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Formulation of a Yam Based Hyperglycemic Flour using Mixture Design

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Abstract
Dioscorea schimperiana is an endangered yam species in Cameroon and an attempt was made to produce antidiabetic flour from *Dioscorea schimperiana*, soybeans (*Glycine max*), cinnamon (C*innamomum verum***)** and neem leaves (*Azadirachta indica*) using mixture design to diversify it end use limited to the production of pounded yam. The nutritional content of the flour blends were assessed. Water, ash, total digestible carbohydrates, crude proteins, lipids, fibers, calcium, zinc, iron, vitamin C, beta carotene and alpha tocopherol were determinate using standard methods. Result show that the yam based anti-hyperglycemic flour satisfies the recommended Acceptable Macronutrient Distribution Ranges (AMDR) according to reference diabetes organizations ensuring by this a balanced diet. It contains bioactive compounds with scientific based evidence of maintaining ideal blood glucose levels, achieving optimal blood lipid levels, reducing the risk for diabetic complications. Therefore, it can be used in diabetes management as nutraceutical.

Keywords: Diabetes, Anti-diabetic Flour, Balanced Flour, Blood Glucose Levels

Introduction

Diabetes and its complications is a major public health problem worldwide. According to the International Diabetes Federation (IDF) Diabetes Atlas, 366 million people suffered from diabetes in 2011 and this number is expected to reach 552 million people by 2030 [1]. In Africa, diabetes, like other non communicable diseases, paid little attention, despite its social, human and economic repercussions [2]. Diabetes is a disorder in sugars assimilation, use and storage provided by food. These results in high blood glucose levels stated as hyperglycemia [3].

Restoring blood sugar balance is the main goal of any hyperglycemia treatment. The search for natural substances able in regulating blood sugar levels is currently the subject matter of several scientific studies. Throughout the world, plants have always been used as medicines. The latter are considered mild even low-toxic compared to pharmaceutical drugs [4]. Medical nutrition therapy (MNT) is an approach that uses nutrition as a therapeutic tool to treat and prevent disease. This approach aims at optimizing health by using specific diets, nutritional supplements and other nutritional interventions to support the treatment of disease and improve overall health. The use of plants in medicine is mainly due to their bioactive substances which have numerous pharmacological properties such as antioxidant, hypoglycemic, anti-inflammatory properties...etc. Many plants due to their exceptional composition in endogenous antioxidants have been reported in several studies [5]. Functional foods and medicinal plants combined or not can provide health benefits in form of nutraceuticals, in addition to being included in the prevention and treatment of diseases (Alissa *et al*., 2012) [6]. A special case is neem and cinnamon. Neem (*azadirachta indica*) has received particular attention because of scientific evidence demonstrating its strong antihyperglycemic potential [7, 8, 9, 10]. Scientific research has shown that components present in cinnamon (C*innamomum verum*) can help reduce blood glucose levels and relieve and prevent signs and symptoms of metabolic syndrome in type 2 diabetes and cardiovascular and related diseases [11, 12, 13, 14]. The combination of cinnamon and neem's leaves products will surely enhance the therapeutic effect but people suffering from diabetes are often advice to consume balanced diet. A mixture of these ingredients with tasty foods such as yam (*Dioscorea schimperiana*), soybeans (*glycine max*) in formulating a balanced diet would certainly be interesting. The choice of these foods is not random. Indeed, *Dioscorea schimperiana* is an endangered yam species with end uses limited to pounded yam. This yam has also a traditional history of being suitable as food for diabetic people. Hence, formulating an antidiabetic flour with this yam aim at diversify it end uses limited to pounded yam. Soy consumption is of particular interest for diabetics because of its high content of polyunsaturated fatty acids [15]. The dietary importance of soybeans is also due to the presence isoflavones which improve the regulation of blood sugar [16] and alpha-galacto-oligosaccharides (α-GOS) which positively modify intestinal flora since alteration is often related the development of type 1 diabetes [17, 18, 19]. Mixing *D. schimperiana* and soy flour, neem's leaves and cinnamon powder in formulating a ready to used anti-diabetic balanced food as nutraceutical have not been implementing. The present work aims at producing a balanced anti-hyperglycemic food based on soybeans and *D. schimperiana* flour, neem leaves and cinnamon powder able in avoiding nutritional deficiencies and ensuring glycemic control and it related complications in diabetic patients. More specifically, it aims at formulating using mixture design, a balanced diet meeting standards goals in terms of macro and micronutrients.

