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**Review article** 

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# Bioactive components in Bambara groundnut (*Vigna subterraenea (L.)* Verdc) as a potential source of nutraceutical ingredients



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Jane N.C. Okafor<sup>a,d,\*</sup>, Victoria A. Jideani<sup>a</sup>, Mervin Meyer<sup>b</sup>, Marilize Le Roes-Hill<sup>c</sup>

<sup>a</sup> Food Science and Technology Department, Cape Peninsula University of Technology, Bellville, 7535, South Africa

<sup>b</sup> Nanotechnology Innovation Centre, Department of Biotechnology University of the Western Cape, Private Bag x17, Bellville 7535, Cape Town, South Africa

<sup>c</sup> Biocatalysis and Technical Biology Research Group, Institute of Biomedical and Microbial Biotechnology, Cape Peninsula University of Technology, Bellville 7535, South

Africa

<sup>d</sup> Nutrition and Toxicology Division, Federal Institute of Industrial Research, Oshodi (FIIRO), P.M.B. 21023 Ikeja, Lagos, Nigeria

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#### ABSTRACT

The utilization of nutraceuticals on a global scale has significantly increased over the past few years due to their reported health benefits and consumer's reluctance to consume synthetic drugs. This paper provides information regarding new and potential value added uses of biologically active compounds in Bambara groundnut (BGN) as ingredients that could be further researched and exploited for various applications. Nutraceutical is a food or part of food that apart from providing basic nutrients, offers medicinal benefits either by prevention and or treatment of an illness. BGN is a legume with rich nutrient profile that is under exploited industrially. It is widely used in African traditional medicine for its various health outcome, but has not been explored scientifically for its numerous nutraceutical potentials. Compared to beans BGN has greater quantity of soluble fiber and also have high dietary fiber. It is rich in polyphenolic compound which include flavonoids subgroups like flavonols, flavonols, anthocyanindins, isoflavones and phenolic acids: both benzoic acid and cinnamic acid derivatives, biologically active polyunsaturated fatty acids, proteins and peptides, antioxidant vitamins and minerals. The rising interest and emphasis in plant-based biologically active components (nutraceuticals) for various health promotion, has positioned this African legume as a potential source of nutraceutical ingredients (bioactive components) that could be exploited for improved nutrition and health.

#### 1. Introduction

Globally, there has been increased interest in the utilization of natural products and their application in promoting health and wellness. There is considerable emphasis on identifying plants with potentials to supply valuable secondary products/metabolites also known as biologically active compounds for various industrial applications (Morris, 2003). Biologically active components also known as bioactive food components are naturally occurring non nutrient components in plant and lipid rich foods that have or possess health promoting property. According to an adhoc Federal working group "Bioactive food components are ingredients contained in foods or dietary supplements that are not the ones required to meet fundamental needs of man, which are accountable for changes in health status" (Federal Register, 2004 Yasmeen et al., 2017), Other scientists however, defined bioactive compounds as" constituents of food that affect the physiological or cellular actions/operations in

animals and people that take them, and examples include carotenoids, flavonoids and vitamins found in various fruits, vegetables and other foods and these compounds possess anti inflammatory, antioxidant, anticancer, and cardio-protective properties, they also show protective effects against metabolic syndrome related conditions like coronary diseases and diabetes (Kris-Etherton et al., 2002, 2004, Oh and Jun (2014). Kris-Etherton et al., however, stated that this definition make these components different from other compounds that are bioactive but shows harmful effects like toxins or carcinogens (Kris-Etherton et al., 2004). The term "Nutraceuticals" is a hybrid coined from 'Nutrition' and 'pharmaceutical' by DeFelice and the foundation for Innovative in Medicine in 1989 (Kalra, 2003). The definition of Nutraceutical as restated and clarified in 1994 in a press release is "any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease. The products could be supplements, nutrients isolated from foods and diets, herbal

\* Corresponding author. E-mail address: zikaokee@yahoo.com (J.N.C. Okafor).

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products, designer foods or genetically modified/engineered foods and foods that are processed such as beverages, cereals and soups (DeFelice, 1994; Wildman and Kelley, 2007; Kathleen and Stephen, 2009). A nutraceutical has health benefit because it protects one from chronic disease (Rajasekaran et al., 2008). On the other hand however, there are various definition of what functional food denotes, the Academy of Nutrition and Dietetics defined functional food as "Whole foods as well as fortified, enriched, or enhanced foods that have a potentially beneficial effect on health when taken as part of a varied diet on a regular basis at effective levels" (Crowe and Francis, 2013). Martirosyan and Singh however, proposed a new definition of functional foods as "Processed or natural foods that possess known or unknown biologically active components; which in quantified amount are effective and non-toxic and shows a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease" (Martirosyan and Singh, 2015). Examples of functional foods are whole foods or processed foods as well as fortified, enhanced or enriched foods with beneficial health outcome within the context of constant well balanced diet (Wang et al., 2016). The difference between bioactive compound, nutraceutical and functional food is that a bioactive food compound is a non nutrient component in food that shows or have biological activity and can promote health or have health benefits, a nutraceutical is a food or its component that has proven biological activity that could prevent, treat or manage a diseases condition and a functional food is a food or its product that has been scientifically proved to contain some bioactive components in specific nontoxic amounts and can confer some health benefits. Many factors are responsible for the significant rise in the nutraceutical market, this includes: rising in healthcare cost, increasing interest in achieving wellness through food, an aging society, some changes in food laws that affects food labeling and product claim and fast approaches in science and technology (Whiteman, 2001). Also, due to some adverse toxic effects of many synthetic drugs, consumers are increasingly turning to nutraceuticals. Scientific evidence shows that many bioactive food components possess certain health benefits and have found application in various functional food and nutraceuticals industries. These biologically active compounds have been used in combating various diseases like coronary diseases, cancer, arthritis, obesity, cholesterol, diabetes, osteoporosis, sleeping disorder, cold and cough, blood pressure, depression, digestion and many others (Pandey et al., 2010; Das et al., 2012; Shinde et al., 2014).

