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PHARMACEUTICAL APPLICATIONS OF DIOSGENIN FOCUSING ON THE TREATMENT OF DIABETES MELLITUS: SCIENTIFIC AND TECHNOLOGICAL PROSPECT

APLICAÇÕES FARMACÊUTICAS DA DIOSGENINA COM FOCO NO TRATAMENTO DE DIABETES MELLITUS: PROSPECÇÃO CIENTÍFICA E TECNOLÓGICA

APLICACIONES FARMACÉUTICAS DE LA DIOSGENINA CON ENFOQUE EN EL TRATAMIENTO DE LA DIABETES MELLITUS: PROSPECCIÓN CIENTÍFICA Y TECNOLÓGICA

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ABSTRACT

Diabetes Mellitus (DM) is an endocrine disease associated with serious complications such as heart attack, stroke, kidney failure, lower limb amputation, vision loss, and nervous system damage. Diosgenin is a steroidal saponin with wide therapeutic applications. It is used in the treatment of hyperglycemia and hyperlipidemia due to its antioxidant, anti-inflammatory, and antiproliferative properties. The objective of this study was to conduct a systematic review of diosgenin and its pharmaceutical applications, focusing on the treatment of diabetes. The journal databases ScienceDirect, PubMed, and the Virtual Health Library were used, as well as the technological databases of the European Patent Office (EPO), World Intellectual Property Organization (WIPO), United States Patent and Trademark Office (USPTO), and the Brazilian National Institute of Industrial Property (INPI). The descriptors used were: Diosgenin, Diabetes, Hyperglycemia, Drug Delivery System, Nanotechnology, Nanosystems, Nanocarriers, Nanoparticles, and their associations in English, using the Boolean operators "AND" and "OR." Publications from 2012 to 2025 and patents from the period covered by each database up to July 2025 were selected. Analysis of the findings in the scientific databases demonstrated interest in the action of diosgenin in diabetes and the complications arising from this pathology. Technologically, diosgenin is used in formulations for medical purposes with action in diabetes; however, the number of patents is quite low compared to published articles. The studies with diosgenin are promising, since it has high pharmacological potential, enabling the execution of new research and technological innovations for the treatment of DM. Nanotechnology appears to be a potential way to improve the effectiveness of this saponin.

Keywords: Diosgenin. Diabetes. Drug Delivery Systems. Nanotechnology.

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RESUMO
Diabetes Mellitus (DM) é uma doença endócrina que está associada ao desenvolvimento de complicações graves, tais como: infarto, acidente vascular cerebral, insuficiência renal, amputação dos membros inferiores, perda de visão e danos no sistema nervoso. A Diosgenina é uma saponina esteroidal com vasta aplicação terapêutica, é utilizada no tratamento de hiperglicemia e hiperlipidemia por possuir propriedades antioxidantes, anti-inflamatória, antiproliferativa. O objetivo deste estudo foi realizar uma revisão sistemática sobre a Diosgenina e suas aplicações farmacêuticas, com foco no tratamento da Diabetes. Foram utilizadas as bases periódicas ScienceDirect, PubMed e Biblioteca Virtual em Saúde; e nas bases tecnológicas do European Patent Office (EPO), World Intellectual Property Organization (WIPO), United States Patentand Trademark Office (USPTO) e o banco de dados brasileiro Instituto Nacional de Propriedade Industrial (INPI). Os descritores utilizados foram: Diosgenina, Diabetes, Hiperglicemia, Sistema de Liberação de Fármacos, Nanotecnologia, Nanossistemas, Nanocarreadores, Nanopartículas e suas associações em inglês, utilizando-se os operadores booleanos “AND” e “OR” sendo selecionadas as publicações de 2012 a 2025 e patentes do período de abrangência de cada base até julho de 2025. A análise dos achados nas bases científicas demonstrou que existe interesse na ação da Diosgenina no Diabetes e sobre as complicações decorrentes dessa patologia. Em bases tecnológicas, a Diosgenina é utilizada para formulações com fins médicos com ação no Diabetes, entretanto o número de patentes é bastante reduzido em relação aos artigos publicados. Os estudos com Diosgenina são promissores, visto que esta apresenta um alto potencial farmacológico, possibilitando a execução de novas pesquisas e inovações tecnológicas para o tratamento do DM. A nanotecnologia vem como perspectiva para melhorar a efetividade dessa saponina.

Palavras-chave: Diosgenina. Diabetes. Sistemas de Liberação de Fármacos. Nanotecnologia.

RESUMEN
La Diabetes Mellitus (DM) es una enfermedad endocrina que está asociada al desarrollo de complicaciones graves, tales como: infarto, accidente cerebrovascular, insuficiencia renal, amputación de miembros inferiores, pérdida de la visión y daños en el sistema nervioso. La Diosgenina es una saponina esteroidal con amplia aplicación terapéutica; se utiliza en el tratamiento de la hiperglucemia y la hiperlipidemia por poseer propiedades antioxidantes, antiinflamatorias y antiproliferativas. El objetivo de este estudio fue realizar una revisión sistemática sobre la Diosgenina y sus aplicaciones farmacéuticas, con énfasis en el tratamiento de la Diabetes. Se utilizaron las bases de datos ScienceDirect, PubMed y la Biblioteca Virtual en Salud; y las bases tecnológicas del European Patent Office (EPO), World Intellectual Property Organization (WIPO), United States Patent and Trademark Office (USPTO) y la base de datos brasileña del Instituto Nacional de Propiedad Industrial (INPI). Los descriptores empleados fueron: Diosgenina, Diabetes, Hiperglucemia, Sistema de Liberación de Fármacos, Nanotecnología, Nanosistemas, Nanotransportadores, Nanopartículas y sus asociaciones en inglés, utilizando los operadores booleanos “AND” y “OR”. Se seleccionaron las publicaciones de 2012 a 2025 y las patentes del período de cobertura de cada base hasta julio de 2025. El análisis de los hallazgos en las bases científicas demostró que existe interés en la acción de la Diosgenina en la Diabetes y en las complicaciones derivadas de esta patología. En las bases tecnológicas, la Diosgenina se utiliza para formulaciones con fines médicos con acción sobre la Diabetes; sin embargo, el número de patentes es bastante reducido en comparación con los artículos publicados. Los

estudios con Diosgenina son prometedores, ya que esta presenta un alto potencial farmacológico, lo que permite la ejecución de nuevas investigaciones e innovaciones tecnológicas para el tratamiento de la DM. La nanotecnología surge como una perspectiva para mejorar la efectividad de esta saponina.

Palabras clave: Diosgenina. Diabetes. Sistemas de Liberación de Fármacos. Nanotecnología.

1 INTRODUCTION

Diabetes Mellitus (DM) is an endocrine pathology of great relevance as it is a prevalent public health problem worldwide and is associated with the development of serious complications in various parts of the body (KIASALARI *et al*., 2016; ANSARI. *et al*., 2025). Possible complications include acute myocardial infarction, stroke, kidney failure, lower limb amputation, vision loss, and nervous system damage that lead to increased mortality and a decreased quality of life for individuals (BISSINGER, 2017).