Material and Methods

Sample collection

Soy (G*lycine max*), cinnamon (*cinnamomum verum*), neem leaves (*azadirachta indica*), were purchased from local market in Douala city. Dried yam slices (*D. schimperiana*) were bought in Baham local market, in the west region of Cameroon. Yam samples were collected in bamboo bags and transported to the laboratory. They were then divided in three groups according to the flesh color: Yellow, red and yellow with red dots. All the samples were kept at room temperature before processing.

Processing technologies

Preliminary treatment of the raw materials

Cleaning and washing

Neem leaves were wash using tape water. Soybeans were manually sorted to remove husks, stones, damaged and colored foreign grains. Noxious seeds, insects and any foreign material were also removed.

Dehulling

Soybeans were completely dehulled to reduce fibers and antinutrients content to minimum levels. They were then roasted over low heat during 20 minutes. Sample were subsequently crushed and varnished to remove the fibrous film and other impurities. They were stored in plastic bags before grinding.

Drying

Neem leaves were placed in simple and aerated layers on pre-weighed drying trays, and dried at 45 ± 5°C in a cross flow cabinet dryer (Binder, FDL 115), with an air flow rate of 24 m^3/h. Drying trays were periodically weighed all along the drying process. Samples were dried to a moisture content of 10%. For each sample, drying experiment was conducted in triplicate and from the three values of tray weight, average of sample moisture was determined as a function of time.

Milling

All dry samples (neem leaves, soybean and cinnamon) were ground into fine flour using a hammer mill (Cullati) or a robot blender (Moulinex®) (neem leaves). Dried yam slices were grounded in a milling machine (Retsch ZM 200) equipped with a 1 mm sieve. Flour was then sieved through a sieve of 500µm, packaged in an air tight polyethylene bags and stored at -18 ° C until analyzed

Formulation of yam-based flour

The methodology of mixture design as a mathematical approach was used to calculate the proportions of ingredients needed in order to have balanced composite flour. Optimal mixture of ingredients in formulating balanced anti-hyperglycemic flour is: 6:2:1.7:0.03 respectively for yam flour, soy flour, cinnamon powder and Neem leaves.

Chemical analysis

Proximate composition

Moisture and ash were determined by AOAC method [20]. Crude protein has been analyzed according to Kjeldahl method [21]. Total fat content was quantified according to Weibull–Stoldt method [22]. Total dietary fiber was analyzed according to the AOAC 985.29 method [23]. Carotenoids profile and alpha tocopherol were determined by HPLC [24]. Total available carbohydrate was calculated as 100% minus the sum of moisture, protein, fat, ash, and total dietary fiber obtained using proximate analysis.

Minerals analysis

Determination of calcium, zinc and iron concentrations in the samples was performed using flame atomic absorption spectroscopy in acid digested ash according to the AOAC, 999.11 methods [25]. Phosphorus ions analysis in acid digested ash was done by antimony-phosphomolybdate colorimetric method AOAC, 1990 [26].

Results

Nutritional quality of the formulated composite flour

Macronutrients content, gross energy and Acceptable macronutrient Distribution Ranges of the formulated composite flour

Proximate composition of the formulated yam based anti-hyperglycemic flour compared to standards is shown in Table 1. Protein, lipids and carbohydrates content are 12.518, 5.126 and 51.128 % respectively. The value of ash content is 3.029% while fibers content is 14.466%. These values were calculated from the model equations. The gross energy of the formulated flour calculated is 300.700 Kcal/100g. Protein, lipids and carbohydrates contributes to about 16.651, 15.338 and 68.011% of the total energy respectively. Fiber's energy density is about 4.822g/100 kcal. The macronutrient contribution of carbohydrates reported in this work is closer to the AMDR for ADA for the United stated of America. Lipid energy distribution fulfills only the AMDR for NDNS of UK and the JDS for Japan. Protein energy distribution fulfills all the AMDR except for ICMR reference. Fiber's energy density reported fulfills all the acceptable density value of standards.

