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Original Paper

Phytochemical and pharmacological reports of the hypoglycemic activity of the *Moringa oleifera* extracts

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Abstract

Moringa oleifera is an arboreal plant belonging to the family Moringaceae distributed in tropical areas and has gained enormous attention in the last decades. This research is a review on the association between aqueous extracts of *M. oleifera* leaves and diabetes mellitus and understanding its pharmacological functions and underlying mechanisms. The research refinement demonstrated the pharmaceutical potential of *M. oleifera* and its phytochemicals, given its antidiabetic effect. The prospective analysis showed the amount of application within IPC A61K in health area. The secondary metabolites present in *M. oleifera*, glucosinolates, flavonoids, and phenolic compounds may be responsible, in part, for the disease control hypoglycemic actions. Glucosinolates, when metabolized by salivary enzymes, give rise to sulforaphanes that act in preventing type 2 diabetes and in reducing insulin resistance. Flavonoids interact with intestinal enzymes by modifying carbohydrate metabolism by regulating glycemic levels, in addition to increasing insulin sensitivity. Phenolic compounds increase the expression of glucose transporters (GLUT4) and reduce the synthesis of fatty acids and cholesterol, contributing to the reduction of glucose resistance and blood sugar control. *Moringa oleifera* can be used as complementary therapy of the type-2 diabetes.

Key words: diabetes, hypoglycemic activity, *Moringa oleifera,* phytochemicals, technological prospecting.

Resumo

Moringa oleífera Lam. é uma planta arbórea pertencente à família Moringaceae distribuída em áreas tropicais e que tem ganhado enorme atenção nas últimas décadas. Esta pesquisa é uma revisão sobre a associação entre extratos aquosos de folhas de *M. oleifera* e diabetes mellitus e compreender suas funções farmacológicas e mecanismos subjacentes. O refinamento da pesquisa demonstrou o potencial farmacêutico da *M. oleifera* e seus fitoquímicos, dado seu efeito antidiabético. A análise prospectiva mostrou a quantidade de aplicação dentro do IPC A61K na área da saúde. Os metabólitos secundários presentes em *M. oleifera*, glucosinolatos, flavonóides e compostos fenólicos podem ser responsáveis, em parte, pelas ações hipoglicemiantes de controle da doença. Os glucosinolatos, quando metabolizados por enzimas salivares, dão origem a sulforafanos que atuam na prevenção do diabetes tipo 2 e na redução da resistência à insulina. Os flavonóides interagem com as enzimas intestinais modificando o metabolismo dos carboidratos, regulando os níveis glicêmicos, além de aumentar a sensibilidade à insulina. Os compostos fenólicos aumentam a expressão dos transportadores de glicose (GLUT4) e reduzem a síntese de ácidos graxos e colesterol, contribuindo para a redução da resistência à glicose e controle da glicemia. *Moringa oleifera* pode ser usada como terapia complementar do diabetes tipo 2.

Palavras-chave: diabetes, atividade hipoglicêmica, *Moringa oleifera*, fitoquímicos, prospecção tecnológica.

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Introduction

Plant species used as medicines usually occupy a predominant position in the results of botanical and ethnobotanical investigations of a determined region or ethnic group (Pasa *et al.*2010). The last two decades, chemical and pharmacological studies on bioactive substances derived from plants have had a major boost. The chemical and pharmacological researches aim to obtain new compounds with therapeutic and/or nutritional properties (Araújo-Leonídio *et al.* 2019).

Moringa oleifera Lam. is an arboreal plant distributed in tropical areas (Faizi *et al.* 1994; Bennett *et al.* 2003), stands out due to its wide diversity of features. This plant is grown worldwide, mainly in places with dry tropical climates (Estrada-Hernández *et al.* 2016). The species adapts to different climatic conditions (Falowo *et al.* 2018) and to semiarid soils (Lorenzi & Matos 2008; Olson & Fahey 2011), typical, for example, of the northeastern hinterland in semi-arid area from Brazil (Bakke *et al.* 2010; Gualberto *et al.* 2014).

Moringa oleifera has been extensively studied due to its chemical and biological properties. Hence, there is a strong appeal for its cultivation, use and rational consumption (Gualberto *et al.* 2014; Tshabalala *et al.* 2019).

This plant is fast growing, with varied applications in agriculture, medicine, livestock, and in biological systems including the human body (Ndubuaku *et al.* 2015). Its leaves, flowers, pods, and seeds have nutritional value, and all parts of the plant have medicinal value (Santos 2014). These parts are used in the treatment of diseases and in the production of drugs against bacteria, fungi, viruses, and other pathogens in humans (Falowo *et al.* 2018). Regarding nutrient composition, recent studies have shown that its leaves, seeds, and stems are rich in proteins, essential amino acids, minerals, vitamins, and other bioactive compounds (Moyo *et al.* 2012a,b; Valdez-Solana *et al.* 2015).

When studying this species, Ruiz *et al.* (2012) highlighted the following non-clinical and clinical pharmacological evidences: cardiac and circulatory stimulant, antitumor, antipyretic, antiepileptic, antispasmodic, diuretic, hepatoprotective. Other studies show improved vision, mental alertness, and bone strength. It has potential benefits in malnutrition and general weakness, also improving the health of lactating mothers, and menopause, depression, and osteoporosis outcomes (Kuete 2017). It is worth noting that its leaves were used to combat malnutrition, especially among babies (Moyo *et al.* 2011).