The stimulation of insulin in the uptake of glucose in adipose and muscle tissues is one of the main actions of the hormone, being essential in the storage of energy (JALDIN-FINCATI *et al*, 2017). This primary regulatory mechanism is mediated primarily by glucose transporter protein type 4 (GLUT4), a key player in glucose homeostasis and the removal of glucose from circulation. Maniruzzaman *et al*. (2017) characterizes Diabetes as a metabolic disorder resulting from malfunction of cells and/or the pancreas, which do not produce enough insulin, raising blood glucose levels. To this end, the American Diabetes Association (ADA) classifies the disease into three main types: (1) *Type I Diabetes Mellitus* (T1DM), commonly mediated by immunological mechanisms; (2) *Type II Diabetes Mellitus* (T2DM), associated with metabolic syndrome problems; (3) Gestational *Diabetes Mellitus* (GDM), due to glucose intolerance developed during pregnancy (KERNER; BRÜCKEL, 2014; ADA, 2020; VARGAS; VIVEK PODDER; ALICIA, 2020).

The International Diabetes Federation estimates that there are approximately 537 million adults aged between 20 and 79 years with diabetes, representing 10.5% of the world's population in this age group, which demonstrates an increase of 16% (74 million) compared to the 2019 estimate, with 6.7 million deaths directly attributed to this disease in 2021 alone ("IDF Diabetes Atlas", 2021). Due to its alarming growth, Gong (2016) emphasizes that early intervention in hyperglycemia should occur for the prevention and treatment of diabetes and its complications.

In addition, it is estimated that worldwide, patients with diabetes have a seven-year reduction in life expectancy compared to the general non-diabetic population, an effect that is closely linked to more severe diabetic outcomes, which include heart disease, limb amputations, end-stage renal disease, and blindness. (Tak Y. *et al.,* 2024)

Thus, DM is a risk factor for coronary artery disease, hypertension, hyperlipidemia, among other diseases, with cardiovascular diseases being the main cause of mortality and morbidity in patients with DM and, therefore, the treatment of hyperglycemia and insulin

resistance is crucial for the maintenance of life (BISSINGER, 2017; SATO; FUJITA; IEMITSU, 2017). Diabetes is associated with long-term damage to the macrovascular and microvascular systems. Although hyperglycemia-induced damage to the macrovascular system, including the coronary arteries and cerebrovascular arteries, is the leading cause of death in individuals with diabetes, hyperglycemia-induced damage to the microvascular network in the kidney, eyes, and nerves is far more common and has a substantial effect on mortality, which makes DM a serious global public health problem (GONG, 2016; KIASALARI *et al*., 2016). ; COLE & FLOREZ, 2020

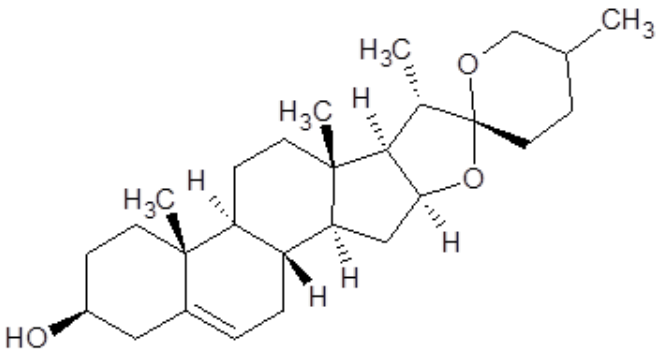
In this context, Diosgenin (DG), 3β-hydroxy-5-spirosthene, is a promising biomolecule, called "medicinal gold", for its valuable pharmacological properties in the treatment of hyperglycemia and hyperlipidemia. It has antioxidant, anti-inflammatory, and antiproliferative properties, as well as acting as a substrate for the synthesis of oral contraceptives, sex hormones, and other steroid compounds. Diosgenin is classified as a steroidal saponin, isolated from a variety of plants, such as *Trigonella foenum greaceum, Costusspeciosus, Polygonatum kingianum* , and several species of the genus *Dioscorea*; its chemical structure (Figure 1) is similar to that of asteroidal hormones (GHOSH *et al*., 2014; BADALZADEH; YAVARI; CHALABIANI, 2015; JESUS *et al*., 2016; LU *et al*., 2016; SUN *et al*., 2017; CIURA, al. 2017; GAN *et al*., 2020).

An important characteristic of Diosgenin is its low aqueous solubility, with a high partition coefficient (logP 5.7), resulting in low oral availability, limiting its use in pharmaceutical applications, making it necessary to improve its particularities and improve its bioavailability and consequently the therapeutic effect of DG (XU *et al*., 2012; GAN *et al*., 2020). Currently, nanotechnology has brought numerous advances and overcome challenges in the treatment of various disorders. Several factors, such as surface size, charge, and hydrophilicity, have received significant attention from nanotechnologists (SHAH *et al*., 2022).

In a recent review paper, HAN. *et al*., (2024), reported numerous studies describing the ability of some microbes to convert saponins into Diosgenin. Highlighting the possibility of co-fermentation with *Gibberella intermedia, Fusarium* (CPCC 400709) and *Septoria* (CPCC 400737) in the production of Diosgenin.

Figure 1

Chemical structure of diosgenin (3β-hydroxy-5-spirosthene)



Therefore, an alternative to improve low bioavailability parameters of diosgenin would be with the use of pharmaceutical nanotechnology in order to facilitate the transport of this metabolite in order to maintain the pharmacological potential for the clinical treatment of patients with DM.

This study aims to develop a systematic technological review on Diosgenin regarding the pathology of Diabetes, in order to describe the scientific production available for this compound and to analyze the number of patent filings through national and international innovation and technology banks.

2 METHODOLOGY

The systematic review was based on research of scientific articles that discussed diosgenin and its dissemination in pharmaceutical nanosystems in their directions to DM, as well as the patents registered in this regard. The research used the following descriptors as reference: Diosgenin or *diosgenin,* and its associations with, Diabetes or *diabetes*, Hyperglycemia or *hyperglycemia*, Nanotechnology or *nanotechnology*, Nanosystems or *nanosystems*, Nanocarrier or *nanocarrier*, Nanoparticles or *nanoparticles*, Drug Delivery System or *Drug Delivey System,* using the Boolean operators "AND" and "OR". The databases of journals used were Science Direct, PubMed and Virtual Health Library (VHL). The search for patent applications was carried out in the database of the Brazilian Patent and Trademark Office (BPTO), the *World Intellectual Property Organization* (WIPO), *the European Patent Office* (EPO), the *United States Patent and Trademark Office* (USPTO), Figure 2.

Figure 2

Flowchart of the scientific and technological databases used in the research of Diosgenin and its correlation with Diabetes

Scientific articles were selected based on the following inclusion criteria: articles published in English and Portuguese when applicable, with abstract and full text, which reported the pharmacological activities proposed by the study. Those articles that presented duplicity in the analysis of the associations were used only in one of the databases and excluded from the others. The time frame used was from January 2012 to July 2025 for the scientific databases and for the technological bases it was according to the period of coverage of each database until July 2025. The collected data were analyzed using the EndNote 20 software and Microsoft Excel 2019.