#### 2. Nutraceuticals definitions and classification

The term nutraceutical was created or invented in 1989 and coined from "Nutrition" and "Pharmaceutical" by the chairman and founder of Foundation for Innovation in Medicine, Stephen DeFelice (Brower, 1998). According to DeFelice, Nutraceutical is a food or part of food that apart from providing basic nutrients, gives medicinal benefit which include prevention and or treatment of an illness or disease (DeFelice, 1994; Wildman and Kelley, 2007). Nutraceutical could equally be described as food components that not toxic which have demonstrated scientifically to possess or manifest health benefits, which include the treatment of a disease or its prevention (Kathleen and Stephen, 2009). However, Health Canada describes nutraceutical as a substance developed or formulated from foods but vended or marketed in powdered form or pills or in medicinal form not normally related with foods (Bull, 2000). Nutraceutical in the European Medicine laws is described as a medicine for two reasons; it can be utilized for prevention, treatment, or curing of a disease condition or be given/applied with the intention of restoration, correction and modification of physiological functions in man (DSHEA, 1994). These nutraceutical products may vary: could be processed foods, dietary supplements, isolated nutrients, specific diet and genetically engineered designer foods, herbal and natural health products (DeFelice, 1994). The word nutraceutical has equally being used for

some lipids, minerals, vitamins, polyphenols, fiber fractions and not long ago, to proteins and peptides (Millward et al., 2008). Nutraceuticals are derived from foods that contain phytochemicals and antioxidants, an example is polyphenol. Phenolic compounds have antioxidant properties and are found in vegetables, fruits, legumes and in other foods from plants and they give or provide quality attribute like flavor, appearance and health-boosting properties. Nutraceutical has brought about a new age of medicine and health that have saddled the food industry with research responsibility. They help in fighting major health conditions like cardiovascular diseases, cancer, arthritis, osteoporosis, obesity, cholesterol, diabetes and others (Das et al., 2012). There are numerous nutraceutical substances, therefore, for easy understanding and application, organization systems are required and this depends on someone's interest and/or circumstance (Wildman and Kelley, 2007).

Nutraceutical factors can be broadly grouped depending on (1) Source of food (2) Mechanism of action and (3) The chemical nature: whether it is for the purpose of developing functional foods, dietary recommendation, clinical trial design or academic instruction (Wildman and Kelley, 2007). (1) Organization of nutraceuticals based on food source: Grouping nutraceuticals based on their prospective source of the food is one of the wider mean of grouping which differentiates them into animal, microbial and plant groups (Wildman and Kelley, 2007). (2) The second broad nutraceutical grouping is according to the mechanism in which they act. In this case, nutraceutical components are grouped or classified together depending on the demonstrated or claimed physiological properties notwithstanding the food source. Under this classification they can be grouped as anti-inflammatory, anticarcinogenic, antioxidants, antibacterial, antiaggregate, antihypertensive, osteoprotective and others, based on their biological activity (Wildman and Kelley, 2007). (3) The third way nutraceuticals are grouped is by classification of nutraceutical components depending on the chemical characteristics. In this grouping, nutraceuticals are categorized under molecular/elemental groups and broadly grouped into: Isoprenoid derivatives, phenolic compounds, carbohydrates and derivatives, amino acid-based components, fatty acids and structural lipids, minerals and microbes. However, in another report, Kokate et al. (2002) and Kalia (2005) demonstrated that the source of food utilized as nutraceuticals components are natural and grouped them according to the different types of phytochemicals present. This grouping categorized nutraceuticals from food sources into: Polyphenols, polyunsaturated fatty acids, dietary fiber, probiotics, prebiotics, antioxidant vitamins and spices.

Bambara groundnut (BGN) is an under-exploited African leguminous crop that has rich nutritional profile and is utilized in folk medicine because of its health benefits (Venter et al., 2000; Na et al., 2004; Koné et al., 2011; Okafor, 2012; Yao et al., 2015). Many phytochemicals which are biologically active components have been reported in BGN (Pale et al., 1997; Okpuzor et al., 2010; Ademiluyi and Oboh, 2012; Nyau et al., 2015a). BGN has higher soluble fiber when compared to other beans, it also contain high dietary fiber (Koné et al., 2011; Jideani and Diedericks, 2014; Maphosa and Jideani, 2016). BGN contains polyphenolic compounds (anthocyanin, catechin, quercetin, kaempferol and their derivatives, iso quercetin, epicatechin, luteolin, rutin, myricetin, chlorogenic acid, p-coumaric acid, ellagic acid, gallic acid, salicylic acid, caffeic acid and their derivatives, t-ferulic acid, quinic acid and medioresinol) (Pale et al., 1997; Ademiluyi and Oboh, 2012; Nyau et al., 2015a; Salawu, 2016; Harris et al., 2018). It is also rich in protein and have high protein quality, which is higher than that of soya bean, groundnut and cowpea (Annan et al., 2003; Okafor, 2012; Mubaiwa et al., 2016). BGN have polyunsaturated fatty acids (Ferrao et al., 1987; Basu et al., 2007; Alhassanm et al., 2014), vitamin A (β-carotene), carotene niacin, thiamine, riboflavin and ascorbic acid in trace quantity (Oyenuga, 1968; Adeyeye et al., 2013). The predominant minerals include calcium, potassium and iron (Bamishaiye et al., 2011). It also contains alpha tocopherol (Yao et al., 2015).