Studies of glucosinolates and isothiocyanates isolated *M. oleifera* show *in vitro* and preclinical studies antibacterial activity, antioxidant and anti-inflammatory response (Fahey *et al.* 2018; Jaja-Chimedza *et al.* 2017; Kim *et al.* 2017; Waterman *et al.* 2014). Other scientific studies using *M. oleifera* have also been shown to be an alternative in chronic diseases such as arthritis, cardiovascular disease, anti-hyperlipidemic, anti-ulcer, regulating blood glucose levels, anti-hyperglicemic, and type-2 diabetes (Kim *et al.* 2018; Kou *et al.* 2018; Gupta *et al.* 2012; John & Chellappa 2005). Many of these properties are related to antioxidant compounds such as flavonoids, phenolic compounds, carotenoids, tocopherols, glucosinolates and isothiocyanates which play an important role in controlling oxidative stress in chronic diseases (Saucedo-Pompa *et al.* 2018; Fahey *et al.* 2018; Jaja-Chimedza *et al.* 2017; Maizuwo *et al.* 2017).

In view of all the positive qualities mentioned above, *M. oleifera* has shown great prominence due to its numerous benefits. Therefore, it has attracted interest for research on its use, mainly on its efficiency for health. This article is a technological, phytochemical, and pharmacological survey on the hypoglycemic activity of aqueous extracts of *M. oleifera*.

Material and Methods

This is a prospective study conducted in patents and scientific databases from July to September 2020. First, the searches were carried out in follows patent databases: a) WIPO PatentScope; b) National Institute of Industrial Property (INPI); c) United States Patent and Trademark Office (USPTO); d) The Lens - Free & Open Patent and Scholarly Search; e) Espacenet; and f) Questel Orbit Intelligence. In each patent database, the term "*Moringa oleifera*" was used in combination with one of the following descriptors: antioxidant, antimicrobial, antibacterial, anti-inflammatory, anticancer, antifungal, hypertension, neuroprotective, antiepileptic, coronavirus, zebrafish, alkaloids, flavonoids, terpenoids, Alzheimer, diabetes, isothiocyanate, glucosinolates, oil and extraction methods. A thorough and detailed analysis of the patent documents "*Moringa oleifera*" AND "Diabetes" was carried out.

The temporal and quantitative search was refined and limited to the following fields: title, summary, and claims, using the Boolean operator AND to combine the terms. In the INPI patent database, the descriptors in Portuguese were used (Tab. 1).

The searches for scientific articles were conducted in the following databases: Science direct, Scielo, Nature, Springer, BMC, Wiley and Pubmed. These searches considered articles that had the descriptors in the title, abstract, and keywords fields, being published from 2000 to 2020. The same terms and Boolean operated used to perform patent searches were also used to perform scientific article searches. The temporal and quantitative search was refined and limited to the following fields: title and abstract. All quantitative research results were analyzed and no filters were performed to prioritize extract type, solvent type or particular type of plant part.

Results and Discussion

Prospecting resulted in 3,594 patents distributed in the search databases WIPO (610 patents), INPI (5 patents), USPTO (447 patents), The Lens (700 patents), Espacenet (765 patents), and Questel Orbit Intelligence (1,067 patents). The Brazilian database INPI presented only five patents, demonstrating that technology in the use of *M. oleifera* is not a priority in the country. The Questel Orbit Intelligence data platform provided 1,067 patents involving all the cited descriptors, and in all descriptors searched showing the greater number of results in relation the others. This validates the choice of this database for the analysis of studies. Correlating *M. oleifera* with diabetes resulted in 79 patents.

China is the country that produces the most patents (Fig. 1) of products with *M. oleifera*, which demonstrates the advance of research and the use of technology involving this plant, in addition to

Table 1 – Search for technological information with *Moringa oleifera* in different patent office and databases.

Descriptors	WIPO	INPI	USPTO	LENS	ESPACENET	Questel orbit
Moringa oleifera and antioxidant	51	1	35	59	57	94
Moringa oleifera and antimicrobial	48	0	24	8	12	24
Moringa oleifera and antibacterial	26	0	59	14	24	54
Moringa oleifera and anti-inflammatory	34	0	31	36	30	44
Moringa oleifera and anticancer	45	1	10	10	8	14
Moringa oleifera and antifungal	5	0	9	7	8	11
Moringa oleifera and antidiabetic	60	1	3	6	5	6
Moringa oleifera and hypertension	4	0	11	25	31	41
Moringa oleifera and neuroprotective	3	0	2	6	1	1
Moringa oleifera and anti-epileptic	0	0	0	1	1	1
Moringa oleifera and coronavirus	20	0	0	0	1	2
Moringa oleifera and zebrafish	20	0	0	0	0	0
Moringa oleifera and alkaloids	0	0	0	16	14	13
Moringa oleifera and flavonoids	0	0	7	13	37	26
Moringa oleifera and terpenoids	0	0	1	0	0	0
Moringa oleifera and alzheimer	2	0	9	18	12	13
Moringa oleifera and diabetes	46	0	1	66	42	78
Moringa oleifera and isothiocyanate	6	0	1	12	10	7
Moringa oleifera and glucosinolates	5	0	12	5	6	8
Moringa oleifera and oil	219	2	118	281	379	514
Moringa oleifera and extraction methods	16	0	114	117	87	116
Total	**610**	**5**	**447**	**700**	**765**	**1,067**

a wide knowledge based on Traditional Chinese Medicine and the culture of a people to make use of plants and other natural products to treat diseases. This stems from their traditional medicinal culture, which dates back to around 2,500 BC and is based on the use of plants with curative powers to treat diseases that affect society over time (Schenkel *et al.* 2003).