3 RESULTS AND DISCUSSION

Scientific and technological development serves as a basis for prospecting, as a fundamental tool to direct research, in addition to being able to directly influence an economy, a society or an industry, and scientific literature supports the knowledge of methodologies, in addition to representing a field of Research and Development (R&D) for technological innovations (MONTECCHI; RUSSIAN; LIU, 2013).

3.1 ARTICLE ANALYSIS

From the analysis of the bibliographic references, it is observed that in relation to all the terms used in the research, the *ScienceDirect* database has a larger collection of

publications related to the theme studied. In addition, there are many articles related to the descriptors: Diabetes, Hyperglycemia, Nanoparticles and Drug Delivery System in all the scientific databases explored.

Table 1

Number of articles in PubMed, ScienceDirect, BVS scientific databases from January 2012 to July 2025

Descriptors	**VHL**	**PubMed**	**Science Direct**	**Total**
Diosgenin or *diosgenin*	966	991	1.864	**3.821**
Diabetes or *diabetes*	382.756	457.632	583.934	**1.424.3**
Hyperglycemia or *hyperglycemia*	34.051	39.959	61.271	**135.281**
Diosgenin and diabetes or *diosgenin and diabetes*	2	85	566	**653**
Diosgenin and hyperglycemia or *diosgenin and hyperglycemia*	11	15	154	**180**
Diosgenin and diabetes and nanotechnology or *diosgeninand diabetes and nanotechnology*	0	1	43	**44**
Diosgenin and diabetes and nanosystems	0	0	4	**4**
Diosgenin *and diabetes and nanoccarriers*	0	0	0	**0**
Diosgenin and diabetes and nanoparticles	0	0	87	**87**
Diosgenin and *drug delivery system*	9	28	277	**314**
Total	**417.841**	**498.711**	**648.205**	**1.564.757**

In the search carried out with the association of the terms Diosgenin and Diabetes or *Diosgenin and Diabetes*, 566 (86.6%) articles were found in the ScienceDirect database, 85 (13.01%) in PubMed and 55 (8.4%) in the VHL, with a total of 695 articles (Table 1). With regard to Diosgenin or *diosgenin* , there is a significant and growing value of interest in this compound, as provided in the

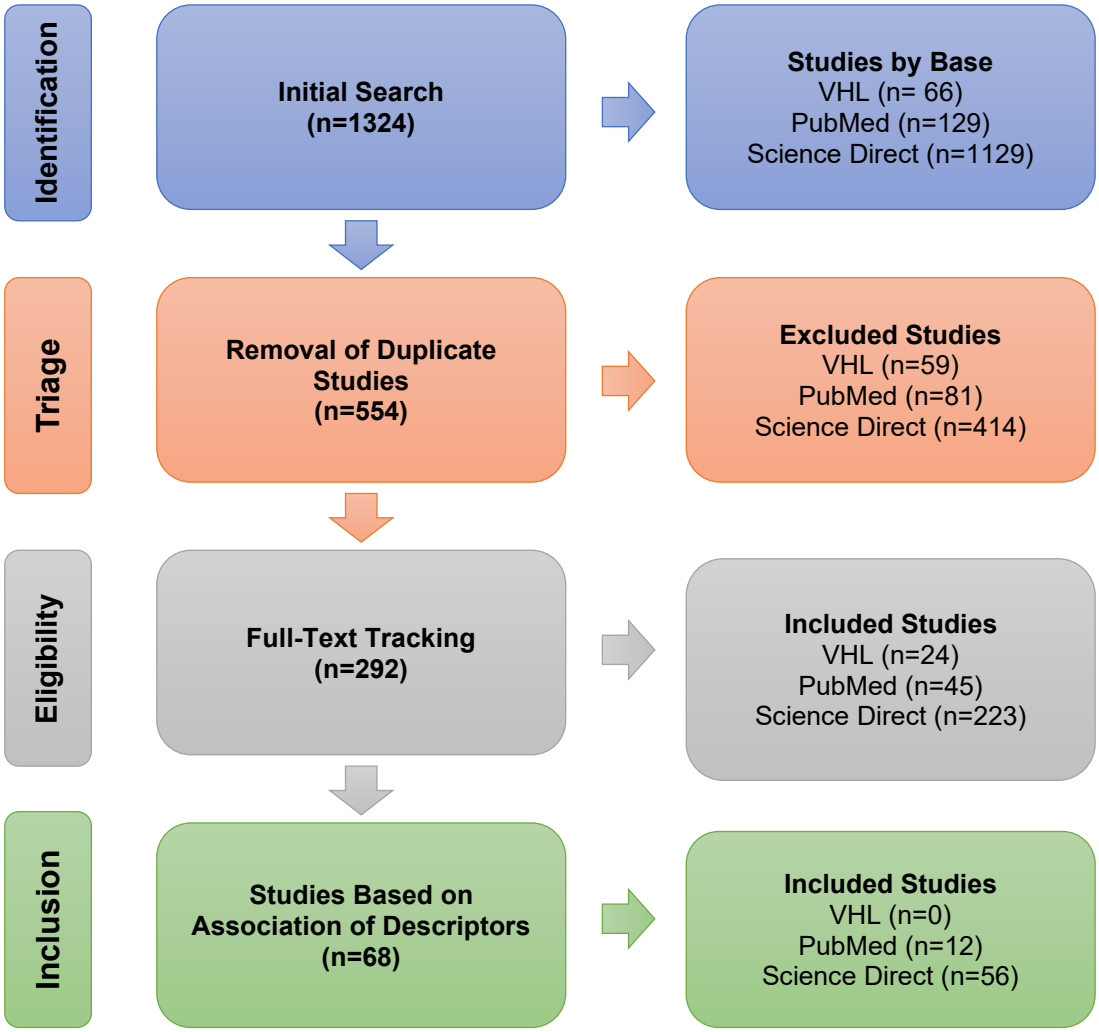
According to the chronological evolution, regarding the number of publications in scientific databases, it is observed that there is a growing increase in the number of articles on Diosgenin over the years, from the total of 3,817 articles in the period from January 2012 to July 2025, the year 2021 there was a greater number of publications with 596 articles, that

is, 15.6% of the total publications, which demonstrates the increase in interest in research on this compound.

After applying the criterion of exclusion of duplicate articles, each title and abstract were read in order to select and classify those that did in fact provide information about diosgenin and its applications in Diabetes. Figure 3 specifies the number of publications selected according to inclusion and exclusion criteria for the evaluation of published articles.

Figure 3

Flowchart for the evaluation of articles and application of inclusion and exclusion criteria in scientific databases, from January 2012 to July 2025 (n=1324)



After a reevaluation, 68 articles with theoretical and practical basis on Diabetes and its associations were obtained, of which the number of selected studies that entered the

systematic review was reduced to 15 (22.7%) articles. Table 2 shows the distribution of these articles.