#### Table 1. The traditional medicine utilization of BGN for various health enhancement in different African countries.

Local name	Type of BGN	Traditional Medicinal use	Country	Reference
Njugo' beans Jugoboon in Afrikaans Jugo in Xhosa, Indlubu in Ndebele; nduhu in Venda	Immature seeds and mature seeds	<ol> <li>To check nausea and vomiting and morning sickness during pregnancy.</li> <li>Treatment of some malignancies and inflammatory disorders</li> </ol>	South Africa	Swanevelder (1995); DPP, 2011; Van der Walt (2005); Na et al. (2004)
Aboboi akyii	Black seeds	To alleviate swollen jaw diseases	Ghana	Swanevelder (1995), 1998
Aboboi akyii	Milled seeds	To treat skin rashes and sick children	Ghana	Swanevelder (1995), 1998
Aboboi akyii	Cream colored BGN seeds mixed with guinea fowl meat	treating diarrhea	Ghana	Swanevelder (1995), 1998
	Seeds of the mature black landrace	Treatment for impotence and in traditional medicine.	Botswana	Karikari et al. (1995); Koné et al. (2011)
Njugu mawe'	Water boiled BGN and maize and	Use for treatment of diarrhoea.	Kenya	Ngugi (1995)
Njugu mawe	Pound BGN leaves and Lantana trifolia L	To wash livestock as a Preventative against ticks. Also use as pesticide on vegetables		Ngugi (1995)
Njugu mawe	BGN leaves pound with mexican marigold and L. trifolia,	Serve as insecticide		Ngugi (1995)
Njugu mawe	leaves are pounded with traditional salt ('mbala'),	Use in treatment of cattles infected with 'tuoolao' (a type of mouth disease)		Ngugi (1995)
Njugu mawe	Roasted BGN seeds	Use for treatment of polymenorrhea.	Luo tribe in Kenya	Koné et al. (2011)
Njugu mawe	roasted seeds	Use for treatment of polymenorrhea.	Luo tribe in Kenya	Koné et al. (2011)
Njugu mawe	Crushed seeds mixed with water	Use for treatment of cataracts.	Luo tribe in Kenya	Koné et al. (2011)
Njugu mawe	BGN seed flour diluted in water or water from cooked BGN seeds	Remedy for internal bruising; speed up the resorption of people suffering hematomas	Luo tribe in Kenya	Koné et al. (2011)
Okpa otuanya in Igbo (Nigeria), Epi roro in Yoruba and Guijiya	Cruised seeds mixed with water and cooked seeds	To treat venereal diseases and protein malnutrition related disorder	Nigeria	Atiku (2000); Koné et al. (2011)
Juga bean	Mature seeds	Recommended for treatment of polymenorrhea.	Zambia	Koné et al. (2011)
Njugu mawe	Seed flour diluted in water/cooking water	Remedy for internal bruising; speed up the resorption of people suffering hematomas	Luo tribe in Kenya	Koné et al. (2011)
Njugu mawe	Boiled or cruised or cooked seeds	Treatment of anaemia in children and peri-partum women within 1 month of delivery	Cô te d'Ivoire,	Koné et al. (2011)
Njugu mawe	Juice obtained from boiling BGN seeds and maize	Treatment of diarrhea	Cô te d'Ivoire,	Goli et al. (1991); Koné et al. (2011)
Njogo bean	BGN flour and flour from fruit of Puvpalia lappacea (L.) (Amaranthaceae)	Use as hemostatic drink, to treat menorrhagia during pregnancy, and rectal bleeding.	Cô te d'Ivoire,	Koné et al. (2011)
Njogo bean	A decoction of seeds with leaves of <i>Terminalia laxiflora</i> (L.) (Combretaceae)	used as a drink to treat gonorrhea	Cô te d'Ivoire	Koné et al. (2011)
Njogo bean	Black BGN seeds mixed with unidentified plant	used for treatment of ulcers	Cô te d'Ivoire	Koné et al. (2011)
Njogo bean	Cooked Protein rich cream colored seeds	Helps to overcome Kwashiorkor, the common protein deficiency disease in young children	Central Africa	Koné et al. (2011)

Despite its numerous phytochemicals with various biologically active components and rich nutritional profile, BGN components have not been exploited as an ingredient in nutraceutical and functional food development. With the global increase in the nutraceutical market and Africa/Middle East being one of the most rapidly rising market section in the nutraceutical industry, with about 31% yearly increase between 2007 and 2011 (Smarta, 2011; Shinde et al., 2014), it becomes very important that this under-utilized legume be promoted for exploitation of its biologically active components for health promotion. The purpose of this review was to give/contribute knowledge concerning new and potential value added uses for BGN biologically active components as an unexploited source of nutraceutical, its health benefits and possible area of application. In concluding, we concentrated on the outstanding investigation to be performed in order for BGN biologically active components to find application in food and related industry.

#### 2.1. Traditional medicinal uses of Bambara groundnut

Ethno-botanical investigation shows that BGN helps in improving the health of communities and people living in various countries where they are grown. BGN plant parts (roots, leaves and seeds) are used for curing various illness and diseases. Table 1 presents the traditional medicine utilization of BGN for various health enhancement in different African countries. BGN is one of the biologically active plants utilized in folk medicine for curing inflammatory disorder and some malignancies or cancerous growth (Na et al., 2004). Some of the health benefits of BGN may be attributed to the content of various phytochemicals including polyphenolic compounds and dietary fiber. BGN seed was reported to contain higher amounts of soluble fiber than other beans and these could help to prevent colon cancer and reduction of the incidence of heart related diseases (Koné et al., 2011). Despite the numerous traditional medicinal uses of BGN and some scientific evidence supporting their health benefits, BGN has not been explored/exploited as a source of biologically active ingredients in the nutraceutical and functional food related industry.

# 2.1.1. Non nutrient components or antinutritional factors in Bambara groundnut

Though legume like Bambara groundnut (BGN) contain high amount of protein and other nutritional components, they possess some antinutrient substances which decrease their nutrient intake, digestibility, absorption and uses and may give rise to other deleterious effects (Akande et al., 2010). These antinutrients or non nutrient components are plant secondary metabolites manufactured or generated in plant to protect them (sort of chemical defence) from their environment and attack by animals, microorganisms and viruses. The antinutrient reported in BGN include protease inhibitors, lectins (haemagglutinin), phytate, tannin, oxalate and others. These compounds can be remarkably and successfully decreased or eliminated from BGN and other leguminous crops by utilizing conventional techniques used in food processing. Food processing treatments such as soaking, cooking, steaming, roasting, germination, irradiation, extrusion, fermentation have been shown to reduce/eliminate anti-nutritional factors in legumes. So they do not present problems with regard to causing harmful effects in processed legume food including Bambara groundnut. Okafor and Ani (2019) reported total elimination of trypsin inhibitor and haemagglutinin activity and reduction of phytate and tannins to safe levels on extrusion cooking of BGN based snacks. Safe levels of 301 mg/100g for phytate and 150–200 mg/100g for tannin have been reported for plant foods (Heaney et al., 1991; Schiavone et al., 2007). Duodu and Apea-Bah (2017) reported that some of these antinutrients are phytochemical constituents with health promoting benefits. Recently, it was shown that seeds of BGN containing low quantity of condensed tannin demonstrated favourable or valuable results in human nutrition and well-being (Akindahunsi and Salawu, 2005). There is rising interest on the additional or other beneficial features and view of these non-nutrient food components or phytochemicals because of their potential health promoting properties (Duodu and Apea-Bah, 2017).

#### 2.2. Biologically active components in Bambara groundnut

Bambara groundnut has been shown to contain many phytochemicals that are biologically active and some of them has been shown to be antioxidants with health promoting effects and they include: dietary fiber, polyphenols, prebiotics, polyunsaturated fatty acids, antioxidant vitamins. Some of the bioactive components in BGN is presented in Table 2, and the potential health promoting benefits of some of these phytochemicals are enumerated below.

