Review

Overview of Ethnobotanical-Pharmacological Studies carried out on Medicinal Plants from the Serra da Estrela Natural Park

Radhia Aitfella Lahlou , Filomena Carvalho , Maria João Pereira , João Lopes , Luís R. Silva *

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Review

Overview of Ethnobotanical-Pharmacological Studies Carried out on Medicinal Plants from the Serra da Estrela Natural Park: Focus on Their Antidiabetic Potential

Radhia Aitfella Lahlou [1], Filomena Carvalho [1], Maria João Pereira [2], João Lopes [3] and Luís R. Silva [1,4,*]

[1] CPIRN-UDI/IPG—Centro de Potencial e Inovação em Recursos Naturais, Unidade de Investigação para o Desenvolvimento do Interior do Instituto Politécnico da Guarda, 6300-559 Guarda, Portugal; radhialahlou@ipg.pt, filomenacarvalho@ipg.pt

[2] CERENA/DER, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, Lisbon, 1049-001, Portugal

[3] iMed.ULisboa, Research Institute for Medicines, Faculdade de Farmácia, University of Lisboa, 1649-003 Lisboa, Portugal

[4] CICS-UBI—Health Sciences Research Center, University of Beira Interior, 6201-506 Covilhã, Portugal.

* Correspondence: luissilva@ipg.pt

Abstract: The Serra da Estrela Natural Park (NPSEs) in Portugal stands out as a well-preserved region abundant in medicinal plants, particularly known for their pharmaceutical applications in diabetes prevention and treatment. This comprehensive review explores these plants' botanical diversity, traditional uses, pharmacological applications, and chemical composition. The NPSEs boast a rich diversity with 138 medicinal plants across 55 families identified as traditionally and pharmacologically used against diabetes globally. Notably, the Asteraceae and Lamiaceae families are prevalent in anti-diabetic applications. In vitro studies reveal their significant inhibition of carbohydrate-metabolizing enzymes, and certain plant co-products regulate genes involved in carbohydrate metabolism and insulin secretion. In vivo trials demonstrate anti-diabetic effects, including glycaemia regulation, insulin secretion, antioxidant activity, and lipid profile modulation. Medicinal plants in NPSE exhibit various activities beyond anti-diabetic, such as antioxidant, anti-inflammatory, antibacterial, anticancer, and more. Chemical analysis identifies over fifty compounds like phenolic acids, flavonoids, terpenoids, and polysaccharides responsible for their efficacy against diabetes. The findings underscore the potential of NPSE medicinal plants as anti-diabetic candidates, urging further research to develop effective plant-based anti-diabetic drugs, beverages, and supplements.

Keywords: Natural Park of Serra da Estrela; Botanical diversity; Medicinal plants; Diabetes prevention and treatment; Pharmacological applications; chemical composition

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease associated with multiple dysfunctions in the endocrine system [1], affecting the metabolism of carbohydrates, lipids and proteins [2]. This disorder is related to a defect in insulin secretion and/or a progressive alteration in its function in the body [3,4]. The onset of hyperglycemia and insulin resistance leads to the accumulation of free fatty acids, lipid peroxidation, disruption of cellular antioxidant defences and inflammatory reactions [5–8]. Although some of the underlying mechanisms are uncertain, all these factors contribute to the disturbance of the integrity of physiological barriers [9], mainly by altering the vascular integrity of tissues, and may contribute to the clinically recognised complications of diabetes (hypertension, diabetic peripheral neuropathy, chronic kidney disease, retinopathy, cardiovascular disease and others) [10–15]. T2DM is often associated with fatty liver, sleep apnea syndrome, depression, cognitive decline, and dementia [16].