Table 2

Publications on Diosgenin and application in Diabetes in ScienceDirect and PubMed databases, from January 2012 to July 2025

REFERENCES	TITLE	OBJECTIVES/MAIN RESULTS
Ghosh *et al*., 2014	Diosgenin from *Dioscoreab ulbifera*: Novel Hit for Treatment of Type II Diabetes with Inhibitory Activity against a-Amylaseand a-Glucosidase.	Isolate and evaluate the bioactive DG; present in *Discorea bulbifera.* The results indicate that DG inhibited *α-amylase* and *α-glucosidase,* in addition to having a non-competitive link demonstrated by a computational study. DG would be a strong candidate in the treatment of T2DM.
Kalailingam *et al*., 2014	Efficacy of natural diosgeninon cardiovascular risk: insulin secretion, and beta cells in streptozotocin (STZ)-induced diabeticrats.	To investigate the effects of GD on cardiovascular risk, insulin secretion, and pancreatic composition by electron microscopy of normal and diabetic rats. The results showed that fasting glucose levels and other biochemical dosages of diabetic streptozotocin (DM-STZ) rats normalized after 30 days of DG treatment.
Saravanan *et al*., 2014	Modulatory effects of diosgenin on attenuating the key enzymes activities of carbohydrate metabolism and glycogencontent in streptozotocin-induced diabetic rats	To evaluate the effects of DG on carbohydrate metabolism enzymes in serum, muscle and kidneys of rats with DM-STZ. DG showed antidiabetic activity, positively altered disordered carbohydrate metabolism, decreasing gluconeogenesis and increasing glycolysis, and finally decreasing hyperglycemia.

Sato *et al*., 2015	Acute administration of diosgenin or dioscorea improves hyperglycemia with increases muscular steroidogenesis in STZ-induced type 1 diabetic rats.	To evaluate acute administration of DG or *Dioscorea esculenta* in conversion of DG to dehydroepiandrosterone (DHEA) and improvement in hyperglycemia. The dose of DG and *Dioscorea esculenta* increased serum DHEA and considerably decreased the blood glucose level of rats with T1DM-STZ. DG acts on the acute reduction of blood glucose level and the restoration of the regulation of impaired muscle glucose metabolism in skeletal muscle in T1D.
Naibu *et al*., 2015	The Diosgeninreorganiseshyperglycaemiaanddistortedtissuelipid profile in high-fat diet-streptozotocin - induceddiabeticrats.	To investigate the effects of fenugreek DG on changes in plasma, liver, heart and brain lipid profile in DM-STZ rats and high-fat diet (HFD). DG reduced body weight gain, blood glucose, insulin, insulin resistance and also modulated lipid profile in plasma and tissues of diabetic and obese rats.
Kanchan *et al*., 2016	Renoprotective effect of diosgenin in streptozotocin induced diabetic rats.	To examine the protective effect of GD on kidney injury in an animal model of DM-STZ. DG treatment reduced oxidative stress, glycemia, lipid peroxidation, increase in endogenous antioxidants. Biomarkers suggestive of kidney damage have been normalized and confirmed by histopathological studies. Reduction of myeloperoxidase levels in groups treated with DG revealed its anti-inflammatory activity.

Kiasalari *et al*., 2016	Diosgen in ameliorates development of neuropathic pain in diabetic rats: Involvement ofoxidative stress and inflammation.	To study the nociceptive behavior of GD in diabetic rats and explore possible involvements in oxidative stress and inflammation. DG showed antinociceptive and antihyperalgesic activity, with reduction of oxidative stress and inflammation, potentiated the antioxidant defense system. Suggests GD as an adjunctive therapy for relief and management of diabetic neuropathic pain.
Hua *et al*., 2016	Diosgenin ameliorates gestational diabetes throug hinhibition of sterol regulatoryelement-binding protein-1.	To examine the effect and investigate the mechanism of DG in mutated rats that have similar symptoms of gestational *diabetes mellitus* in humans. DG reduced the content of thiobarbituric acid reactive substances, increased glutathione, superoxide dismutase, catalase, the expression of the transcription factor binding to the sterol regulatory element-1 (SREBP-1) and attenuated abnormal changes in lipid profiles. SREBP-1 may be the main target of DG to mediate its antidiabetic activity.
Pi *et al*., 2017	Combination of Morroniside and Diosgenin Prevents High Glucose-Induced Cardiomyocytes Apoptosis.	To investigate the protective effect of myocardium with Morroniside (Mor) from *Cornus officinalis*, Diosgenin (Dio) *from Dioscore aoposita* and in combination (M+D) in diabetic cardiomyopathy (DCM). Increased viability and inhibition of cell apoptosis, decreased levels of reactive oxygen species (ROS). M+D produced a greater protective effect on DCM.

Yan *et al*., 2017	Intake of total saponins and polysaccharides from *Polygonatumkingianum* affects the gut microbiota in diabetic rats.	Investigate *Polygona tumkingianum* on DM based on gut microbiota regulation and determine DG concentration. Administration of *Polygona tumkingianum preparations* prevented an increase in fasting blood glucose, had a significant improvement in the gut microbiota of rats with DM-STZ could prevent DM2
Wu *et al*., 2018	Diosgen in glucoside protects Against myocardial injury in diabetic mice by inhibiting RIP140 signaling.	To investigate the protective efficacy of DG glycoside against myocardial injury in type 2 diabetic mice and its mechanism of molecular action. Long-term treatment with GD improved glucose tolerance, reduced the production of IL-1b, IL-6 and TNF-a and decreased serum levels of indicators of cardiac injury, also inhibited RIP140 signaling, revealing a new mechanism of GD.
Leng *et al*., 2020	Neuroprotective effect of diosgenin in a mouse model of diabetic peripheral neuropathy involves the Nrf2/HO-1 pathway.	To evaluate the antioxidant effects of diosgenin in diabetic mice. DG decreased blood glucose levels and increased body weight of diabetic mice, improved behavioral and morphological changes in diabetic peripheral neuropathy, reducing oxidative stress.
Oyelaja *et al*., 2020	Protective role of diosgenin Against hyperglycaemia-mediated cerebral ischemic brain injury in zebrafish model oftype II *Diabetes Mellitus*.	To investigate the glucose reduction and neuroprotective capacity of Diosgenin (DG) in relation to hyperglycemia-induced brain injury in zebrafish models of type 2 diabetes. GD reduced blood glucose concentration and showed improved catalytic activity. Proteroor activity was visible from the suppressed inflammation. Potential as an anti-inflammatory, antidiabetic, and neuroprotective agent.
Mahmoudi *et al*., 2021	Diosgenin Attenuates Cognitive Impairment in Streptozotocin-Induced Diabetic Rats: Underlying Mechanisms	To study the effect of diosgenin on improved learning and memory decline in streptozotocin (STZ)-powered rats with type 1 diabetes.