#### 2.2.1. Dietary fiber (DF) and its health implication

In comparison with other beans BGN have higher soluble fiber content and contain high dietary fiber (Maphosa and Jideani, 2016). Dietary

## Table 2. Chemical composition and biologically active components in Bambara groundput

8			
Class/type of Nutraceutical	Raw	Cooked	Reference
Phenolic compounds (mg	/g)		
Quercetin	0.007–6.39	3.94	Salawu (2016); Harris et al. (2018)
Quercitrin	2.05	1.58	Salawu (2016)
Isoquercitrin	0.42	0.29	
Kaempferol	0.052-2.18	3.15	Salawu (2016); Harris et al. (2018)
Rutin	0.427-24.46	3.16	
Myricetin	0.062 - 1.800	-	
Luteolin 1.09	1.09	1.67	Salawu (2016)
Catechin	0.01-2.34		
Epicatechin	1.15	0.39	
Caffeic acid	3.65	3.75	Salawu (2016); Harris et al. (2018)
Ellagic acid	0.005-1.09	1.42	
Cholorogenic acid	0.03-2.37	0.50	
Gallic acid	0.05-1.03	0.41	
Dietary fiber			
Total dietary fibre, TDF (% of seed)	1.61–10.30		Mazahib et al. (2013); Abiodun and Adepeju (2011); Yao et al. (2015)
Soluble dietary fiber (% of TDF)	3.00-7.00	-	Yao et al. (2015)
Insoluble dietary fibre, IDF (% of TDF)	9.60–10.00	-	
Ursonic acid (% of IDF)	10.6–11.5	-	Maphosa and Jideani (2016)
Amino acids (% of protein	n		
Arginine	1.20-8.25	-	Yao et al. (2015); Baptista et al. (2016)
Isoleucine	0.89	-	Baptista et al. (2016)
Leucine	1.33–10.22	-	Yao et al. (2015); Baptista et al. (2016)
Lysine	0.99-8.54	-	
Glutamic acid	3.21-21.38	-	
Fatty acids (mg/100 g)			
monounsaturated fatty acids (MUFA)	1073	-	Baptista et al. (2016)
polyunsaturated fatty acids (PUFA)	2100	-	
Saturated fatty acids	1690	-	
Tocopherols and tocotries	nol (mg/100 g)		
α-Tocopherol	0.26	-	Baptista et al. (2016)
β-Tocopherol	-	-	
γ-Tocopherol	1.05	-	
δ-Tocopherol	6.64	-	
α-Tocotrienol	0.10	-	
β-Tocotrienol	-	-	
γ-Tocotrienol	0.18	-	
δ-Tocotrienol	-	-	
Phytosterols (% of total s	terol)		
Campesterol	0.73–3.93	-	Adeyeye et al. (2015)
Stigmasterol	0.68-1.78	-	
β–Sitosterol	1.89-2.23	-	

fiber (DF) can be described as macromolecules found in foods that withstand digestion by endogenous enzymes found in man, they are made up of constituents of cell wall of plants like polysaccharides and lignin (Tharanathan and Mahadevamma, 2003). They constitute different types of chemical materials like pectin, gums, hemicellulose, cellulose, resistance starch, mucilage, lignin, non-carbohydrate polymer of propane residue and other polysaccharides. Dietary fiber could be grouped into insoluble dietary fiber (IDF) and soluble dietary fiber (SDF). The SDF are water soluble and are basically natural gel- forming fibers such as mucilage, gum, pectin and several hemicellulose which give particular health benefit, IDF on the other hand are not water soluble and contain lignin, hemicellulos and cellulose (Stephen, 1995). It has been shown that DF play a significant part in the reduction or blocking the chances of developing diseases like obesity, cardiovascular disease, diabetes mellitus and colon cancer. Some medicinal advantage linked with consumption of foods high in fiber include: increase in fecal bulk, ability to lower blood lipids, delayed nutrient absorption, prevention of colon cancer, rise in fecal passage time, fermentability attributes and blocking digestion movement of the contents of the intestine. It has been demonstrated that individuals who consume abundant quantities of dietary fiber have less danger of hypertension (Whelto et al., 2005), stroke (Steffen et al., 2003), cardiovascular disease (Lui et al., 1999), gastrointestinal disorder (Petruzziello et al., 2006), obesity (Lairon et al., 2005) and diabetes (Montonen et al., 2003). Also, increased consumption of foods containing high DF has been shown to enhance or boost blood lipoprotein level (Brown et al., 1999), reduced blood pressure (Keenan et al., 2002), reduced lipids in blood (Anderson and Akanji, 1993; Behall and Howe, 1993), enhanced blood glucose control in people with diabetes, promotes cell regulation (Cummings, 2001) and helps in weight loss management (Birketvedt et al., 2005). It has equally been shown that specific soluble fibers boost human immunity (Watzl et al., 2005). Dietary fiber are added to processed foods for its functional properties (gelling, thickening) and health boosting (fermentation in the colon and adsorption of toxic carcinogenic metabolites). Their outcome on the gastrointestinal function include reduction on transit time, increase in fecal bulk, decrease in postprandial glucose response and blood cholesterol preservation. Soluble dietary fiber on dissolving in water become very viscous and this is useful when passing through the intestine as it influences absorption by slowing down gastric evacuation, hindering mingling in the upper small intestine, changes the site of absorption and slow down bowel movement which aids in modification of post-prandial lipid and glucose levels (Tharanathan and Mahadevamma, 2003). By causing fermentation in the large intestine and reduction of colon cancer development, the SDF aids in protection from colon cancer. Similarly, it can also decrease the quantity of low density lipoprotein (LDL) and cholesterol in the serum. Its absorption of bile salt affects cholesterol metabolism, that is; loss of cholesterol, bile salt not been available for development of micelle (which result in inhibition of lipids and cholesterol absorption), the rise in fecal bulk caused by SDF in the lower intestinal tract weakens/dilutes the bile acids and generate short chain fatty acids (SCFAs) particularly the propionate that has been implicated in the inhibition of hepatic cholesterol synthesis (Scheppach et al., 1988). The released SCFA (propionate and butyrate) apart from reducing the pH of the colon and preventing diarrhea have other numerous health benefits.

As mention earlier, BGN as a legume is rich in dietary fiber and this has food and non- food use potential applications (Fasoyiro et al., 2012). The rising in people's perception and knowledge of the physiological benefits of DF has been increased and so also is research for other possible sources of DF (Dalgetty and Baik, 2003; Daou and Zhang, 2011). Recently, a technology for production of dietary fiber supplement from BGN was developed and patented by our group (Jideani and Diedericks, 2014). This dietary fiber supplement produced from BGN is a bioactive component that could be exploited for various food applications. Similarly, a process was developed for extraction of IDF and SDF from four BGN landraces using a wet milling technique (Maphosa and Jideani, 2016). These bioactive components from BGN could be further researched for tailored/specific applications. The approved dietary fiber to be consumed by children and adults are 14 g/1000 kcals (Anderson et al., 2009), while Pilch (1987) reported 20–35 g/day.