The chart shows an increase in publications between the years 2013 and 2018, with 108 documents published. However, this number decreased in the subsequent year, with only 4 publications. The year 2020, until the time of this research, presented 1 document. This fact may be due to the new COVID-19 pandemic, where attention is focused on the discovery of a vaccine. This chart helps in identifying possible target markets for this technology, and highlights the need for investments in research on *M. oleifera* in Brazil to conduct a double blind and randomized clinical study to prove its effectiveness and safety and then make its pharmacological properties better known for a possible commercialization of the plant in the country.

The search for diabetes and *Moringa oleifera* (Fig. 2) in the Questel Orbit® database resulted in 79 patents, among which 15 patents were assigned to A61K36 (medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, *e.g.*, traditional herbal medicines).

The 15 patents mentioned were: a functional food based on *M. oleifera* and chaya (*Cnidoscolus aconitifolius*), with biological properties, used as an aid in the control of diabetes and its complications, as well as for other types of circulatory and gastric disorders (MX2018004530); a composition containing *Moringa oleifera* for the treatment of hyperglycemia and hyperlipidemia (CN105833109); a technological method for oil extraction of *Moringa oleifera* seed (CN110856518); powders from *Anacardium occidentale*, *Moringa oleifera*, *Sclerocarya birrea*, and *Prosopis africana* extracts for the treatment of diabetes-related diseases (WO 02/94299); a pharmaceutical product obtained from *M. oleifera* for the treatment of diabetes-related diseases; a herbal medicine for the treatment of diabetes-related diseases (OA11761); a herbal formulation with high concentrations of polyphenols, having antioxidant, anti-inflammatory, antiviral, and microbial properties, for the control of diabetes and cholesterol and for the regulation of the immune system (WO2018/220428); synergistic herbal compositions combining extracts, fractions or phytochemicals, or mixtures derived from *Moringa oleifera*, *Murraya koenigii*, and *Curcuma longa* for the purpose of increasing lean body mass and

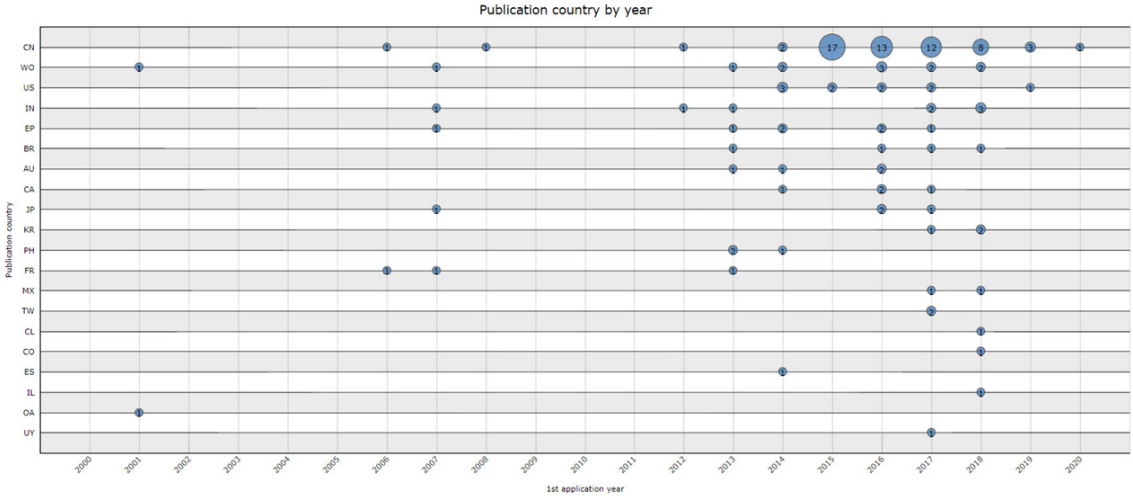

Figure 1 – Patent publications by countries per year between 2000 and 2020. Abbreviations by country. CN = China; WO = World; US = United States of America; IN = India; EP = Europe; BR = Brazil; AU = Austria; CA = Canada; JP = Japan; KR = Korea; PH = Phillipines; FR = France; MX = Mexico; TW = Taiwan; CL = Chile; CO = Colombia; ES = Spain; IL = Israel; OA = African Intellectual Property Organization; UY = Uruguay. Source: Questel Orbit Intelligence 2020.

brown adipose tissue (accelerating its conversion from white adipose tissue), and inhibiting excessive generation of advanced glycation products and related pathological conditions (WO2019/077629); a dietary supplement comprising 65–85 parts of a *M. oleifera* extract, 5–12 parts of hydroxytyrosol, 5–12 parts of oleuropein, and 5–11 parts of piperine, which may include a nutraceutical carrier with antioxidant and anti-inflammatory properties and can be used in the preparation of medicines and health products (CN107518399); a dietary supplement comprising 80–90 parts of *M. oleifera* extract and 10–20 parts of piperine, which may also comprise carriers and/or nutraceutical and/or pharmaceutical adjuvants to compose oral dosage forms, the supplement having excellent antioxidant and anti-inflammatory effects and possibility of use in the preparation of medicines and health products (CN107456470); a dietary supplement consisting of hydroxytyrosol, oleuropein, piperine, and moringa oil extracts, with antioxidant and anti-inflammatory effects, which can be used in the manufacture of medicines (CN107518399); a formulation based on medicinal herbs, comprising *M. oleifera*, (malunggay), *Capsicum frutescens*, (cayenne pepper), *Siling labuyo* (kolikot), and *Azadirachta indica* (neem), used to control diabetes, decrease hypertension, balance heart and prostate conditions, eliminate infection conditions, and improve the immune system (PH12013000032); a nutritional powder for the adjuvant treatment of diabetes, hypertension, cardiovascular disease, obesity, low immunity, and neoplasia, prepared from the leaves, flowers, fruits, seeds, and branches of *M. oleifera* through their respective spraying and mixing (CN1903232); a traditional Chinese medicine and a health product to balance metabolism to radically treat early type II diabetes (CN107802770).