		The administration of diosgenin to the group of diabetic rats reduced functional performance deficits, in addition to attenuating the activity of acetylcholinesterase. Together, diosgenin was able to improve cognitive deficits in diabetic animals with STZ, presenting itself as a neuroprotective potential.
Wang *et al*., 2022	Diosgenin protects Against podocyte injury in early phase of diabetic nephropathy through regulating SIRT6	To evaluate the effects of diosgenin involved in the improvement of podocyte damage in the early stage of diabetic nephropathy (DN). The group of animals that received high dose diosgenin (DH) had abnormal changes alleviated compared to the low dose (DL) group in the first part of the experiment. In the second part of the experiment, the effect of the DH group was positive for both SIRT6 groups. Diosgenin may protect against podocytic injury in the early stages of diabetic nephropathy by regulating SIRT6.
Nie *et al*., 2023	Diosgenin attenuates non-alcoholic fatty liver disease in type 2 diabetes through regulating SIRT6-related fatty acid uptake	This study aims to investigate the mechanism of how diosgenin alleviates non-alcoholic fatty liver disease in T2DM and the relationship with the SIRT6 gene. The results of the in vivo study indicated that diosgenin protected against lipid accumulation, oxidative stress, cell injury, and mild liver inflammation in db/db mice and regulated SIRT6 and fatty acid transporter expression.
Tak Y. *et al*. 2024	Fenugreek derived diosgenin as an emerging source for diabetic therapy.	In this review article, the importance of fenugreek, also known as Bird's Foot and Fenugreek, a member of the Fabaceae family, originated in India and North Africa, as a promising source for the production of Diosgenin, was demonstrated. The authors also highlighted the importance of consuming the plant and its seeds as a new nutraceutical in the market that promises to cure diabetes in particular.

Han, S. *et al*. 2024	Screening and Selection of a New Medium and Culture Conditions for Diosgenin Production via Microbial Biocatalysis of SYt1.	The study highlights the production of diosgenin using microbial consortium systems.
Seyed M. 2025	Diosgenin-based nanomedicine: Advances in formulation strategies, biomedical applications, and translational challenges, Nano-Structures & Nano-Objects,	This review work examined a number of studies on the application of Diosgenin in the preparation of nanomaterials, as well as the use of nanomaterials for the production, application or administration of Diosgenin itself.
Shanshan J. *et al.*, 2025	Modulating the gut microbiota and inflammation is involved in the effect of diosgenin against diabetic nephropathy in rat.	In this study, the authors investigated the dual therapeutic potential of diosgenin: in modulating the gut-kidney axis and inflammasome activity, to verify the potential use of the molecule in the prevention of diabetic nephropathy, a serious complication of diabetes, which has been increasingly associated with dysbiosis of the gut microbiota and inflammatory dysregulation.
Ansari P. *et al*., 2025	Therapeutic Potential of Medicinal Plants and Their Phytoconstituents in Diabetes, Cancer, Infections, Cardiovascular Diseases, Inflammation and Gastrointestinal Disorders	This review showed 35 most commonly reported plants for the treatment of these major disorders, with particular emphasis on their traditional uses, phytoconstituent content, pharmacological properties, and modes of action.

Diosgenin has a wide practical application, as it has a broad pharmacological profile and is used in the treatment of different pathologies and/or associated complications. In the work developed by Ghosh *et al*. (2014) by isolating the DG present in *Dioscorea bulbifera* it was possible to prove the inhibition of α-amylase and α-glucosidase in the porcine and murine models, respectively, in addition to demonstrating the chemical bonds by computational study.

Yan *et al*. (2017) in their studies proved significant improvement in the gut microbiota and reduction of fasting glucose in rats with Streptozotocin-induced Diabetes (DM-STZ), from the oral administration of *Polygonatum kingianum* preparations with expressive values of DG in the composition. These works support the promises for diosgenin to be an alternative for the prevention and treatment of *type 2* diabetes mellitus.

Regarding the treatment of pathologies associated with DM, Wang *et al*. (2022) demonstrated in their study the positive effect of the use of DG under the treatment of Diabetic Nephropathy (DN), indicating that high doses of diosgenin can protect rats with DM against injury to podocytes regulated by SIRT6, promoted by the reduction in lipid accumulation in these animals. This effect was previously proven by Kanchan *et al*. (2016), where they observed that DM-STZ rats treated with DG had reduced oxidative stress, lipid peroxidation, myeloperoxidase levels, and increased levels of endogenous antioxidants, in addition to a significant reduction in blood glucose when they used the 20 mg/kg dose of DG, and thus concluded protective activity of the kidneys, mainly by reducing blood glucose.

Regarding the neuroprotective activity in diabetic rats, Kiasalari *et al*. (2016) pointed out that from behavioral studies of nociception, DG demonstrated antinociceptive and anti-hyperalgesia activity through suppression in the production of IL-1β (interleukin that directly participates in the pathogenesis of nerve degeneration and pain transmission), through the reduction of oxidative stress and inflammation. Mahmoudi *et al*. (2021) administering doses of DG to rats with type 1 DM-STZ orally (40 mg/kg/day) for 5 weeks, observed improvements in the cognitive deficit of these animals, due to the potential neuroprotective action of this substance, in addition to the improvement of oxidative stress, inflammation, glucose and a possible improvement in cholinergic function.

Leng *et al*. (2020) studied mice with diabetic peripheral neuropathy and explained that the Nrf2 protein is a critical factor of the antioxidant defense system and promotes the expression of detoxification enzymes. In the presence of high glucose content, Nrf2 levels decreased and treatment with DG increased Nrf2 expression, proving to be effective in potentiating the antioxidant defense system.

DG showed a cardioprotective effect in the study by Pi *et al*. (2017) from a model of myocardial injury induced by high glucose which characterizes diabetic cardiomyopathy (DCM), GD was extracted from *Dioscorea opositae* associated with *Morroniside* (Mor) obtained from *Cornus officinalis*, together they increased cell viability, inhibited apoptosis through the suppression of the expression of Bax proteins with an increase in Bcl-2, thus

regulating the balance of Bcl-2 and Bax, an anti-apoptotic mechanism; in addition to decreasing the levels of reactive oxygen species (ROS), and thus, the combination of *Morroniside* and *D. oposita* acted in synergism and produced a greater protective effect on DCM, when compared in isolation.

Still on cardioprotective activity, Wu *et al*. (2018) found that long-term treatment with GD decreased serum levels of creatine kinase and lactate dehydrogenase (indicators of cardiac injury), in which it also revealed a novel mechanism of GD's anti-inflammatory effect against myocardial injury, through the inhibition of RIP140 signaling pathways (plays an important role in the expression of pro-inflammatory cytokines).

This steroidal saponin acts by regulating blood glucose, through insulin and glucagon signaling, in DM1, DM2 and DMG, as its target tissues are the pancreas, liver and skeletal muscle (HUA *et al*., 2016; SATO; FUJITA; IEMITSU, 2014). Kalailingam *et al*. (2014) in studies with DM-STZ rats, proved with tests that glycemia, glycated hemoglobin, total cholesterol, LDL (low-density lipoprotein), HDL (high-density lipoprotein), glucose-6-phosphatase and the number of β cells of the pancreas were restored to reference values after 30 days of treatment with GD at the daily oral dose of 10 mg/kg.

Saravanan *et al*. (2014) in their study also demonstrated the modulatory effects of GD in attenuating the altered activities of key carbohydrate enzymes in the kidneys and muscles of rats with DM-STZ, where the values were significantly reverted to levels close to normal, being compared with glibenclamide (standard drug for oral hypoglycemia).