#### 2.2.2. Bambara groundnut polyphenols

Polyphenols are organic substances naturally distributed in vegetables, fruits, legumes, cereals and other plants. They are plants secondary metabolites which protect them from reactive oxygen species, stress from photosynthesis or aggression by pathogens (Beckman, 2000). They add to the flavor, color, astringency, bitter taste, odor and stabilizes oxidation of food. There are up to 8,000 various groups or categories of polyphenol and the most common ones found in foods are the flavonoids and phenolic acids. Flavan-3-ol, flavones, flavonols, anthocyanins and flavanones are the most important class of flavonoids (Das et al., 2012).

Polyphenols that have many hydroxyl groups can successfully get rid of free radicals as well as O<sub>2</sub>- and singlet oxygen. Many population based investigation have demonstrated reversed association between chronic diseases and consumption of polyphenol rich foods (Arts and Hollman, 2005; Scalbert et al., 2005; Scalbert et al., 2005, 2005). Polyphenols destabilizes series of oxidative reaction in cell constituents due to fact that its phenolic group takes or receive electron to form or stabilize phenoxyl radicals (Clifford, 2000). Polyphenols have been demonstrated to have beneficial properties and exhibit biological activities such as protective effect against cancer formation, diabetes, cardiovascular diseases, osteoporosis and neurodegenerative diseases (Arts and Hollman, 2005). They possess antioxidant, anti-inflammatory, anti-allergic, antimicrobial, antiviral, anti-proliferative, anti- mutagenic effects and the ability to scavenge free radicals, regulate cell cycle arrest, apoptosis and other health promoting properties. They show chemoprotective and chemopreventive properties and could regulate several crucial cell signalling pathways involved in cancer development (e.g. nuclear factor erythroid 2 associated factor (Nrf2), mitogen-activated protein kinases (MAPK), activator protein-DNA binding (AP-1), nuclear factor kappa-B (NF-kB), kinase/protein kinase B (Akt), phosphoinositide 3 (PI3) and extracellular signal-regulated protein kinase (ERK) (Han and Loa, 2007).

Research has shown that various BGN landraces contain phenolic compounds namely: phenolic acids, tannins and flavonoids. HPLC-PDA-ESI-MS- based identification of bioactive components in BGN revealed that brown BGN contain catechin dimer, (E) GC hexoside, catechin glucoside, medioresinol, epicatechin, salicylic acid, p-coumaric acid, tferuric acid and caffeic acid derivatives, in addition to these compounds, red BGN landrace have quercetin -3-O-glucoside, quercetin -3-O-rutinoside and myricetin hexoside (Nyau et al., 2015a). Similarly, an evaluation of eleven species of Vigna (Fabaceae) for phytochemical content showed that prevalent flavonoid in the samples were kaempferol and it was indicated that kaempferol-3-O-glucoside was basically confined to four BGN varieties (Onyilagha et al., 2009). In an earlier experiment, isolation of three major anthocyanin pigment from BGN was reported, they include malvidin -3-O-\beta-glucoside, delphinidin -3-β-glucoside and petunidin -3-O-β-glucoside (Pale et al., 1997). HPLC-DAD quantification of phenolic components in methanol extracted raw and cooked BGN showed the presence of catechin, epicahechin, rutin, quercetin, iso quercetin, kaempferol, luteolin, galic acid, chlorogenic acid, caffeic acid and ellagic acid (Salawu, 2016). Similarly, Harris et al. (2018) reported major flavonoids in methanol extracted BGN to include: quercetin, kaempferol, rutin and myricetin while tannins are methyl gallate, catechin, chlorogenic acid, ellagic acid and gallic acid. These BGN bioactive constituents are phenolic compounds that possess numerous health enhancing/preventing and curative potentials.

Various in vivo and in vitro research have demonstrated the preventive, treatment and management potentials of BGN phenolic bioactive compounds against chronic diseases' molecular targets and these are shown on Table 3. The Chemopreventive or chemoprotective property of BGN seed extract rich in polyphenols and flavonoids has been demonstrated (Na et al., 2004). In that study using the skin of mouse and MCF-10A (human breast epithelial), it was demonstrated that BGN seeds extracted with methanol prevented COX-2 expression which was induced

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Phytochemical	Biological effects	Experimental model	Molecular targets	Reference
BGN seed extracts rich in polyphenols and flavonoids	Antimutagenic and anticarcinogenic activity	mouse skin	Inhibition of tetradecanoyl-phorbol-3 acetate (TPA) induced expression of the COX-2 gene through suppression of NF- <i>k</i> Bactivation	Van der Walt et al. (2005)
BGN seed extract rich in polyphenols and flavonoids	Chemopreventive or chemoprotective activity	human breast epithelial (MCF10A) cells and in mouse skin	Inhibition of TPA-induced COX-2 expression by suppression of DNA binding of NF- $\kappa$ B	Na et al. (2004)
Phytochemical rich extracts of BGN seeds	Inhibition of cancer cell proliferation	Hep-2 cancer cell line (human hepatic carcinoma), DU 145 (prostate cancer cell line) and noncancerous Vero cell line	Cytotoxic to cancer cells	Wanyama et al. (2017)
Phytochemical rich extracts Of fermented BGN seed	Modulation of activities of some enzymes relevant to erectile dysfunction	penile tissues of male wistar albino rats	Inhibition of arginase, phosphodiesterase-5 (PDE-5), acetylcholinesterase (AChE), and stimulation of ecto-5' nucleotidase activities relevant to erectile dysfunction	Ademiluyi et al. (2017)
BGN seed Phenolics and peptides rich extracts	Demonstrated hypoglycemic and anticholinesterase activity	diabetic albino rats	Modulatory effect on $\alpha$ -amylase, $\alpha$ -glucosidase and acetylcholinesterase activities.	Ademiluyi et al. (2015)
BGN seed Phenolics rich extract	Antioxidant activity and DNA protection against oxidative damage.	pBR 322 plasmid DNA	protection of plasmid DNA against AAPH-induced oxidative damage	Chinnapun (2018)
BGN seed protein hydrolysates and peptides	Antihypertensive and antioxidant activity	Angiotensin converting enzyme (ACE) and Renin inhibition assay	Inhibition of angiotensin converting enzyme (ACE), renin enzyme, peroxidation of linoleic acid and free radical scavenging activities.	Arise et al. (2017)
BGN seed protein hydrolysates and peptides	Protection from cardiovascular diseases (CVD) and type-2 diabetes (T2D) and Oxidative stress	In vitro ACE activity, DPP-IV inhibitory activity and antioxidant assays. Simulated gastro intestinal digestion	Inhibition of angiotensin-converting enzyme (ACE), dipeptidyl peptidase-IV (DPP-IV), resistance to simulated gastrointestinal digestion (SGID) and antioxidant activity.	Mune et al. (2018)
Fermented BGN seed extract	Protection from hepatic tissue damage and oxidative stress	Diabetic Wister rats	Modulation of hepatic enzymes and oxidative stress	Ademiluyi and Oboh (2012)
Phenolic-rich extracts of fermented/unfermented BGN seeds	protection against oxidants and lipid peroxidation	Cow's liver homogenate in vitro	Inhibition of lipid peroxidation by prevention of TBARS production	Oboh et al. (2009)