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According to current diabetes statistics, more than 90% of cases worldwide are T2DM; the older generation is the most affected of the 500 million people suffering from the disease[17]. About 422 million people worldwide have T2DM, most living in low- middle-income countries, and 1.5 million deaths are directly attributed to diabetes yearly [18]. In Portugal, the incidence of T2DM is much higher than in other types of diabetes [19,20]. Epidemiological studies show that Portugal (9.1%) is among the countries with the highest rates in Europe, alongside Turkey (14.5%), Spain (10.3%), Andorra (9.7%) and Serbia (9.1%) [17]. It is estimated that T2DM affects 13.6% of the Portuguese population aged between 20 and 79; An equivalent rate of 5.9% of people are unaware that they have the disease [21]. The data for 2021 already show an increase in the number of new cases identified [19]. Around 857,272 people with T2DM have been registered with the Portuguese National Health Service, including 74,396 new diagnoses [19]. Approximately 200 new patients are diagnosed with diabetes daily in Portugal [19].

T2DM can occur for a variety of reasons. Hyperglycaemia, obesity, hypertriglyceridaemia, poor eating habits, lack of exercise, ageing, family history, alcohol consumption, smoking, stress, anxiety and depression are the main risk factors for the onset of the disease in adults [22–26]. Statistics show it is present in young people due to poor diet and lifestyle [17,27,28]. Multiple studies have shown that people from different ethnic backgrounds may have specific phenotypes that increase susceptibility to hypertension, insulin resistance and dyslipidaemia [29]. People of Latin American, East, Southeast and South Asian, sub-Saharan African, Middle Eastern and North African origin living in Europe were 1.3 to 3.7 times more likely to have T2DM than white European populations [30]. In the United States, 14.7% of American Indians and Alaska Natives are diagnosed with diabetes, compared with 7.5% of non-Hispanic white Americans [31]. Regarding the gender factor, both men and women are affected, but worldwide, an estimated 17.7 million more men than women have T2DM [17,32,33]. Insulin sensitivity and response capacity are significantly higher in women than men [34]. Genetic polymorphisms between the two sexes, differences in the mechanism of action of sex hormones, visceral and hepatic adiposity, hypoadiponectinemia, adiponectin, insulin-sensitive hormone, resting energy expenditure and lipid metabolism may contribute to higher insulin sensitivity in men than in women [35–39].

The accumulation of excessive body fat (obesity) triggers a broad spectrum of metabolic issues and diseases, comprising insulin resistance, atherogenic dyslipidaemia [high plasma triglyceride and low HDL (high-density lipoprotein) cholesterol content], non-alcoholic fatty liver disease (NAFLD), -cell dysfunction, pre-diabetes, and T2DM [40,41]. Obesity strongly influences T2DM in adults, children, and adolescents [42,43]. It's a serious concern associated with poorer mental outcomes, reduced quality of life, and the leading cause of death worldwide [44]. Obesity increases the risk of developing T2DM by at least a factor of six [17,45]. The prevalence of obesity in adults (age ≥20 years) was 38.8% between 2013 and 2016 [46]. If the obesity trends continue, projections are that one in three adults will have type 2 by 2050 [47,48]. The prevalence of T2DM is also positively correlated with the duration of obesity and body mass index (BMI) in childhood [43,49,50]. The proportion of T2DM is higher in people who were obese in childhood and of normal weight in adulthood than in people of normal weight in childhood [43,51]. Obesity and type T2DM represent the greatest threat to the development of atherosclerosis and CAD (coronary artery disease) [52]. These two health conditions are oxidative damage, inflammation, and insulin resistance [5]. Indeed, under diabetic or hyperglycaemic conditions, excess reactive oxygen species (ROS) are released in various tissues and may play a role in developing many complications [53]. This state can persist even when hyperglycaemia is controlled. A disequilibrium occurs with the antioxidant defence systems. This modification scenario is known as oxidative stress [54]. It mainly causes endothelial dysfunction, leading to vascular lesions, abnormal production of plasma lipids, activation of platelets and increased coagulation, and activation of inflammatory processes [54,55]. This damage can be prevented when adequate glycaemic control is established early but is not easily reversed if poor control is maintained over a prolonged period [56]. Oxidative stress causes potential damage to lipids, DNA and proteins and is responsible for altering intracellular signalling pathways, leading to insulin resistance [57]. The hyperglycemic environment and free fatty acids lead to the appearance of

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metabolic stress because of an increase in ROS and a change in the mitochondrial electron transport chain [58–60]. ROS are considered key signalling molecules that play an important role in the progression of inflammatory disorders, contributing to the development of insulin resistance and the predicted long-term complications of T2DM [57,61]. Activation of the immune system and increased circulating acute-phase inflammatory markers can significantly and directly impact insulin resistance or blood glucose levels [62].

