p>≡ Hepatic phospholipid (5%); Hepatic gene expression of NPC1L1, SRB1, SREBP2, HMGR, LDLR, and CYP7A1</p> <p>↑ Fecal excretion of sterols (cholesterol) and liver triacylglycerol; ABCA1 gene expression</p>	Hoi, et al. (2009)
Hyperlipidemic rats	Extracts of phenolic compounds in	2 weeks	<p>↓ Triacylglycerol, LDL-c and total</p>	Chung, et al. (2011b)

		dichloromethane and ethyl acetate.;			cholesterol in plasma (50 and 300 mg/kg of extract in ethyl acetate) ↑ HDL-c in plasma (50 and 300 mg/kg of extract in ethyl acetate)	
		Oral intake of 50 and 300 mg/kg				
	Diabetic rats	Extracts of phenolic compounds in acetonitrile. Oral intake of 100 and 250 mg / kg	2 weeks		↓ Glycaemia, triacylglycerol and total cholesterol in plasma (250 mg/kg) ↑ Insulin, urea, uric acid and creatinine in plasma (250 mg/kg)	Chung, et al. (2011a)
Diabetes, dyslipidemia and cardiovascular risk	Diabetic rats	Extract of phenolic compounds Oral intake of 400 and 600 mg / kg	2 weeks		↓ Triacylglycerol, total cholesterol, LDL-c, glycaemia, area under the curve for glucose in plasma (400 and 600 mg/kg), PEPCK and p38 expression ≡ Glutamic oxaloacetic transaminase and glutamic pyruvic	Kim, J. and Park (2012)

transaminase in
 plasma; insulin,
 GLUT4
 translocation
 and Akt
 phosphorylation
 ↑ AMPK
 expression

Table 3: Continued

Related pathology	Animal	Fraction and doses used	Duration of the study	Observed effects (effective treatment)	References
Dyslipidemia, cardiovascular risk and diabetes	Mice	Oral administration of 0.5% and 1% sorghum methanolic extract in mice fed a with high-fat diet	6 weeks	↓ Triacylglycerol, total cholesterol, LDL-c, glycaemia, insulin, area under the curve for glucose in plasma; adiponectin expression (0.5 to 1%) ↓ Tumor necrosis factor- α (1%). ≡ HDL-c, alanine and aspartate amino-transferase ↑ PPAR- γ expression (1%) ↑ <i>Bifidobacterium</i> (mainly a phylotype related to <i>B. animalis</i>) and HDL-c	Park, Ji Heon, et al. (2012)
	Mice	Modified AIN-93 M diet (37) supplemented with 0%, 1% and 5% grain sorghum lipid	3 weeks	↓ <i>Coriobacteriaceae</i> (mainly unclassified phylotypes yet) and non-HDL-c	Martínez, et al. (2009)
Inflammation	Mice	Application of ethanolic extract of white, bronze, red and black sorghum in the ear of the mice	-	↓ Ear edema of mice, generated induced inflammation (bronze and black sorghum) and	Burdette, et al. (2010)

				myeloperoxidase activity (black sorghum) ≡ Albumin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphates, creatinin, total protein, albumin, blood urea nitrogen, chloride, sodium, potassium, and calcium; cell structure and formation (liver, kidney, spleen, lungs, and heart) ↓ Nitric oxide in Raw264.7 cells ↓ Inducible nitric oxide synthase and anti-cyclooxygenase (COX)-2, 12-O-tetradecanoylphorbol-13-acetate-induced ear edema	
	Rats	Oral administration of 0.62 a 5g/kg of golden gelatinous sorghum rich in phenolic compounds	2 weeks		Shim, et al. (2013)
Inflammation, oxidative stress, diabetes, dyslipidemia	Normolipidemic Wistar rats	Whole sorghum (21.2 to 26.4%) added to the hyperlipidic diet	5 weeks	↓ TBARS in liver, tumor necrosis factor- α in plasma (red sorghum without tannin) ≡ Glucose, fructosamine,	Moraes, et al. (2012a)

				cholesterol, HDL-c, triacylglycerol, alanine and aspartate amino-transferase, superoxide dismutase, IL-8 and IL-10	
Cancer	Normolipidemic rats	Diets containing 6% of bran from white (contains phenolic acids), brown (contains tannins), or black sorghum (contains 3-deoxyanthocyanidins)	10 weeks	↓Number of aberrant crypts (black and brown sorghums) ↑Superoxide dismutase activity (black sorghum) and glutathione peroxidase activity (three genotypes)	Lewis (2008)
	Mice	Application of methanolic extract of sorghum rich in phenolic compounds by subcutaneous injection		↓ Cell growth and metastasis in breast cancer cells (MDA-MB 231 and MCF-7)	Park, Jin Hee, et al. (2012)