Prospecting showed that the search for patents with the term diabetes was concentrated in the pharmaceutical area, followed by the areas of food chemistry, fine organic chemistry, polymers, biotechnology, analysis of biological materials, and chemical analysis, measurement and chemistry of materials. These data suggest that the genus *M. oleifera* can be applied in the medical-therapeutic area as a nutraceutical in complementary and alternative medicine. The number of Chinese patents demonstrated its potential use. However, in Brazil, ANVISA Resolution No. 1478, of June 3, 2019, prohibits the marketing, distribution, manufacturing, import and advertising of all foods containing *M. oleifera* due to the lack of scientific studies to prove the safety of *Moringa oleifera* in foods with therapeutic claims to treat cancer, depression, epilepsy, treatment of diabetes and cardiovascular disease. Nevertheless, data from the technological and scientific databases presented in this study demonstrate that *M. oleifera* has potential biological activities as an antioxidant and antidiabetic.

Therefore, it is also necessary to meet the requirements of ANVISA's public notice

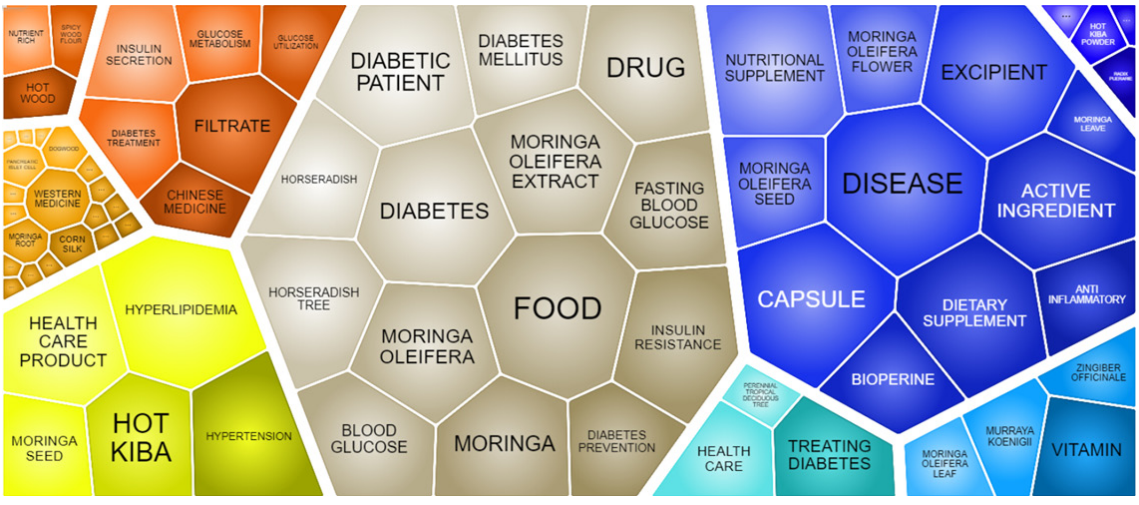

Figure 2 – Concepts grouped for the search term "*Moringa oleifera* and diabetes". Source: Questel Orbit Intelligence 2020.

07/2019, which establishes an exhaustive search to collect data and information on the safety of use of *M. oleifera* in food, including data on evidence of adverse reactions, safety of use based on randomized controlled clinical trials conducted from clinical trials on *M. oleifera*. Other evidence of the history of use should be demonstrated from the combination of scientific evidence, historical records, official commercial information on production and sales during a given period. A history of use based on research data on food acquisition or consumption and documents published by international authorities, which attest to the consumption of food, by a given population, for two or more generations, under the proposed conditions.

Regarding patent status, the majority (64.1%) of the patents granted are active, which denotes their relative importance. This shows that there are possible practical applications for these products, including the involvement of large companies and universities that enable their maintenance.

The incidence of diabetes is increasing in the developing world, with an increase in the number of diabetes patients in younger age groups. Therapeutic management of diabetes without side effects remains a challenge. In response, there is a growing interest in evaluating herbal remedies, which are seen as less toxic (Gupta *et al.* 2012), but like as medicines, the herbal medicines also have side effects and possible interaction with drugs when intake in combinations, then its necessary clinical trials to proven the efficacy, safety and low risks of side effects during combined treatments.

Diabetes mellitus (DM) is a chronic metabolic disease, in which insulin production ceases, increasing blood glucose levels (hyperglycemia). This condition remains for long periods and can affect organs, nerves, and blood vessels (Diabetes Brazilian Society 2019). Studies show that *M. oleifera* leaves oil are a rich source of secondary metabolites, revealing various therapeutic or medicinal properties, with great antidiabetic potential. This explains the strong appeal for its cultivation, use, and rational consumption (Gualberto *et al.* 2014). Lack of insulin at the metabolic level causes derangement of carbohydrates, fats, and proteins, eventually leading to a series of long-term microvascular and macrovascular complications (Divi *et al.* 2012).