Postprandial hyperglycaemia in people with T2DM can be managed by several approaches, including lifestyle modification, i.e. regular physical activity and a healthy diet [63]. The administration of pharmacological drugs accompanies these measures. Some of these can delay carbohydrate absorption by reducing the digestion of polysaccharides and their bioavailability (e.g. α-glucosidase inhibitors) [64,65]. Others are mainly used to increase the availability of endogenous insulin. These include sulphonylureas, such as Glibenclamide, and glinides, insulin analogues that act on the sulphonylurea receptor in the pancreas to promote insulin secretion. Glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors can also increase endogenous insulin by acting on ileal cells in the small intestine. Other drugs used to improve insulin sensitivity include thiazolidinediones, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, and metformin, a biguanide [66,67]. All these drug treatments are prescribed either as monotherapy or with other hypoglycaemic agents [68]. Administration of exogenous insulin remains the primary treatment for some patients with T2DM who are unable to control their blood glucose with oral hypoglycaemic agents [68,69]. If all types of oral hypoglycaemic agents and insulin are administered correctly, and with a healthy lifestyle, people with T2DM can manage and reduce the side effects of the disease. However, certain iterations linked to the risk of hypoglycaemia or co-morbidities have been observed [70]. These occur following a progressive decline in β-cell function and a reduction in therapeutic efficacy due to inappropriate or ineffective dosing regimens, altered drug metabolism, lack of target specificity, and solubility and permeability problems [68]. In treated patients, weight gain, weakness, fatigue, lactic acidosis, nausea or diarrhoea, abdominal discomfort and a metallic taste have been observed [71,72].

In this context, medicinal plants have a well-established record of circumventing the problems mentioned about the conventional use of drugs [73]. Medicinal compounds derived from plants could provide new, straightforward approaches to preventing and treating T2DM and its complications [74–76]. Traditional knowledge and practices have enabled the development of most modern medicines [73,77]. Many natural resources have been used to develop almost 25% of the major pharmaceutical compounds and their derivatives currently on the market [78,79]. These plant resources have great potential as alternative hypoglycaemic medicines because of their safety, efficacy, affordability and availability. They constitute an almost unlimited source of bioactive compounds, and their use as antidiabetic agents has been exploited in various ways [74,75]. Secondary metabolites, such as flavonoids, phenolic acids, alkaloids, tannins, terpenoids, saponins, triterpenoids, steroidal glycosides, etc., have shown innumerable promising results against T2DM [80–83]. They are effective in different stages of diabetes. They can control insulin resistance, impact glucose absorption, regulate multiple glucose and lipid metabolism stages and inhibition and/or activation of the expression of genes involved in glucose homeostasis [81]. These natural antidiabetic agents can act alone or with conventional treatments to strengthen the body's ability to cope with the disease [84]. However, some of these compounds have not yet been studied in depth. As some of the antidiabetic actions of many medicinal plants are still unexplored, researchers are focusing more and more on finding new treatments that work quickly and at lower costs [85].