FIGURES

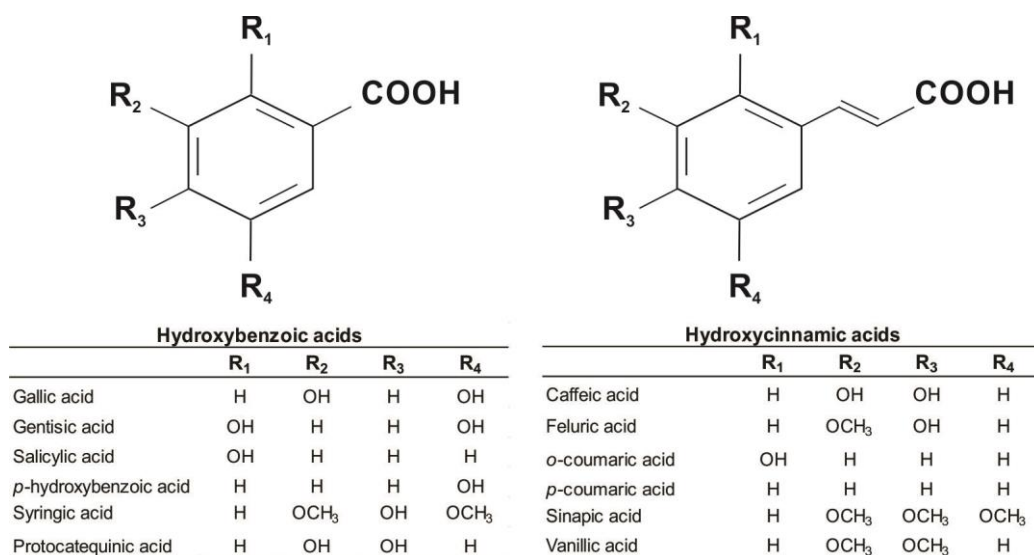


Figure 1. Structure of the major phenolic acids present in foods, including in sorghum.

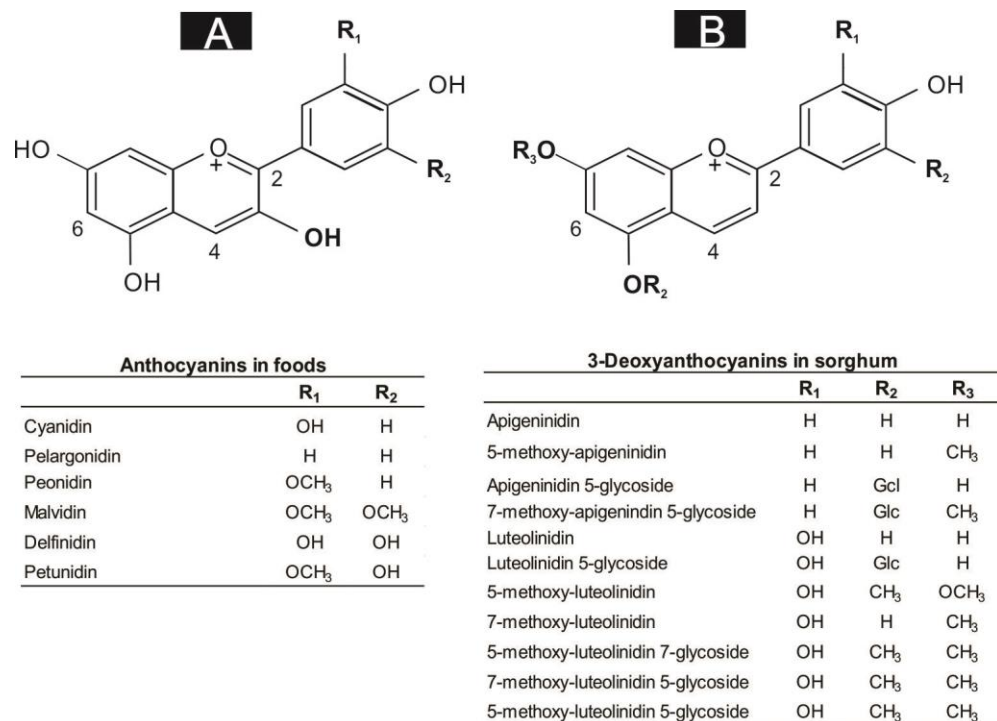


Figure 2: Structure of common anthocyanins in foods (A) and 3-deoxyanthocyanins in sorghum (B).