Table 3. In vitro and in vivo experiments showing the preventive, treatment and management potentials of BGN bioactive compounds against chronic diseases' molecular targets.

by 12-O-tetradecanoylphorbol-13-acetate in the mouse skin and MCF10A cells. The molecular mechanism by which BGN polyphenol rich methanol extract was able to prevent COX-2 expression was by hindering DNA binding of NF- $\kappa$ B which was activated by the TPA in MCF10A and mouse skin cells, and activation of NF- $\kappa$ B is one of the principal transcription factors accountable for regulation of COX-2 expression.

Similarly, the Antimutagenic and anticarcinogenic activity of white and black BGN extracts have been investigated (Van der Walt et al., 2005). It was shown that the aqueous ethanol extracts of these two BGN landraces possess anticancer properties, this was proved by their ability to also prevent tetradecanoyl-phorbol-1- acetate (TPA) induced COX-2 gene expression by inhibition of NF- $\kappa$ B activation, which has been shown to promote carcinogenesis (Van der Walt et al., 2005), the BGN extract also exhibited antimutagenic activity by inhibiting Daunomycin mutagenicity.

In another experiment, it was shown that six BGN cultivers extracted with methanol-dichlomethane demonstrated cytotoxic and anti-cancer/ anti proliferative effects against Hep-2 cancer cell line (human hepatic carcinoma), DU 145 (prostate cancer cell line) in vitro (Wanyama et al., 2017). The anti-cancer potentials of these BGN extracts was evidenced by their ability to effect cytotoxicity, anti proliferation and cancer cell inhibition at very low concentrations and IC50 of less than 30 µg/mL for the dark brown and cream spotted cultivars and IC50 values of less than 100 µg/mL for the red, brown, black and light spotted varieties. According to the United State National Cancer Institute (US-NCI) a crude extract that has IC50 value less than 100  $\mu$ g/mL is said to be active and those below 30 µg/mL are consider promising for purification and exploitation of the bioactive component as potential anticancer agents (Boik, 2001), the crude extracts of the dark brown and cream spotted cultivars in this experiment recorded IC50 of less than 30 µg/mL showing its promising/capability for further purification as potential anticancer agent.

The anticancer effect of several polyphenols like flavanones, isoflavones, ellagic acid, quercetin, catechin, lignans, curcumin, resveratrol and phenolic acids have been tested. The result demonstrated that these compounds showed protective effect against skin, stomach, duodenum, mouth, colon, liver, lung and mammary gland cancer, though in each case the effect was via a different mechanism of action (Johnson et al., 1994; Yang et al., 2001). Many population-based investigations indicated a positive relationship between intake of foods rich in polyphenol and a decrease in various non-communicable diseases. In a study not too long ago, polyphenol intake was associated with significant reduction in danger of having cancer of the breast in women that have past menopause, also an inverse association was established between phenolic acid consumption and the development of cancer of the breast by these women (Gardeazabal et al., 2019). It was demonstrated that 0-50 mg/mL<sup>-1</sup> extract of Manuka honey with abundant phenolic components (gallic acid, caffeic acid, kaempferol, quercetin and luteolin) showed potent anti-cancer effects on HCT-116 (human colon cancer) and LoVo cells (Afrin et al., 2018). It was reported that the intense suppression capability of the extracts was accomplished through decrease in the multiplication/spread of the colon cancer cells, induction of apoptosis and arrest of cell cycle (Afrin et al., 2018). Numerous related investigations on honey revealed that Nenas honey, India commercial honey and Gelam honey with caffeic acid, kaempherol, quercetin and luteolin demonstrated anti-cancer and cancer suppressing capability on HTC-15, HCT-116 and HT-29 colon cancer cells and these antiprolifrative and cancer slowing down ability of the various honey was attributed to the vital role its phenolics played in suppressing the growth of cancer cells (Jaganathan and Mandal, 2010; Wen et al., 2012; Tahir et al., 2015; Kee et al., 2016; Afrin et al., 2017). In a recent experiment, it was demonstrated that various anatomical parts (whole seed, cotyledon and seed coat) of Bambara groundnut inhibited the proliferation of Caco-2 and HT-29 colon cancer cells in a dose dependant manner with the

seed coat showing highest cytotoxicity/antiproliferative capability against colon cancer cells, the anti-cancer potential of the BGN fractions was attributed to the high content of polyphenol (Okafor et al., 2021).

BGN has also been shown to exhibit antidiabetic capability and acetylcholinesterase activity: Dietary supplementation of fermented powdered BGN have been shown to regulate high blood sugar and performance of acetylcholinesterase in Wister rats induced diabetes with streptozotocin. The possible mechanism by which BGN was able to achieve hypoglycaemic effect is probably due to increase/strengthening of the peripheral uptake of sugar and/or activation of the pancreatic cells insulin secretion, other mechanism could be due to inhibition of starch hydrolysing enzymes (a- amylase and \beta-glucosidases). These hypoglycaemic effects might be as a result of the bioactive components in the BGN seed probably the phenolic compounds (Ruzaidi et al., 2008; Ademiluyi et al., 2015). Tannins, flavonoids and phenolic acids which are phenolic compounds have been shown to inhibit the activities of enzymes that digest carbohydrates to glucose, these enzymes include  $\alpha$ -amylase and α-glucosidase (Iwai, 2006; Tadera et al., 2006). It has also been demonstrated that flavanols (catechins) a subclass of flavonoids could enhance cholinergic abnormality and cognitive disorder associated with diabetic condition and additional minor changes in the nervous tissues due to high blood sugar and oxidative stress caused by diabetes (Bhutada et al., 2010).