Macronutrient value of the formulated composite flour when using total diet replacement (TDR) pattern

The daily portion intake of carbohydrates, protein, lipids and fibers as a function of the quantity of flour needed to satisfy estimated energy requirement when using total diet replacement (TDR) pattern is presented in Table 2. They were calculated according to the estimated energy requirement. Standard energy requirement and the Macronutrient Distribution Ranges (AMDR) were used to calculate the theoretical amount of proteins, carbohydrates and lipids provided by utilizing the following factor of conversion: 1g carbohydrates or protein = 4Kcal; 1g lipids = 9Kcal. These theoretical values were compared with experimental values. When using CDA reference, the quantity of flour needed to fulfill the daily requirement standard energy is 914.531g. This quantity fulfills the calculated RDA for protein (103.125-137.5g). The carbohydrates and fibers level is slightly higher (1.13 and 2.65 respectively) than the upper limit of the range (412.5

and 50g respectively). The lipids level is less (1.30) than the recommended lower value (61.11g). The quantity of flour needed to fulfill the ICMR daily energy requirement is 716.66g. This quantity do not fulfills the calculated RDA for protein, lipids and carbohydrate. The quantity of protein and carbohydrates provided by the composite flour was higher (1.11 and 1.13 respectively) than the upper limit of the range (80.813 and 323.25g respectively) recommended value. The amount of lipids was lower (1.96) than the lower recommended value (>71.833). When using NDNS standard, the quantity of composite flour needed to fulfill the daily requirement energy is 831.392g. This quantity fulfills the calculated RDA for protein only. The carbohydrate level provided by the composite flour is slightly higher (1.13) than the upper limit of the range (375g). The lipids level is less (1.3) than the recommended lower value (42.61g). When using The European Association for the Study of Diabetes (EASD), the quantity of composite flour needed to fulfill the daily requirement energy is 332.557g. This quantity fulfills the calculated RDA for protein. The ADA and Japan Diabetes Society on medical nutrition therapy individualize the protein requirement allowance as 0.8 and 0.8-1.5 g/kg BW/day respectively. Japan Diabetes Society and ADA preferred to give a lower RDA limit as 150 and 130g/d of carbohydrates respectively.

Table 1: Macronutrients content, gross energy and macronutrient Distribution Ranges (AMDR) of the formulated composite

	Composite flour		Acceptable Macronutriment Distribution Ranges (AMDR)						
Proximate analysis	Macronutrients content (g/100g)	Macronutriment Distribution Ranges	CDA Canadian diabetic association (1)	Indian Council of Medical Research (ICMR) **(1)**	National diet and nutrition survey (NDNS) of UK **(1,2)**	Traditional guidelines for T2DM management **(1)**	American Diabetic Association (ADA) **(3)**	The European Association for the Study of Diabetes **(4)***	The Japan Diabetes Society on medical nutrition therapy JDS (2020) **(5)**
Moisture	10.756±0.01								
Ash	3.029±0.05								
Protein	12.518±0.03	16.651	15–20% %	10–15%	10–20%	15–25%	10 to 35	10-to-20 15-to-20 23-to-32	≤20%
Lipids	5.126±0.02	15.338	20- 35%	> 30%	<35%	20–35%	20 to 35		≤30%
Carbohydrates	51.12±0.03	68.011	45–60%	50–60%,	47–60%	45-60	45 to 65		50–60%
Fibers	14.462±0.04	4.822/100 kcal			>1.5/100kcal	1.4/100kcal	1.4/100kcal	4/1000KJ	≥20%
Gross energy (Kcal/100g)	300.700		2750	2155	2500		1800-2200		

(1) Prasathkumar *et al*, (2022) [1].
(2) Diabètes UK (2018) [27]
(3) American Diabetes Association (2024) [28].
(4) Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), 2023 [29]
(5) Japanese Clinical Practice Guideline for Diabetes 2019 [30]
*****10–20% and 15–20% of total energy intake is recommended, respectively. In the case of obesity and normal renal function, a short-term protein intake of 23–32% is acceptable; a total of 10–15% protein intake is recommended for stage 3 nephropathy.