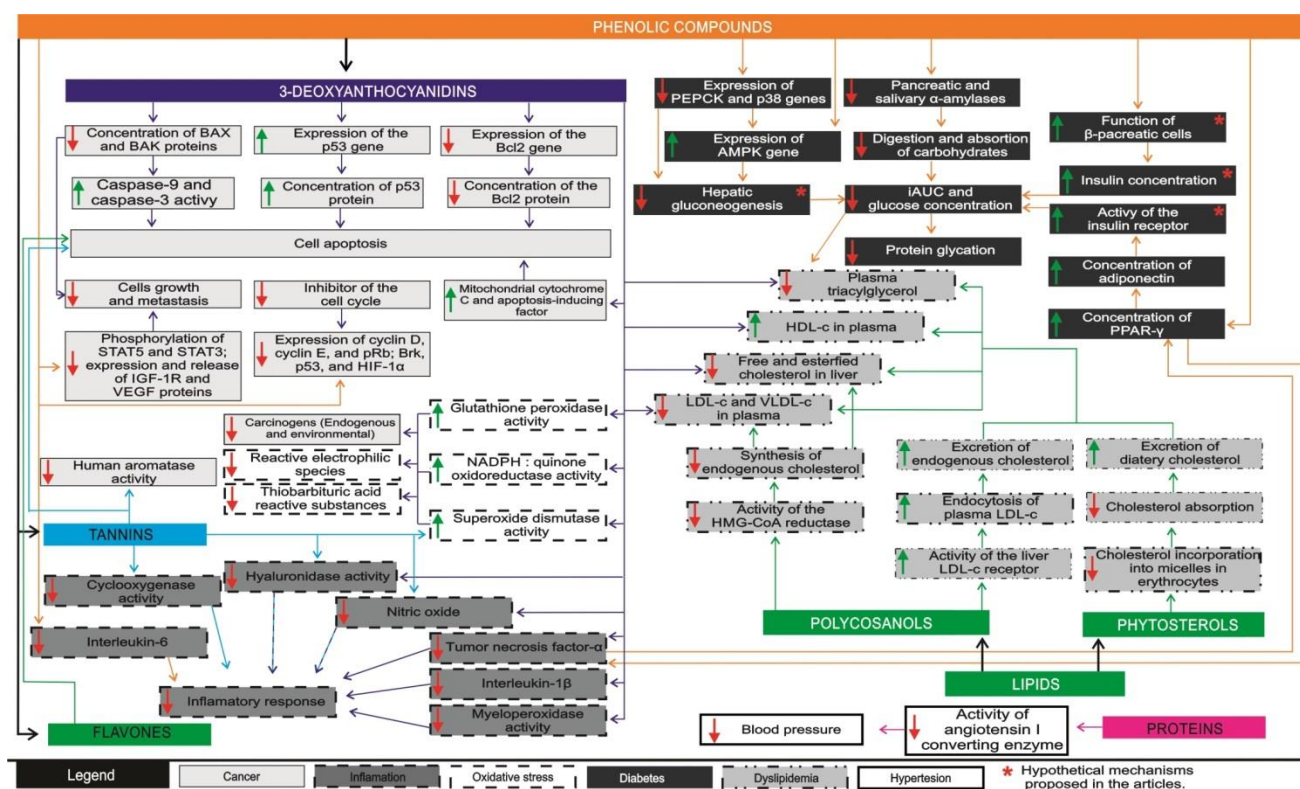


Figure 3: Main mechanisms of action of the sorghum on parameters related to noncommunicable diseases (diabetes, dyslipidemia, inflammation, cancer, oxidative stress and hypertension), proposed based on results of *in vitro* and animal studies.