The information needed to assess the efficacy of potentially important medicinal plants and to prove their antidiabetic value must be effective and well-validated [74,86]. One method of sourcing information on medicinal plants is ethnopharmacological studies [87]. They provide rich information from the local community and contribute to discovering and developing natural medicines [86]. Analysis of the medicinal literature concerning the NPSEs (The Serra da Estrela Natural Park) shows that documentation on local medicinal plants is weak and almost non-existent, hence the importance of an in-depth study [88–98]. Therefore, to obtain a complete perspective on the potential use of

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medicinal plants from the NPSEs as alternative solutions for combating diabetes, the most relevant studies concerning the botanical diversity, known traditional uses of local plants, the validation of their antidiabetic activities (*in vitro* and *in vivo* studies), the underlying mechanisms of action, their pharmacological activities, the plant-derived chemical compounds that may be responsible for these activities, the challenges and prospects for the antidiabetic activity of medicinal plants from the NPSEs have been critically analysed in this review.

2. Materials and Methods

2.1. Geographical and Climate Features of the Serra da Estrela Natural Park

Continental Portugal has several mountain ranges. The highest is in the centre-east, the "Serra da Estrela" (40º20'N, 7º35'W) (Figure 1) [99]. Its massif forms the western part of the Cordillera Central, with its highest point called "La Torre" at an altitude of 1993 m [88–91]. Part of the Iberian Peninsula is traversed by this mountain range, over 500km long, stretching from almost the Atlantic coast to just north of Madrid [88–91]. Most of these mountains lie within the boundaries of the NPSEs, created in 1976 [100–102] and covering around 100,000 hectares [88–91]. This area is a biological and community interest site integral to the Natura 2000 network [100,101,103]. Six municipalities (Seia, Gouveia, Celorico da Beira, Guarda, Manteigas and Covilha) (Figure 1) and two districts (in the north, the district of Guarda and the south, the community of Castelo Branco) have joined forces to draw up this project [88–91,100–103]. The mountains are mainly composed of granite in the central part and schist in the periphery, dominating the Mondego and the Zezere plains (a tributary of the Tagus) [88–91]. In the north-east, the landscape is characterised by the watersheds of three major basins: the Douro (the largest river on the Iberian Peninsula), the Tagus (the longest river on the Iberian Peninsula) and the Mondego (the largest river in Portugal) [88–91].

The climate of Serra da Estrela is influenced by several factors: temperature, atmospheric pressure, wind, humidity and precipitation, as well as geographical factors [104,105]. Its high altitude among the surrounding land, the general organisation of the relief and the relative proximity of the Atlantic Ocean, some one hundred kilometres away, play a decisive role in the complex mosaic of local climates that characterise the region [88–91]. Thus, all the climate factors are controlled by the overall latitudinal position of the mountains and influenced by the north-south temperate climate and the southeast-northwest Mediterranean macroclimate [99,104,105]. They are also controlled by the Atlantic's longitudinal position and the Iberian Peninsula's interior (maritime influences mainly to the west and continental influences to the east and west) [88–91]. Average annual rainfall is around 2,500 mm at the summit, while the plateaux record more than 2,000 mm [88,89,99,106]. The highest number of precipitation days is observed in the western part of the mountains, while the lowest values are in the basal areas, in the north-western and south-eastern sectors, with around 1,000 to 1,200 mm [88–90,99,106]. The region is characterised by hot, dry summers and wet winters, with snowfall more frequent between December and March [99,104,105]. The most striking aspects of the relief are the glacial forms and deposits. The snowfall is heaviest in the higher mountain areas but lightest and most irregular in the lower regions [88–91].