In the research conducted by Naidu *et al*. (2017) with DM-STZ rats with a high-fat diet during the same period of treatment with DG, the animals showed a reduction in body weight gain, blood glucose, insulin, insulin resistance, in addition to having a lipid profile modulated in plasma and tissues, but at a dose of 60 mg/kg/day of Diosgenin.

In studies by Oyelaja *et al*. (2020) with DM-STZ zebrafish, the animals showed a significant reduction in blood glucose and body weight loss after 28 days of treatment with DG at doses of 20 and 40mg/kg. The decrease in blood glucose levels was induced due to the inhibitory effect on α-glucosidase, already proven in the studies of Ghosh *et al*. (2014). Oyelaja *et al*. (2020) pointed out that changes in body weight would explain the possibility of GD promoting muscle tissue repair, causing changes in gluconeogenesis, and increasing insulin production.

Sato, Fujita, and Lemitsu (2017) demonstrated that doses of DG and *Dioscorea esculenta* increased serum dehydroepiandrosterone (DHEA) and improved hyperglycemia in

rats with T1D-STZ. The reduction in glycemic levels was induced by DHEA through the activation of skeletal muscle tissue signals, and was associated with an increase in muscle levels of dehydrotestosterone (DHT) and GLUT4 translocation. And so DG is a drug candidate to act on the acute reduction of blood glucose level and the restoration of the regulation of impaired muscle glucose metabolism in skeletal muscle in T1D.

Studies have shown that diosgenin does not cause systemic toxicity or genotoxicity (OKAWARA *et al*., 2014; CHEN *et al*., 2012). And according to studies presented in this work, it is concluded that Diosgenin has anti-inflammatory, antioxidant, antinociceptive, anti-hyperalgesia activity, acts on the intestinal microbiota, regulates skeletal muscle glucose metabolism, ROS markers and insulin resistance, and thus promotes a protective effect on important organs such as the heart, brain, kidneys.

Vinotha *et al*. (2019) report the fabrication of nanoparticles using diosgenin extracted from *Costusigneus* leaf, the antidiabetic action was proven through α-amylase and α-glucosidase inhibition assays. In addition, the antidiabetic action of these nanoparticles proved to be more effective than the extract of *Costusigneus leaves.*

Nie *et al*. (2023) evidenced in its study that more than 70% of patients with type 2 diabetes (DM2) suffer concomitantly from non-alcoholic fatty liver disease. Studies have already shown that SIRT6 could protect hepatocytes from steatosis by promoting fatty acid β-oxidation, inhibiting triglyceride (TG) synthesis and relieving oxidative stress. It was concluded that diosgenin can attenuate nonalcoholic fatty liver disease in T2DM through regulation of SIRT6-related fatty acid uptake.

From the analysis of the scientific databases and in view of the above, it is verified that there is a growing interest in the use of diosgenin to prevent and treat diabetes, and after investigating the 68 articles defined by the inclusion/exclusion criteria, only one study was found that directed the use of nanostructured pharmaceutical forms containing diosgenin for the treatment of *Diabetes Mellitus*

making it necessary and promising to study this steroidal sapogenin in nanostructured form.

3.2 PATENTS

Through patents, it is possible to analyze information from countries, laboratories, companies and universities, in addition to allowing the identification of relevant technologies, technological routes, innovations, processes, products, research, development and

innovation, through the dissemination of information and its applicability in many other technical fields, in addition to enabling the development of new products, forecasting and technology transfer (MONTECCHI; RUSSIAN; LIU, 2013; SHARMA; TRIPATHI, 2017). And in this way, it represents a promising tool for the treatment of diseases that affect the population on a global scale, by fostering research that enables the improvement of people's quality of life.

The technological evaluation was carried out in specialized databases, including patents filed according to the period of coverage of each of the databases, thus, INPI from 1992, WIPO since 1996, USPTO from 1976 and EPO from 1836, to July 2022. The selection of patents was based on inclusion criteria: patents published in English or Portuguese, which presented the descriptors: Diosgenin, Diabetes, Hyperglycemia, Nanotechnology, Nanosystems, Nanocarriers, Nanoparticles, Drug delivery system and their associations in the title and abstract.

The results for the term Diosgenina, of the total of 10,402 filings, were as follows: 5 (0.05%), 3,532 (33.96%), 2,010 (19.32%) and 4,855 (46.67%) for the patent application filed in the databases of the INPI, WIPO, USPTO and EPO, respectively. In the EPO database, patent filings were found for the terms "*diosgenin and diabetes*", "*diosgenin and nanoparticles*", which totaled 937 (0.2%) and 85 (0.01%) patents, respectively. For the term "*diosgenin and diabetes and nanocarriers"* and there was no filing, out of the total of 3,536 patents of the descriptors in associations. Table 3 presents the data for the analysis of descriptors, considering the number of patent applications filed per database.

Table 3

Number of patents filed in the INPI, WIPO, USPTO, and EPO technological databases by descriptors for the period covered by each database until July 2022

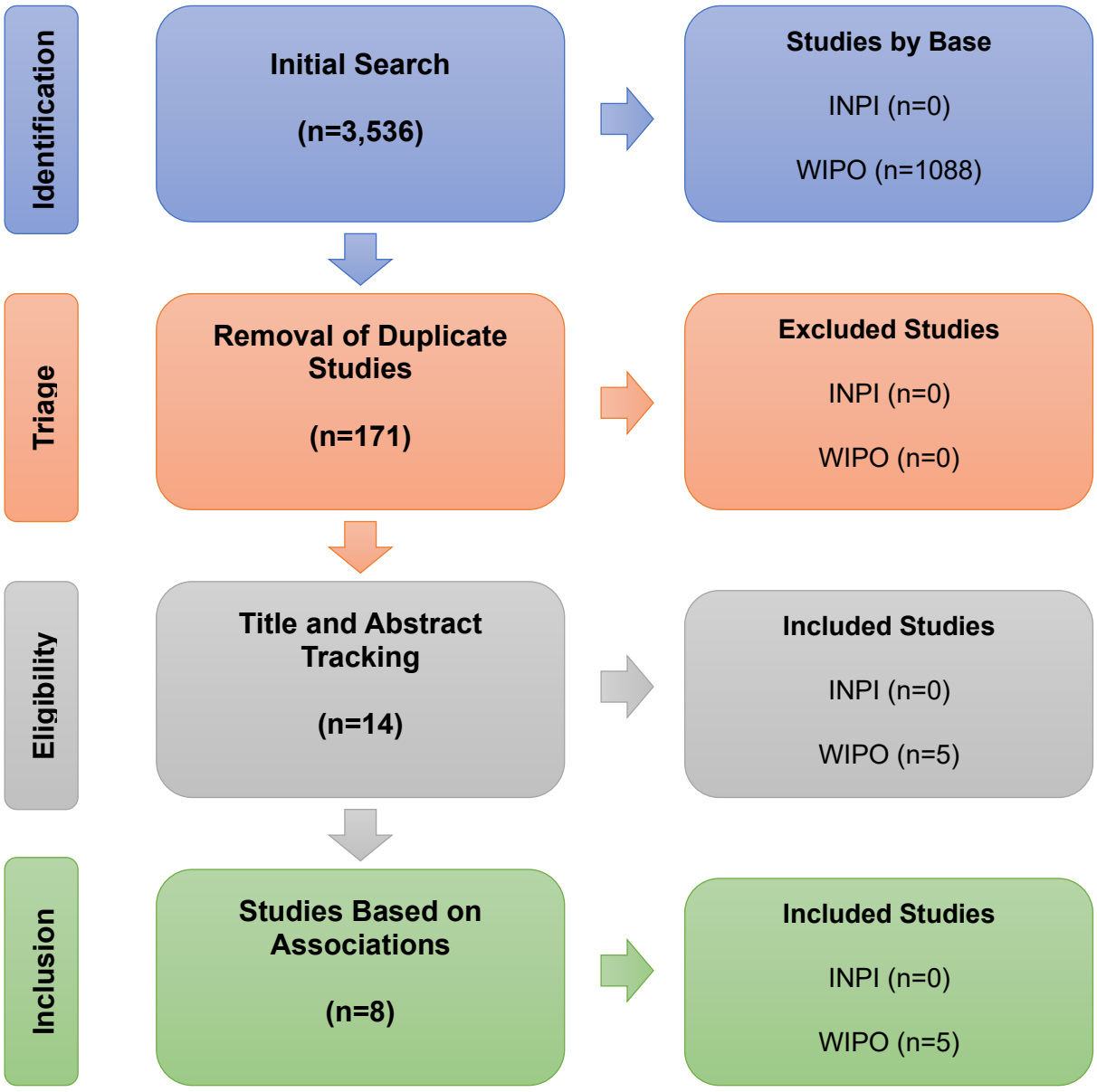
Descriptors	**INPI**	**WIPO**	**USPTO**	**EPO**	**Total**
Diosgenin or *diosgenin*	5	3.532	2.010	4.855	**10.402**
Diabetes or *diabetes*	1.812	690.495	313.249	398.299	**1.403.855**
Hyperglycemia or *hyperglycemia*	205	55.688	43.731	55.688	**155.312**
Diosgenin and diabetes or *diosgeninand diabetes*	0	930	519	937	**2.386**
Diosgenin and hyperglycemia or *diosgeninandhyperglycemia*	0	149	108	222	**479**