In a similar experiment, the modulatory effects of fermented BGN powder on in Wister rats induced diabetes with streptozotocin was investigated. The study revealed that the diabetic rats fed or treated with fermented BGN diet for 14 days had remarkably reduced amount of AST, ALP, ALT and malondialdehyde with increase activities of catalase, glutathione-S- transferase and also increased plasma glutathione, total protein and vitamin C, which was the reversal in diabetic rats not treated or given BGN diets, thus indicating the possibility of oxidative stress modulation effected by BGN treatment (Ademiluyi and Oboh, 2012). It was suggested that returning back the diabetic rats to normalcy must have been effected by the BGN diet showing their modulation of oxidative stress. And this may have been achieved probably due to content of some phytochemicals particularly phenolic compounds which were present in the BGN (Ademiluyi and Oboh, 2012). An important attribute of polyphenols discovered not too long was their ability to prevent long-term diabetes complication which includes nephropathy, retinopathy and neuropath. The result of these finding suggest that intake of flavonoids, anthocyanins and other phenolic components may promote and bring about new methods of boosting the life standard of people with diabetes (Cui et al., 2008b; Li et al., 2008, 2012; Bhutada et al., 2010). Phenolic compounds in diets has also been shown to regulate or modify peripheral glucose utilization in sensitive tissues that are either quick to react to insulin or otherwise. An investigation revealed that the manner or way in which phenolic acids revitalize or invigorate the intake of glucose is similar to those of conventional glucose lowering medicine like thiazolodinedione and metformin that are taken orally (Prabhakar and Doble, 2009). Experiments have indicated that resveratrol, epigallocatechin gallate (EGCG) and quercetin (phenolic compounds) boost glucose intake that are dependent on insulin in adipose tissues/cells and muscles through relocating GLUT4 (glucose transporter) to plasma membrane, which is achieved by AMP-activated protein kinase (AMPK) track motivation (Park et al., 2007; Zhang et al., 2011). AMPK is a vital detector or component that determines the vitality or vibrant condition of cells because of its major part in controlling metabolic process. The actuation or triggering of this metabolic path by AMPK is been given attention as the latest therapy or cure for metabolic syndrome, obesity and type -2 diabetes (Zhou et al., 2001; Towler and Hardie, 2007). It is worthy to note that polyphenols have demonstrated 50-200 fold more potential and capability in triggering or wakening of AMPK compared to metformin (Zang et al., 2006).

Several studies have also demonstrated the antioxidant capability of various BGN extracts. It has also been shown that raw and heat processed Songkhla 1 BGN variety (red seed coat) extracted with 80% methanol

exhibited the ability to prevent oxidation and protected DNA from destruction by oxidation (Chinnapun, 2018). In that investigation, the ability of heat processed BGN to prevent oxidation was assayed (DPPH, ABTS\*radical scavenging activity, metal chelating capability and FRAP) and plasmid DNA (pBR 322) protection against AAPH-induced oxidative stress was investigated, the result obtained showed that both raw and heat processed BGN extracted with 80% methanol exhibited strong antioxidant activity and protected plasmid DNA against oxidative stress induced by AAPH (Chinnapun, 2018). Also, in another study using an in vitro antioxidant assays (DPPH and FRAP) and homogenate of Cow's liver (in vitro), phenolic-rich extract of fermented and unfermented BGN seed demonstrated elevated reducing power, capability to scavenge for free radicals, suppressed peroxidation of lipids by preventing TBARS production and protection against oxidants (Oboh et al., 2009). The antioxidant capability and protection against lipid peroxidation observed in these studies were attributed to the phytochemicals present in BGN especially the polyphenols (Oboh et al., 2009; Chinnapun, 2018). In another in vitro study, the effect of some fermented legumes including BGN on major enzymes responsible for erectile dysfunction was investigated (Ademiluvi et al., 2017). It was demonstrated that aqueous extract of BGN and that of other legumes inhibited the activities of key enzymes like ecto-5' nucleotidase, arginase, acetylcholinesterase and phosphodiesterase-5 (PDE-5) that are principally responsible for erection disorder or problem and this was probably achieved by the modulation of the activities of this key enzymes by the action of some biologically active compounds (phenolic compounds) present in BGN and other legumes (Ademiluyi et al., 2017). In a different research, DPPH and FRAP assay was used to determine the antioxidant capability of aqueous and methanol extracts of two BGN varieties (red and brown), the result indicated that these BGN varieties demonstrated potent antioxidant capacity which was attributed to its polyphenol composition (Nyau et al., 2015b). In another study, it was revealed that water, ethanol and acetone extracted BGN seed coats showed powerful antioxidant and antimicrobial properties that was also attributed to the action of polyphenolic components in BGN (Klompong and Benjakul, 2015). The presence of antioxidant compounds like phenolics, tanninis and flavonoids in raw and processed BGN seeds were probably responsible for its high antioxidant activity and may have offered DNA protection against oxidative damage (Chinnapun, 2018). These biologically active components present in various BGN varieties makes BGN a good material or resource to be explored further research for various applications. Bambara ground nut also contain various anthocyanin pigments. Anthocyanin is a group of flavonoid that is found in various plants and they are accountable for the bright colors found in fruit, vegetable and other foods. They are natural plant pigments that are soluble in water and possess powerful antioxidant capability. Three major anthocyanin pigments have been extracted from BGN namely: petunidin 3-O-β-glucoside, delphinidin 3-β-glucoside and malvidin 3-O-β-glucoside (Pale et al., 1997). Anthocyanin consumption has been shown to decrease the danger and possibility of developing some chronic diseases (cardiovascular disease, cancer, diabetes and arthritis) partly because of their ability to prevent oxidation and inflammation (Lila, 2004; Prior and Wu, 2006; Wang and Stoner, 2008).