Table 2: Estimated Energy Requirements and daily intake of carbohydrates, protein, lipids and fibers as a function of amount of flour needed when using a total diet replacement (TDR) pattern

Standards	Energy (kcal/j)	Carbohydrate g or g/day	Proteins (g/day) or (g/kgbw/day)	Lipids (g/day)	Fiber (g/day) or g/100kcal/d	Quantity of flour needed (g)	Proteins (g/day)	Fibers	Lipids (g/day)	Carbohydrates
	Theoretical values					Quantity provided when using total diet replacement (TDR) pattern				
CDA Canadian diabetic association	2750	309.375-412.5	103.125-137.5	61.11-106.944	30-50g	914.531	114.48	132.30	46.87	467.58
Indian Council of Medical Research (ICMR)	2155	269.375-323.25	53.875-80.813	>71.833		716.66	89.71	103.67	36.73	366.41
National diet and nutrition survey (NDNS) of UK	2500	281.25-375	93.75-156.25	55.56-97.22		831.392	104.07	120.27	42.61	425.07
Japan Diabetes Society on medical nutrition therapy		>150g/d	0.8-1.5 g/kgbw/day		≥ 20 g					
The American Diabetes Association (ADA)		130 g/day	0.8g/kgbw/day		1.4g/100kcal					
The European Association for the Study of Diabetes (EASD)	1000–1200*	-	10-to-20 ** 15-to-20 23-to-32	-	≥35 g 1.67g/100kcal	332.557	16.651	48.108	17.042	170.028

*(1000–1200 kcal/day) is commonly advocated with obesity.

Alpha tocopherol, β Carotene and mineral composition of the formulated composite flour

The levels of β-carotene and alpha-tocopherol in the yam based anti-hyperglycemic formula are presented in Table 3. The values were calculated from the model equations. Alpha tocopherol (the highest fraction of vitamin E) content of the formulated flour is 114.54-373.70g/100g. The yellow yam flesh has the highest content in iron. The anti-hyperglycemic flour contains beta carotene (64.517-216.61µg/100g) among provitamin A carotenoids and vitamin C (64.517 µg/100g). The values vary according to the color of the yam flesh. The red yam flesh color has the highest (216.61 µg /100g) and the yellow with red dot yam flesh the lowest (75.567g/100g). The calcium content of the formulated yam flour is 431.176g/100g. Zinc and iron content is 7.693-19.972 and 6.757-14.788 respectively. The yellow with red dot yam flesh has the highest contain in zinc while the yellow yam flesh has the highest content in iron.

Micronutrient value of the formulated composite flour when using total diet replacement (TDR)

Standard daily energy requirements were used to calculate the quantity of composite flour needed to satisfy these energy requirements when using total diet replacement (TDR) pattern in Medical Nutrition Therapy. In general, these quantities meet the calculated INL98 (at least 50%) for vitamin A, vitamin C, zinc, iron and calcium. When using CDA, ICMR, NDNS and IOM standards, the quantities of flour needed to satisfy the energy requirements fulfills 100 % of the RDA value for vitamin A, C, zinc, iron and calcium. The daily quantities of composite flour satisfy only 4.13-81.82% of apha tocopherol recommended values in function the flesh coloration. These results show that apha-tocopherol is the limiting micronutrients.

Table 3: Recommended dietary allowance and daily portion intake of mineral and vitamin as a function of quantity of flour needed when using a total diet replacement (TDR) pattern