Diosgenin and diabetes nanotechnology or diosgeninand *diabetes andnanotechnology*	0	9	7	6	**22**
Diosgenin and diabetes nanosystems or *diosgeninand diabetes andnanosystems*	0	0	4	4	**8**
Diosgenin and diabetes and nanocarriers or *diosgeninand diabetes andnanoccarriers*	0	0	0	0	**0**
Diosgenin and diabetes and nanoparticles or *diosgeninand diabetes andnanoparticles*	0	0	182	85	**267**
Diosgenin and Drug Delivery System or *Diosgeninand Drug Delivery System*	0	0	353	21	**374**
Total	**2.022**	**750.803**	**360.163**	**460.117**	**1.573.105**

Based on the criteria for exclusion of duplicate patents, each title and abstract were read in order to select and classify those that provided information about diosgenin and its applications in diabetes, as well as how to convey this metabolite. Figure 4 specifies the number of publications selected according to inclusion and exclusion criteria for evaluation of filed patents.

Figure 4

Patent evaluation flowchart, and application of inclusion and exclusion criteria in scientific databases, in the period covered until July 2025 (n=626)

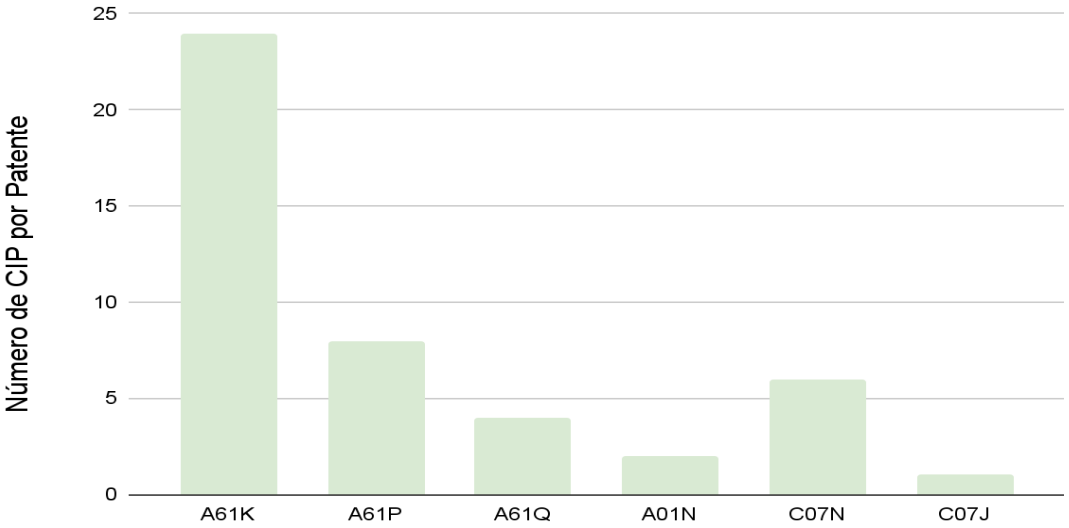


By analyzing each patent of Diosgenin and associations, it was possible that EPO presented a significant value in the number of patents in all associations, but in reading the title, abstract and body of the text it was possible to see that there is an analogy of the descriptor Diosgenin to the terms estrogen, cholesterol and dehydroepiandrosterone (DHEA), due to the similarity in chemical and/or functional characteristics. Another important observation is that DG is a metabolite present in several species, in addition to being a chemical derivative and precursor of other substances.

The International Patent Classification (CIP) represents the set of knowledge that can be considered specific to the field of invention patents, arranged in eight sections, which are at the highest level of hierarchy juxtaposed from A to H; comprises 21 subsections, 120 classes, 628 subclasses and 69,000 groups (WIPO, 2017). Thus, the 8 patents filed for Diosgenin were analyzed, which proved the allegation of activity in Diabetes and the way this compound was transmitted. According to the CIP, it was observed that section A (human needs) is the most deposited, followed by section C (chemical and metallurgical) Figure 5.

Figure 5

Patents filed in the technological databases by class and subclass according to the international classification code



While class A61 refers to products of medical or veterinary science and hygiene, where subclass A61K deals with preparations for medical, dental or hygienic purposes, A61P addresses specific therapeutic activity of chemical compounds or medicinal preparations, A61Q contains products for specific use of cosmetics or similar preparations for personal hygiene, A01N deals with agriculture, forestry, animal husbandry, hunting and fishing; class C07 refers to substances available in the area of organic chemistry, where C07J deals with steroids and C07H with sugars, derivatives, nucleosides, nucleotides and nucleic acids.

Of the eight patents listed in Table 4, six of them reported on Diosgenin through different methods of obtaining and the pharmacological actions described were: anti-inflammatory, analgesic, regulatory and insulin potentiating action, control of glucose

tolerance, action on hyperglycemia by reducing blood glucose levels. In this way, the DG could act in the prevention and treatment of Diabetes and its complications. And only one of the patents deals with a way to convey Diosgenin in pharmaceutical nanosystems.