In view of the rich phytochemical profile of *M. oleifera*, advances in biotechnological techniques have enabled the generation of new paths aimed at improving the overall commercial value of this plant (Gupta *et al.* 2018). Furthermore, the secondary metabolites contained therein are of high interest because of their medicinal value (Saralaya *et al.* 2010). The nutritional value of the plant stems from these numerous compounds being present in all its parts (Mansour *et al.* 2019). Researchers have identified more than 200 compounds in its leaves, stem, roots, and seeds, which can be classified in groups as hydrocarbon ketones, fatty acids, alcohols, aldehydes, terpenes, and others (Falowo *et al.* 2018). Research on phytochemical sources, which demonstrates a variety of secondary metabolites in the chemical composition of various parts of *M. oleifera* by gas chromatography coupled with mass spectrometry, identified the following constituents: carotenoids, polyphenols, alkaloids, isothiocyanates, tannins, saponins, and oxalates. Secondary metabolites were also detected: phenolic acids, glucosinolates, and flavonoids (Maghu *et al.* 2017). Stohs & Hartman (2015) also identified prominent phytochemicals: chlorogenic acid, rutin, kaempferol, myricetin, benzylamine, phenolic acids derivatives (gallic acid, 4-Isopropylbenzoic acid, and caffeic acid); nitriles glycosides: niaziminin and niazinin, while Faizi *et al.* (1994) identified thiocarbamate glycosides: niaziminin A and B with hypotensive activity.

Phytochemical investigations of *M. oleifera* revealed the presence of 4-o-acetyl-α-1-rhamnopyranosyloxy) benzyl isothiocyanate, 4-(-l-rhamnopyranosyloxy) benzyl isothiocyanate, niazimicin, pterygospermin, isothiocyanate α-benzyl, and 4-(rhamnopyranosyloxy) benzyl glucosinolates in different part of plant including leaves, flowers, seeds, pods (drumsticks), roots, bark, gum and oil (from seeds) (Fahey 2005). Bennett *et al.* (2003) carried out an exhaustive study investigating the phytochemical composition of *M. oleifera* and *M. stenopetala* using samples from Africa and Central America, using different plant parts (leaves, seeds, branches, stem bark, roots) and with identification by LC-MS and with confirmations by analytical standard techniques. This phytochemical study demonstrated the presence of different phytochemicals such as glucosinolates [4-(RL-rhamnopyranosyloxy)-benzylglucosinolate, benzyl glucosinolate, monoacetyl isomers of this glucosinolate], flavonoids glycoside (quercetin-3-O-glucoside, quercetin-3-O-(6'-malonyl-glucoside), kaempferol-3-O-glucoside, kaempferol-3-O-(6'-malonyl-

glucoside), quercetin 3-O-rhamnoglucoside), chlorogenic acid derivatives (3-caffeoylquinic acid and 5-caffeoylquinic acid) and phenolics (flavonoids, anthocyanins, proanthocyanidins, and cinnamates). The extensive literature documenting the diversity of glucosinolate applications in biomedicine indicates a promising potential for use in future areas of research in: 1. Antibiotics, antifungal, and antiviral agents; 2. Prevention of biofilms in medical implants, catheters, and industrial equipment; 3. Nutritional additives with anticancer properties; 4. Advanced food packaging technology to improve the shelf life of food products (Melrose 2019).

Considering these functionalities, the bioactivity of *M. oleifera* has gained enormous attention in the last decade, which has led to the increasing exploration and understanding of its pharmacological functions and underlying mechanisms (Biswas *et al.* 2012). When using Moringa parts to treat different human diseases. Sileshi *et al*. (2014) demonstrated *in vivo* pharmacological evidences using animal model for 70% ethanol extracts of *Moringa stenopetala* leaves. The 70% crude ethanol extract and ethanol liquid-liquid subfraction presented antihyperglycemic effect at a dose of 500 mg/kg with significant reduction of blood glucose levels at 2h (53.44%) and 4.5h (46.34%) in diabetic mice.

Vásquez-León *et al*. (2017) show that phytochemicals; glucosinolates, flavonoids, and phenolic acids; stand out with hypoglycemic effects, and there may be variations in the chemical composition of *M. oleifera* depending on the part of the plant, climate, and soil parameters.

Some phytochemical constituents found in the genus *M. oleifera* are considered responsible for hypoglycemic, delipidemic, antioxidant and anti-inflammatory activities, namely: flavonoids (quercetin, rutin, apigenin, kaempferol, similarin, apigetrin), phenolic acids (vanillic acid, gallic acid, salicylic acid), cinnamic acids (caffeic acid, ferulic acid, cinnamic acid), hydroxycinnamic acids (p-coumaric acid), hydroxycinnamic esters (chlorogenic acid), benzylamine-type alkaloids, moringine, in addition to glucosinolates and their active metabolites isothiocyanates, thiocyanates and nitriles (Coskun *et al.* 2005; Bour *et al.* 2005; Prabhakar & Doble 2011a; Amara *et al.* 2021; Faizi *et al.* 1994; Fuentes *et al.* 2015; Wang *et al.* 2017; Ghosh *et al.* 1935; Iffiú-Soltész *et al.* 2010). The aurantiamide acetate is an unusual dipeptide derivative inhibited the secretion TNFα and IL-2 from lipopolysaccharide-stimulated peripheral blood lymphocytes in culture (Sashidhara *et al.* 2009). Tab. S1 (available on supplementary material <https://doi.org/10.6084/m9.figshare.21350460.v1>) shows some of these substances and their pharmacological activities in *in vitro* or preclinical studies.