	Standard Energy requirement (Kcal)	Quantity of flour	Beta carotene (µg/100g)	Vitamin A µg retinol equivalent (RE)	Vitamin E mg (α-Tocopherol) (µg/100g)	Vitamin C (mg/100g))	Zinc (mg/100g)[4]	Iron (mg/100g)[5]	Ca (mg/100g)
Macronutrient composition of the composite flour			75.567-216.61	12.595-36.1	114.54-373.70	25.406±0.02	7.693-19.972	6.757-14.788	431.176±0.01
Standard references									
Reference Nutrient Intake (INL98) [35]				550	8.8 mg	45	3.6; 6.0, 11.9 (4)	14.3; 18.0; 21.6; 43.1 (5)	1000
Daily ration of the formulated complementary Food (at least 50% of INL98)				225	4.4	32,258	1.8; 3.00; 5.95	7.15; 9; 10.8, 21.55	500
ANSE [36]	2000-2500			650-750	9-10	100-110	7.5-11.76	42675	950-1000
IOM, 2014 [37]	1900-2900			700-900	15	75-90	45604	43313	1000-1200
EFSA [38]	1624-2340.5			650-750	11-13	110-95	45602	7.5-16.3	750-1000
Anti-diabetic formula									
CDA Canadian diabetic association	2750	916.67		1053,33-3019.38	1.047-3.42	232.345	70.36-182.65	61.79-89.70	3943.24
Indian Council of Medical Research (ICMR)	2155	718.33		647.17-1855.10	0.820-2.68	182.074	55.14-143.13	48.42-70.29	3090.07
National diet and nutrition survey (NDNS) of UK	2500	833.33		870.56-2495.46	0.95-3.11	211.22	63.96-166.05	56.18-81.54	3584.76
IOM, 2014	1900-2900	666.33-967.67		502.87-3364.78	0.72-3.60	160.53-245.02	48.61-126.20	42.69-142.62	2724.42-4158.33
EFSA	1624-2340.5	541.28-780.08		442.35-2187.04	0.619-2.90	137.21-197.75	41.55-155.47	36.49-115.10	2328.66-3356.06

[4] Zinc values are given for high, medium and low dietary zinc bioavailability [31];
[5] Iron values are given for 15, 12, 10 and 5% dietary iron bioavailability [31];