Table 4

Patents related to the technological applications of Diosgenin with application in Diabetes and associations filed in the USPTO, WIPO, EPO databases, for the period covered by each database until 2025

References	Year	Title	Description
US 20080008775 (A1)	2008	Method for treatingdiabetic vascular complications	It presents a method for the medical treatment of diabetic vascular complications, with the administration of a therapeutically effective amount of a product with extract of a Dioscorea species (DG is one of the metabolites).
CN102702300 (A)	2012	Compound for preventingortreatingautoimmune diabetes andpreparationmethodandapplicationthereof	It describes a compound to prevent or treat autoimmune diabetes and method of preparation and application of the same. The dual drug compound: Diosgenin with ibuprofen or

			aspirin capable of preventing or effectively treating damage to beta cells of the islets of the pancreas caused by autoimmune diabetes, as well as improving anti-inflammatory action, pain and the like. It provides a new choice for clinical medication.
US 20140127333 (A1)	2014	Preparation, processand a regenerativemethodandtechnique for prevention, treatmentandglycemiccontrolof diabetes	Medicinal preparation, process, nutritional composition of regenerative method and insulin enhancer for humans and mammals, in the prevention, treatment of diabetes, hyperglycemia, from extract obtained from *Costuspictus* (diosgenin, as one of the metabolites) to produce the above effect at a

			dose of 500-200 mg/day in humans and 50-200 mg/kg/day in rats.
CN104530150 (A)	2015	Compoundwith amino benzeneanddiosgenin-diglucosidestructureandpreparationmethodandapplicationthereof	The invention refers to the field of diabetes-relevant drugs, in particular an SGLT2 inhibitor with a structure of amino benzene and diosgenin-diglucoside, a method of preparation and application of the SGLT2 inhibitor (sodium dependent glucose transporter type 2) in the elaboration of diabetes drugs.
CN104447906 (A)	2015	Alcoxylphenylgroupdiosgenin-diglucosidederivativeandpreparationmethodandapplicationthereof	The invention refers to SGLT2 with the structure of alcoxyl-phenyl diosgenin-diglucoside, the method of preparing SGLT2, and the application in the preparation of diabetes drugs.

CN104447907 (A)	2015	Compoundcontaining nitro biphenyldiosgenin-diglucosidestructureandpreparationmethodandapplicationthereof	It refers to the field of diabetes-related medications in particular. Dual compound containing nitro biphenyldiosgenin-glucoside in the structure of the SGLT2 inhibitor, a method of preparation of it and application in diabetes drug preparation.
CN105535947 (A)	2016	Pharmaceuticalcomposition for treating II-type diabetes andpreparationmethodofpharmaceuticalcomposition	The invention describes a pharmaceutical composition for the treatment of type II diabetes, composition and the method of preparation of pharmaceutical composition, which has 38-76 parts of diosgenin. It treats hyperglycemia and improves the glucose tolerance level of a muscular body based on the regulation of

			normal diet, regulates various abnormal indicators of the muscular body, and reduces the side effects of the drug.
CN105662965 (A)	2016	Nanometer acne-removingemulsioncontainingnanoparticlesandpreparationmethodthereof	Emulsion containing anti-acne lipid nanoparticles and their method of preparation. The invention of nanoparticles containing Diosgenin, nanometric acne removal emulsion and its preparation method.

It is observed that in the innovations of Ziyang (2012, 2015) structural modifications of Diosgenin were proposed with the incorporation of carboxylic derivatives and nitrogenous compounds, improving the stability and action of GD, and thus, provides clinical application aimed at the treatment of Diabetes.

Experimental protocols tested in rats using Diosgenin orally, showed reduced bioavailability due to its low aqueous solubility, which results in incomplete absorption of the drug (OKAWARA *et al*., 2013) for this it is observed that Antony (2014) in his innovation with application in humans and rats, used the extract of *Costuspictus*, containing Diosgenin as one of the main metabolites, in high concentrations to obtain good results in the prevention and treatment of Diabetes. Haiwe *et al*. (2016) presented the feasibility of transporting Diosgenin in nanosystems, but its technological innovation has therapeutic application for the treatment of acne in humans.

Wu (2008) presents an innovation aimed at the treatment of vascular complications resulting from DM, where he demonstrated the results of a patient treated with an extract of a species of the genus *Dioscorea*, which has GD as a metabolite, with a therapeutically effective dose to treat diabetic vascular complications.

Developed countries have a greater number of patent files, a fact that can be explained by having the largest databases specialized in commercial patents, facilitating access to technological information. China has the highest number of patents filed on diosgenin in the last decade.

As for the filing of patents, it is possible to detect a growing increase in the number of patents over the years (Figure 6). However, the number of patent protected works on diosgenin in diabetes is quite small when compared to the number of publications in scientific databases, especially when considering the pharmacological relevance of this compound**.**

Therefore, based on these results, it is observed that the path of research is vast and that there is great room for the emergence of new products, through patents, as well as innovations that bring benefits to the population, facilitating adherence and, mainly, acquisition of a more effective treatment for chronic diseases such as diabetes and complications associated with this pathology.

Experiments with animal models of diabetes in the last ten years, such as those developed by Ghosh *et al*., Kalailingam *et al*. Saravanan and Sato *et al*. (2014); Naibu *et al*. (2015); Kanchan *et al*., Kiasalari *et al*., and Hua *et al*. (2016); Pi *et al*., Yan *et al*. (2017), Wu *et al*. (2018); Leng *et al*. and Oyelaja *et al*. (2020) present positive results that prove the performance of Diosgenin in reducing blood glucose, preventing and treating Diabetes, as well as diseases resulting from this pathology, and thus improves renal, cardiac, neurological and metabolic function. In this way, these studies confirm the therapeutic potential of Diosgenin.

Among the research developed, most of them can be protected and deposited in the form of patents, as these studies prove that Diosgenin is very promising for the treatment and prevention of Diabetes and its complications.

In addition, there are ways to convey diosgenin in order to improve its pharmacokinetic properties, through pharmaceutical nanotechnology, which have not demonstrated cellular toxicity and good stability parameters have been obtained, as confirmed by Liu *et al*. and Quiñones *et al*. (2017). However, in the works of Liu *et al*. (2017) did not perform *in vivo* tests to analyze the behavior of nanosystems in living organisms; and Quiñones *et al*. (2017) was

developed to improve agricultural production. Thus, these studies show great possibilities of inventions and ways to improve the therapeutic efficiency for Diosgenin in Diabetes.

4 FINAL CONSIDERATIONS

From the analysis of the scientific and technological bases, the results show that there is pharmacological interest in Diosgenin with a view to the treatment of Diabetes, opening possibilities for new research and technological innovations, especially in the area of nanotechnology, which are scarce, which could guarantee greater bioavailability and better efficacy of this saponin.

The number of patents filed with Diosgenin focused on Diabetes and its associations is much smaller than the number of national and international scientific articles. In addition, the absence of Brazilian patents with Diosgenin and *Diabetes Mellitus* and their dissemination with nanometric carriers was accurate, which encourages the continuity of research with the aim of filing patents involving this theme.

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