Glucosinolates are a diverse group of secondary plant metabolites that are particularly abundant in cruciferous vegetables as Brassicaceae and are a heterogeneous group of sulfur and nitrogen containing glycosidic secondary metabolites and water-soluble found in *M. oleifera* (Bennett *et al.* 2003; Tshabalala *et al.* 2019). However, these compounds are broken down during metabolism by plant enzymes known as myrosinases, or salivary enzymes that transform glucosinolates into isothiocyanates (ITCS), among them sulforaphane (SFN) (-)-[1-isothiocyanato-4-(methylsulfinyl)-butane], a natural compound that has antioxidant and anti-inflammatory properties, renoprotective and modulates the risk of type 2 diabetes (TD2) (Fig. 3) (Guerrero-Beltrán *et al.* 2010).

The findings of preclinical studies and in vitro studies in Tab. S1 (available on supplementary material <https://doi.org/10.6084/m9.figshare.21350460.v1>) show that the aqueous extracts of *Moringa oleifera* and active constituents present in the aqueous extracts show that *Moringa oleifera* are considered safe for nutritional or therapeutic consumption at doses ≤ 1,000 mg/kg/day (Awodele *et al.* 2012; Asare *et al.* 2012; Adedapo *et al.* 2009; Isitua & Ibeh 2013; Villarruel-López *et al.* 2018).

Moringa oleifera and its secondary metabolites can act in the control of hypoglycemia, diabetes mellitus and metabolic syndrome through some pharmacological pathways, which were cited below in the next paragraphs.

Moringa oleifera aqueous extract and polyphenolic compounds (Phenolic acids, hydroxycinnamic acids, hydroxycinnamic esters

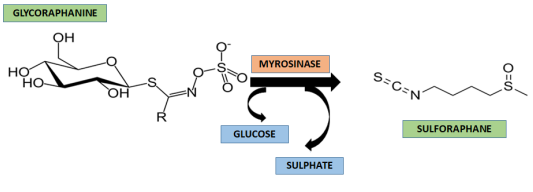

Figure 3 – Sulfuraphane (SFN) formation by enzymatic hydrolysis of glycoraphanine. Source: Adapted from Melrose 2019.

and flavonoids: silymarin, quercetin, apigenin, apigetrin) can exert antioxidant action on hepatocytes and pancreatic cells by scavenging free radicals, decreasing oxidative stress by reactive oxygen species (ROS). Alteration of the cellular antioxidant defense system occurs by increasing the activity of antioxidant enzymes (SOD, CAT, GST, GSHPx) and decreasing lipid peroxidation by reducing levels of (LPO, MDA, NO), resulting in β-cell protection of the pancreas against oxidative stress and decreasing the hyperglycemia generated by ROS (Ndong *et al.* 2007; Jaiswal *et al.* 2009, 2013; Coskun *et al.* 2005; Sharma *et al.* 2008; Wang *et al.* 2017; Zhang *et al.* 2020).

Moringa oleifera extract enriched with isothiocyanates and isothiocyanates significantly reduce inflammatory response which involves different signaling elements as cytokines (interleukins 1β and 6, IL-1β and IL-6, and TNF-α), nitric oxide (NO) produced by nitric oxide synthase (iNOS) during chronic inflammatory diseases. In addition, isothiocyanates, sufurophane and sufurophene upregulate the nuclear factor (erythroid-derived 2)-like 2 (NrF2), an important transcription factors, which activates multiple antioxidant and chemoprotective genes, including phase II detoxification enzymes such as NAD(P) H:quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO1) and glutathione S-transferase (GST) inhibiting inflammatory signaling (Waterman *et al.* 2014, 2015; Chen *et al.* 2018; Jaja-Chimedza *et al.* 2017; Cheng *et al.* 2019). The SFN mechanism (Fig. 4) protects cells against oxidative damage, inducing phase 2 detoxification enzymes. Its mechanism of action is by activation of the nuclear factor E2 mediated by the transcription factor nuclear erythroid type 2 (Nrf2) (Song *et al.* 2009; Cheng *et al.* 2019), which through breaks down from the complex forming together with protein 1 associated with Kelch type ECH (keap 1). Breaking out of the complex; SFN acts on the cell nucleus via the Antioxidant Response Element (ARE), modulating the gene expression of the antioxidant enzymes NADPH quinone oxidoreductase (NQO1), hemeoxygenase-1 (HO-1), and g-glutamylcysteine ligase (YGCL), also interacting with the mitogen-activated protein kinase (MAPK) pathway.

Sulfurophane also activates the transcription factor NrF2 during alcohol-induced hepatic steatosis and subsequently activate the heme oxygenase-1 promoting lowered oxidant stress by the decline in lipid peroxidation and decreased the accumulation of lipid in liver cells cultured in presence of ethanol (Zhou *et al.* 2014). Another important mechanism of isothiocyanates, sulfurophanes and sulfurophenes is related to anti-diabetic, anti-obesity activity, in the inhibition of adipogenesis. Isothiocyanates promote the reduction of insulin, leptin, resistin, cholesterol and hepatic glucose 6-phosphate (Waterman *et al.* 2015).

Reports by Choi *et al.* (2014) demonstrated sulfurophanes decreased the expression of peroxisome proliferator-activated receptor γ (PPARγ), CCAAT/enhancer binding protein α (C/EBPα) and leptin in the adipose tissue mice, in addition of increase adiponectin expression and subsequent attenuation of visceral adiposity, adipocyte hypertrophy, fat accumulation and triglyceride in the liver and serum total cholesterol.