#### 2.2.3. Bambara groundnut bioactive protein and peptides

Not too long ago, research has demonstrated that many legume proteins and peptides are classified as nutraceuticals because they exhibit health promoting properties that are similar to proteins and peptides isolated from milk, meat, fish and eggs (Carbaonaro et al., 2015). Peptides that are biologically active have been reported to exhibit several normal structural attributes, consist of ten to twelve acid residues that are short length, amino acids that are hydrophobic, content of arginine, lysine and proline and the ability to resist proteolysis (Carbonaro et al., 2015). These peptides based on the succession of the amino acid demonstrate various health enhancing effects like anti-cancer potential, anti-inflammatory, antimicrobial activity, weight management, sensitivity to insulin, mineral absorption, regulation of immune cells, promotion of bone and cardiovascular health, and also endocrine and neurological effects (Hartmann and Meisel, 2007; Janan-Mihan et al., 2011; Carbonaro, 2011; Senechal and Kussmann, 2011; Rebello et al., 2014). Some biologically active proteins and peptides have been isolated from BGN and were identified using multidimensional protein identification technique (MudPit) and liquid chromatography-matrix-assisted laser desorption ionization tandem time-of-flight (LC-MALDI TOT-TOF) (Okpuzor et al., 2010). Some biologically active peptides in BGN and the manner of disease prevention is shown on Table 3. In Table 3, it was shown that BGN protein hydrolysate and their peptide fraction possesses antioxidant ability and has potential in the prevention or management of oxidative stress related metabolic disorder and high blood pressure (antihypertension) by hindering the action of the enzyme that convert angiotensin (Arise et al., 2016, 2017). In another study, it was demonstrated that the biological active peptides produced from Bambara bean protein hydrolysates demonstrated antioxidant activity, antihyperglycaemic activity (dipeptidyl peptidase (DPP-IV) inhibitory activity) cardio- protecting effect by lowering the pressure of the blood (suppression of the action of angiotensin-converting enzyme) and resistance to simulated gastro-intestinal digestion (Mune et al., 2018). Peptides isolated from legumes such as soybean and lupin seed has been extensively studied and have demonstrated health beneficial properties. Soybean and lupin seed's storage proteins are the most studied legume protein as source of bioactive peptides, and have been shown to display opioid, immune modulating effect, ability to reduce glucose, cholesterol and blood pressure (antihypertensive) depending on the type of investigation (in vivo and in vitro) (Carbonaro et al., 2015). This studies suggest that these bioactive peptides could probably be useful nutraceutical components in development of anti-diabetic foods (Carbonaro et al., 2015). Other protein components present in BGN with potential health benefits are the amino acids: Lysine, leucine, isoleucine, glutamic acid and arginine. Lysine has been used successfully in the treatment of cold sore infection (herpes labialis) caused by herpes simplex virus (Griffith et al., 1987), Leucine and isoleucine were demonstrated to be potent in the treatment of hepatic encephalopathy in its early stage also known as minimal or latent hepatic encephalopathy (Plauth et al., 1993), Arginine was reported to be used as medication in the cure of chronic heart disorder in which the heart does not pump blood effectively due to coronary artery disease (congestive heart failure) (Hambrecht et al., 2000), while glutamic acid has been shown to be probably utilized in curing of oral mucositis (a kind of mouth ulcer) caused by complication resulting from chemotherapy administration (Cockerham et al., 2000).

#### 2.3. Polyunsaturated fatty acids (PUFA) in Bambara groundnut

The polyunsaturated fatty acids (PUFA) which are the needed/ indispensable fatty acids carry out a very important part in the functioning of the human body. There are two major PUFA gotten from the food we eat and these are the omega-3-(n-3) fatty acids and omega-6-(n-6) fatty acids. The main omega-3-(n-3) fatty acids include docosahexanoic acid (DHA) α-linolenic acid (ALA) and eicosapentanoic acid (EPA). The α-linolenic acid (ALA) are majorly found in foods like canola, soybeans, flaxseed, nuts such as walnut and red or black current seeds, they are also found in some fatty fishes, ALA is the precursor of EPA and DHA (Institute of Medicine, 2002). Arachidonic acid (ARA), linoleic acid (LA) and  $\gamma$ -linoenic acid (GLA) are the main omega-6-(n-6) fatty acids available. Many studies have demonstrated various health benefits derive from omega-3-(n-3) fatty acids intake, these includes promotion of cardiovascular health, anti-arrhythmic, hypolipidemic and antithrombotic effects, it also have beneficial outcome on depressive and bipolar disorder, asthma, diabetes, dysmenorrhea and pre mature child wellbeing (Edwards et al., 1998; Carlson, 1999; Pepping, 1999; Stoll et al., 1999; Connor, 2000; Hiroyasu et al., 2001; Leray et al., 2001; Buchner et al., 2002; Nemets et al., 2002). It has been shown that BGN contain both the omega-3-(n-3) fatty acids and omega-6-(n-6) fatty acids.

It was demonstrated that fatty acid in BGN contain 21%  $\alpha$ -linolenic acid (Minka and Bruneteau, 2000) and another study recorded 1.30 %  $\alpha$ -linolenic acid (omega-3-(n-3) fatty acids) and 36% omega-6-(n-6) fatty acids in BGN (Yao et al., 2015). Alhassanm et al. (2014) indicated the existence of arachidic acid (eicosanoic acid) among different PUFA found in BGN. The content of these polyunsaturated fatty acids in BGN is an indication that BGN may play a very important or crucial part in promoting the various health benefits linked with these PUFAs when consumed.

Appreciable amounts of thiamine, niacin, riboflavin, vitamin A ( $\beta$ -carotene), carotene and very small amounts of ascorbic acid are also present in BGN (Oyenuga, 1968; Adeyeye et al., 2013). The mineral elements present in BGN are phosphorus, as the major mineral, magnesium and calcium, and trace elements (iron, copper and zinc), also substantial amount of  $\alpha$ -tocopherol has been reported (Yao et al., 2015).

#### 3. Conclusions

BGN has been used mainly as food in most countries where they are cultivated and to some extent in folk medicine, animal feed and as forages. From this review it is evident that BGN contains biologically active phytochemical compounds that could be explored/exploited in various food application. Although, some of these bioactive components in other plants have been established to have medicinal applications and have been utilized in the, prevention and management of numerous degenerative diseases, they have not been commercially extracted from BGN varieties, also in-vitro and in-vivo studies are limited. Nevertheless, for BGN's biologically active components' (nutraceutical) benefit to be fully harnessed, there are still some scientific needs to be met. The greatest scientific need involves characterization and standardization of these bioactive components (nutraceutical compounds) in BGN. Therefore, more research (both in vitro and in vivo) need to conducted leading to clinical trials to demonstrate the basis for health claims that will convince the consumers, food and related industries as well as support the commercialization of BGN products.

#### Declarations

#### Author contribution statement

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Data included in article/supplementary material/referenced in article.

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The authors declare no conflict of interest.

#### Additional information

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