Discussion

Estimated Energy Requirements were given by most reference organization for people with diabetes on the basis of those of healthy adults. All these references insist on respecting Acceptable Macronutrients Distribution Range (AMDR) as a percent of energy intake for fats, carbohydrates, proteins and fibers to ensure a nutritionally balanced adequate diet. Based on estimated recommended energy requirements by diabetes organizations, the daily quantities of composite flour to be eaten in order to satisfy the daily allowance in a total diet replacement (TDR) pattern were calculated. Results show that the AMDR for carbohydrates were close to the ADA reference standards distributions range at all daily quantities of composite flour needed. Although of the existent of AMDR, the most recent nutritional guideline from the ADA or the Japan Diabetes Society (JDS) on medical nutrition therapy suggest that the macronutrients needs should be set individually since an ideal carbohydrate/fat/protein ratio does not exist for diabetic patients. In all cases, the amount of carbohydrates intake required for optimal health in humans is unknown. If some reference standards guide insist on the minimum RDA (19 years and older) value of 130g/d, it is because this quantity was determined based on the glucose requirements necessary for the proper functioning of the brain. For EASD, a wide range of carbohydrate intakes are acceptable, provided recommendations relating to dietary fiber, sugars (10% of total energy intake), saturated fats (<10% of total energy intake) and protein intakes are met [29]. AMDR for protein fulfills all standards except for ICMR reference. Proteins into adult body play a crucial role in maintaining and repairing damaged tissues. Insufficient protein intake can lead to malnutrition or sarcopenia or frailty, whereas too high protein intake can cause diet related kidney damage [32]. For this reason, the daily quantity of protein in diabetic's diet should be personalized based on age, weight, nutritional and metabolic status. The ADA and Japan Diabetes Society on medical nutrition therapy personalized the protein requirement allowance as 0.83 and 0.8-1.5 g/kgbw/day respectively. In all cases, the total energy intake should be no less than 0.8 g/kg BW/day and 30–35 kcal/kg BW/day to prevent risk of undernutrition and sarcopenia [33]. If some reference guidelines accept slightly higher values of protein, it is in relation to the general characteristics of the population. In the Japanese population where the proportion of elderly people is high, the prevalence of sarcopenia and frailty leads in tolerating consumption of slightly higher quantities, notably 1.3 (1.5) g/kg BW/day [34]. In Western and North American societies, the AMDR standard for proteins is low. Indeed, the prevalence of obesity in the diabetic population is very high and the objective of reducing weight is the priority of any Medical Nutrition Therapy. In this case, reduction in protein and carbohydrate intake is important to increase insulin sensitivity in obese and type 2 diabetes patients [29]. EASD advises an energy restriction (840 kcal/day) for 12–20 weeks and a step-down approach starting with 4200 kJ/day or 5000 kJ/day (1000–1200 kcal/day) is commonly advocated with obesity. In Cameroon, the percentage of obese people among patients suffering from diet related non-communicable diseases is low (19.2% of adult (aged 18 years and over) women and 7.5% of adult men) [35] and malnutrition even among adults (5.8% of adult women and 6.8% of adult men) exist [36]. For this reason, the consumption of slightly higher quantities of protein should be tolerable but at a threshold where the risks of nephropathy (diabetic kidney disease), malnutrition/sarcopenia and frailty and cardiovascular diseases are reduced. The average daily level of protein intake for people with diabetes without kidney diseases is typically 1–1.5 g/kg body weight/day or 15–20% of total calories [37]. However, some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety [28]. This is a confirmation that AMDR for protein of the composite flour is in conformity with reference standards. AMDR for lipid fulfills only the AMDR for NDNS of UK and the JDS for Japan. In all cases, there are not an optimal percentage of calories from fat for people with or at risk for diabetes [28]. The type of fats consumed is more important than total amount when looking at metabolic goals and cardiovascular diseases (CVD) risk. However, it is recommended that the percentage of total calories from saturated fats should be limited [28]. Large epidemiological studies have shown also that consumption of polyunsaturated fats or polyunsaturated fatty acid biomarkers is associated with a lower risk of type 2 diabetes [34]. Consumption of soy is therefore interesting due to its high content of polyunsaturated fatty acids [38]. Soybean stand as the main source of proteins and lipids in the composite flour and multiple benefits could arise after its consumption, thereby improving the nutri-therapeutic value of composite flour with respect to anti-diabetic potential. The use of the glycemic index (GI) and glycemic load (GL) to rank carbohydrate-rich foods based on their effects on blood sugar continues to be of interest to people with diabetes and those at risk for diabetes [37]. *Dioscorea schimperiana* stand as the main source of carbohydrates in composite flour and this yam has a traditionally history of suitable for consumption by diabetic patient. Therefore, the presence of *Dioscorea schimperiana* flour in the composite flour would surely enhance the anti-diabetic potential of the composite flour. Though there is no specific recommendation for nutrients and minerals at present, a nutrient deficiency in diabetic patients must be seriously addressed [1]. The composite food contains beta -carotene among pro-vitamin A carotenoids. The biological activity of carotenoids is estimated as retinol equivalent [38]. The retinol equivalent activity of the composite flour meets the recommended values of at least 50% INL98 (32.258), and all the requirement of **standards**. A part from provitamin A activity, beta carotene is associated with antioxidant activity. The composite flour contents Vitamin C which exhibits also an antioxidant activity. The content in vitamin C meet the recommended values of at least 50% INL98 (32.258) and all the requirement of standards. Alpha tocopherol which displays an antioxidant activity is also present in the composite flour even though the standards values were not meeting. This result shows that the anti-diabetic flour is enrich in antioxidant vitamin. Calcium, iron and zinc as minerals are present in the composite flour. The mineral content meets the INL98 (at least 50%) specifications values for calcium, zinc and iron (500) and others standards. Preview study report a high content of polyphenols in cinnamon [13, 14]. Neem leaves contain glycosides, terpenoids and flavonoids as bioactives compounds responsible for anti-diabetic activity [10]. These findings suggest that yam based anti-diabetic formulation have a great potentiality as anti-hyperglycemic flour. The optimal formulation respects the recommended AMDR for macronutrients ensuring by this a nutritionally balanced adequate diet. It can offer several healths' beneficial do to the presence of bioactive compounds. The health benefits of the composite flour regarding antidiabetic activities are likely to result from the additive and synergistic effects of different kinds of phytochemicals able in maintaining ideal blood glucose levels, achieving optimal blood lipid levels, reducing the risk for diabetic complications, and maintaining healthy body weight through a balanced diet. Therefore, it can be used in managing diabetes by preparing adequate anti-hyperglycemic food with flours blended according to the percentage of ingredients stipulated in the optimal formula.

Conclusion

Yam based composite flour produced from *D. schimperiana*, soybean, cinnamon and neem leaves using optimal formula has a great potentiality as anti-diabetic flour as it can satisfies the recommended AMDR for macronutrients according to reference organizations ensuring a balanced diet. It contains bioactive compounds with scientific based evidence of maintaining ideal blood glucose levels, achieving optimal blood lipid levels, reducing the risk for diabetic complications. Therefore, it can be used in diabetes management as nutraceutical.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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