The report by Eseberri *et al.* (2015) showed quercetin (0.5–10 μM) is able to inhibit the differentiation of preadipocytes into adipocytes by reducing C/EBP*β* gene expression, SREBP1 mature protein levels, and PPAR*γ* gene expression and reducing triacylglycerol (TGA), but it is concentrations greater than 10 μM are required to reduce TGA in the maturation phase of adipocytes. Report by Peng *et al.* (2018) has demonstrated that phenolic compounds, Chlorogenic acid (CGA), act strongly regulating the phase of differentiation of pre-adipocytes into adipocytes, by acting in the upregulated expression of the differentiation PPAR*γ*2 and decreased intracellular triacylglycerol synthesis. Chlorogenic acid also acts in the upregulated expression of the lipolysis but cannot act in the lipid synthesis. Report by Chen *et al.* 2018 demonstrates that Sulfurophene (SE) is

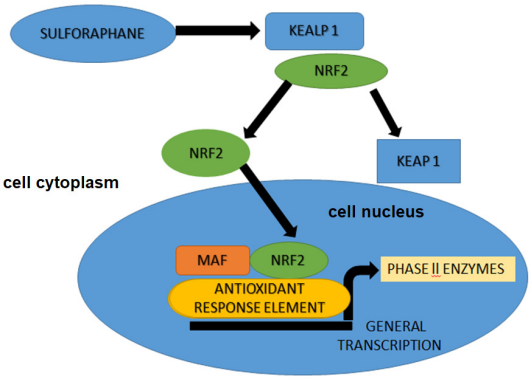

Figure 4 – Mechanism of action of sulfuraphane via Nrf2. Source: Adapted from Fuentes *et al.* 2015.

more effective than sulfurophane (SA) inhibiting adipogenesis in 3T3-L1 adipocytes by suppressing the PPARγ and CCAAT/enhancer-binding protein α (C/EBPα) reducing fat accumulation in 3T3-L1 adipocytes. SE inhibits adipocyte differentiation and may be an effective natural agent for preventing adipocyte hyperplasia and obesity. Sakuma *et al.* (2022) by the same mechanism demonstrated that sulfurophane may be a more potent adipocyte differentiation inhibitor than allyl isothiocyanate demonstrating a possible strategy for the prevention of obesity and metabolic syndrome.

Flavonoids are of interest because of their importance in carbohydrate metabolism and glycemic homeostasis. They act by interacting with intestinal enzymes, inhibiting α-glycosidase, whose function is to degrade starches and carbohydrates, giving rise to glucose. They also act on α-amylase, inhibiting starch metabolism (Cazarolli *et al.* 2008). According to Williamson (2013), the inhibition of Na^+-dependent glucose transporters (SGLT-1) impairs glucose transport. Valle (2016) compiled data from studies on flavonoids and diabetes. The author observed that this secondary metabolite increases insulin sensitivity, evidencing the role of flavonoids in glycemic control since deregulation of postprandial sugar levels is an important indicator of glycemic disorders involving carbohydrate metabolism. The study also showed that the flavonoid quercetin and the drug glibenclamide have similar action, reinforcing the possible hypoglycemic effect (Rodriguez de Sotillo & Hadley 2002).

There are two important ways of activating the GLUT4 glucose transporter, which are PI3K and PPARγ. The PPARγ pathway includes Grb, SOS, Ras, Raf, and MAP kinase. In turn, the PI3K pathway comprises PDK, Akb, protein kinase B, and other mediators. Some commercial drugs act by increasing the expression of PPARγ and GLUT4. Activation of PPARγ by its agonist or by PI3K increases glucose uptake in 3T3-L1 adipocytes. PI3K is a signaling molecule in the insulin cascade which induces glucose uptake by the cell via the activation of GLUT4 translocation (Prabhakar & Doble 2011b).

Phenolic acids significantly increase the expression of GLUT4 and PI3K, whereas chlorogenic and cinnamic acids significantly affect the expression of the PPARγ gene. These hydroxycinnamic acid derivatives (Fig. 5) act differently in the expression of the negative regulators of the insulin cascade. Thus, it can be assumed that hydroxycinnamic acid derivatives increase the uptake of 2-deoxy-d-glucose (2DG) mediated by PI3K-dependent translocation of GLUT4, while chlorogenic acid and cinnamic acid increase 2DG uptake through the translocation of GLUT4 via PPARγ. These secondary metabolites also significantly reduce the expression of fatty acid synthase (an enzyme that regulates the synthesis of fatty acids) and HMG-CoA reductase, which is a cholesterol-synthesis limiting enzyme. A reduction in the synthesis of fatty acids and cholesterol can reduce resistance to insulin, therefore being a strong contributor in the prevention of type 2 diabetes (Hemmerle *et al.* 1997; Karthikesan *et al.* 2010; Prabhakar & Doble 2011b).

Phenolic acids increase glucose uptake by activating PI3K or PPARγ. Caffeic, chlorogenic, and cinnamic acids reduce the expression of the enzymes HMGCoA reductase and FAS, which play an important role in complications secondary to hypoglycemia (Prabhakar & Doble 2011b).

The alkaloid moringinine (a benzylamine) was initially purified from M. oleifera root bark (Ghosh *et al.* 1935). The early study using an intraperitoneal treatment with *M. oleifera* extracts which contain the alkaloid moringinine has been shown to prevent hyperglycemia response in alloxan-induced diabetic rats. Benzylamine treatment resulted in a decrease in plasma free fatty acids in both fed and fasted conditions.