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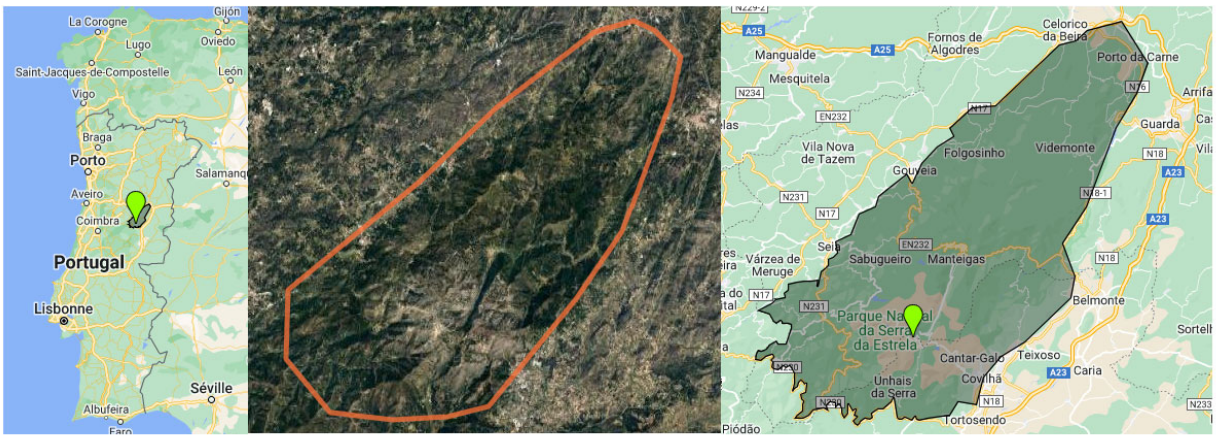

Figure 1. Geolocalization of Serra da Estrela Natural Park [107].

2.2. Ethnobotanical Data Collection and Selection Criteria

The information on the plant species of the Serra da Estrela region has been collected from the databases of the World Checklist of Vascular Plants [108]. It's an international collaborative programme with editors, compilers and reviewers from all over the world. The main objective of the database is to provide high-quality, expertly reviewed taxonomic data on all vascular plants based on the nomenclatural data provided by the International Plant Name Index (IPNI).

The Flora-On database is also used; it is a portal coordinated by the Portuguese Botanical Society containing photographic, geographical, morphological and ecological information for all vascular plant species in Portugal [109]. The search was supported by the INaturalist database [110]. It is a joint initiative of the California Academy of Sciences and the National Geographic Society. It is also a species identification system and a tool for recording the occurrence of organisms. It can be used to record sightings, get help with identifications, collaborate with others to collect information for a common purpose, or access sighting data collected by iNaturalist users [110]. All databases were screened using a combination of the keywords "Family", "Species", "Species Synonyms", and "Subspecies". This approach enabled us to find 97 different families. The total number of species is 888 (a complete list of the taxa is given in Table S1). Based on this list of plants, a systematic literature search on their traditional and diabetic uses was conducted. Data were obtained from scientific databases, including NCBI, Scopus, Web of Science and Google Scholar (Figure 2). The preliminary selection was initially performed using the search terms "Serra da Estrela" and "medicinal plants" to cover the maximum range of medicinal plants used against diabetes. As the number of studies was small, we carried out another selection, but universal, by searching by keyword for all medicinal plants from the Serra da Estrela region and their possible worldwide uses. The Boolean operator "AND" followed by the keyword "Diabetes" or "Hypoglycaemic" was used for this search to cover literature reports dealing exclusively with T2DM and anywhere in the world. This search was carried out specifically for each plant on the databases, using the leading taxonomic designation of the species and other botanical synonym names, followed by the keywords mentioned. The names of each plant and combinations of the terms "Traditional", "Ethnobotanical", "Ethnobotany", "Folk remedies", and "Ethnomedicinal" were used to search the above databases (Figure 2).