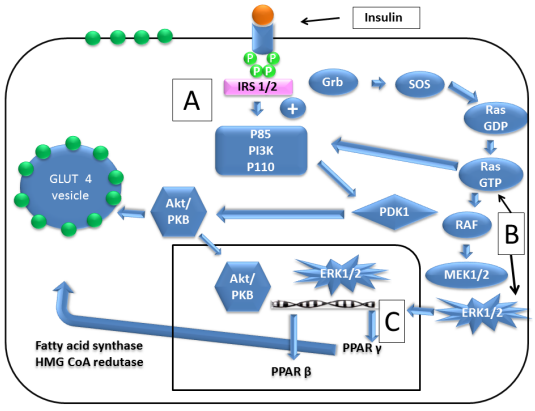

Figure 5 – Mechanism of action of hydroxycinnamic acid derivatives and commercial drugs. A = ferulic acid, eugenol, p-coumaric acid, cinnamic acid, caffeic acid and chlorogenic acid; B = chlorogenic acid, cinnamic acid; and C = thiazolidinedione; (+) denotes an increase and (-) denotes a decrease. Source: Adapted from Prabhakar & Doble 2011b.

Benzylamine treatment improved glucose tolerance as shown by the reduction of hyperglycemic response to intra-peritoneal glucose load (Bour *et al.* 2005). Preclinical study in mice rendered insulin-resistant when fed a High-Fat-Diet (HFD) and receiving or not benzylamine in their drinking water showed lower body weight gain and fasting blood glucose, lower total plasma cholesterol and hyperglycemic response to glucose load when compared to HFD control. In adipocytes, insulin-induced activation of glucose transport and inhibition of lipolysis remained unchanged (Iffiú-Soltész *et al.* 2010).

The controlled study with untreated diabetes type-2 patients examined the effect of *M. oleifera* addition to a standardized meal, taken after an overnight fast, affected the 1-h and 2-h post-prandial glucose levels (PPG), in relation to the standard meal alone oral glucose load. Only the *M. oleifera* leaf-supplemented meal elicited a lower response (-21%, P <0.01). Plasma insulin AUCs did not differ significantly between the two meals, suggesting that the hypoglycemic effect of *M. oleifera* leaf supplementation was not due to increased insulin secretion (William *et al.* 1993) (Tab. S2, available on supplementary material <https://doi.org/10.6084/m9.figshare.21350460.v1>).

A clinical study with a group of 60 diabetes mellitus type 2 patients. Patients in the experimental group were prescribed two *M. oleifera* leaf tablets/day, one after breakfast, the other after dinner for 90 days. In the control group, Blood glycated haemoglobin (HbA1c) and post-prandial glucose levels (PPG) progressed downwardly with time, but the change was not significant. In the experimental group, in contrast, HbA1c decreased by 0.4% point (from 7.8 ± 0.5 to 7.4 ± 0.6; P<0.01). PPG in the experimental group progressively decreased with treatment duration, by 9% after 30 days, 17% after 60 days, and 29% after 90 days (P<0.01), indicating that *M. oleifera* medication can induce with time better glucose tolerance (Ghiridhari *et al.* 2011) (Tab. S2, available on supplementary material <https://doi.org/10.6084/m9.figshare.21350460.v1>).

The hypoglycemic effect of *M. oleifera* leaf dietary consumption over a 40-day period in diabetes mellitus type 2 patients. The fasting plasma glucose levels and post-prandial glucose levels at the end of the protocol (final) were compared to baseline levels. They were significantly reduced in the experimental group (Fasting plasma glucose: FPG: -28%, P < 0.01; Post-prandial glucose, PPG: -26%, P < 0.05) (Kumari 2010) (Tab. S2, available on supplementary material <https://doi.org/10.6084/m9.figshare.21350460.v1>).

The combination of herbal medicine that have phenolic acids with hypoglycemic properties with thiazolidinedione and metformin allows an increase in the hypoglycemic effects of these commercialized drugs. This increase, in turn, allows a reduction in their dose and, consequently, in their side and adverse effects. The action of phenolic acids in 2DG uptake is time and dose-dependent (Prabhakar & Doble 2011b).

The pharmacological properties of *M. oleifera* are studied worldwide, resulting in a vast patent production. This was reinforced by this technological prospecting that led to numerous patents, enabling the identification of applications within IPC A61K (medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, *e.g.*, traditional herbal medicines), with the most varied biological functions. Noteworthy, 79 of these patents correlated with diabetes. The study demonstrated the application of the plant mainly in the pharmaceutical area and secondly in food chemistry.

Among the secondary metabolites present, glucosinolates, flavonoids, and phenolic compounds have antidiabetic potential and can control hyperglycemic. Glucosinolates, when metabolized by salivary enzymes, give rise to sulforaphanes that act in preventing type 2 diabetes and in reducing insulin resistance. Flavonoids interact with intestinal enzymes by modifying carbohydrate metabolism by regulating glycemic levels, in addition to increasing insulin sensitivity. Phenolic compounds increase the expression of glucose transporters (GLUT4) and reduce the synthesis of fatty acids and cholesterol, contributing to the reduction of glucose resistance and blood sugar control.

Moringa oleifera has a significant antihyperglycemic action and can control the overweight. The preclinical and clinical data presented in the scientific literature using extracts and powder of the *M. oleifera* plant has shown a reduction in hyperglycemia and type-2 diabetes mellitus. The *M. oleifera* has shown to be a promising plant for the preparation of extracts, teas and herbal products for health, especially to be used as complementary therapy for the treatment

of type-2 diabetes, combined or not with oral antihyperglycemic drugs and since that advised by doctors and other health professionals.

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