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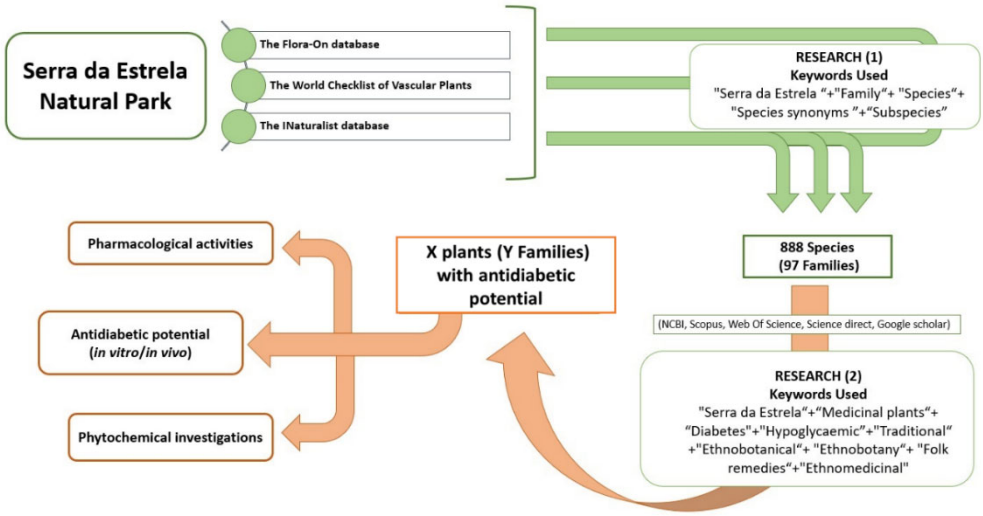

Figure 2. Diagram of the systematic literature review.

3. Results

3.1. Botanical Diversity of NPSE and Ethnopharmacological Uses of Medicinal Plants with Antidiabetic Potential

Mountains have always been an excellent challenge for humankind, who has never ceased climbing, cultivating, and domesticating. They are open-air laboratories of knowledge, home to species and communities that have adapted to their environment in various ways. They provide fertile ground for observing and understanding the evolution of species and the distribution of organisms in similar contexts, from one mountain to another thousands of kilometres away. They are, therefore, important ecosystems because they harbour high levels of biodiversity and endemicity [111]. They provide essential services such as climate regulation, freshwater supply and purification, and nutrient cycling [112–116].

The inaccessible NPSE vegetation is the best preserved in the region [88,89]. The isolation of the summits and the extreme conditions that prevail there have encouraged the appearance of new species and facilitated species isolation, speciation, extinction, and migration [115]. According to Jansen et al. [88], the flora of this mountainous region shows significant contrasts as you go up in altitude. The vegetation is divided into several levels, the boundaries of which vary according to exposure. Within this tiering, the transitions in vegetation are distinguishable, and each level corresponds to a well-defined ecosystem. In addition, the isolation of the summits and the extreme prevailing conditions have encouraged the appearance of new species. Many species are endemic to these areas, making the NPSE one of the wealthiest regions in Portugal for certain groups of plants [88,89].

The climatic heterogeneity contributing to the region's high biodiversity has attracted botanists' interest [99]. Floristic expeditions from the 18th century to the present day have enabled a rigorous characterisation of the ecosystems' flora, which is essential for their in-depth knowledge and conservation [93]. According to the three bioclimatic levels (Meso-Mediterranean, Supra-Mediterranean, Oromediterranean) defined in the Serra da Estrela region, three vegetation ranges (basal, intermediate and upper) have been characterised. The three combined levels have identified approximately 900 vascular species and subspecies [88]. Endemic Iberian species belonging to the Mediterranean and Atlantic flora are particularly well represented and distributed in an area more or less delimited by the altitude of the massif and the climatic, edaphic and sun exposure conditions [88,89,91,102]. Some relict plant populations from northern and central Europe have also invaded the area [88].

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The botanical census of NPSE diversity enabled us to identify 97 families, 112 genera, and 888 vascular species (after eliminating synonyms) (Table S1). The number of native species on the Iberian Peninsula is 133, while there are only 9 endemic species in Portugal. By contrast, the number of introduced species is 36 [108,109,117].

The Asteraceae is the family with the most species/subspecies (sp) in the region (108 sp). It is followed by Poaceae (81 sp), Fabaceae (74 sp), Caryophyllaceae (60 sp), Brassicaceae (33 sp), Apiaceae (29 sp), Lamiaceae (29 sp), Rosaceae (28 sp), Plantaginaceae (27 sp), Polygalaceae (22 sp), Ranunculaceae (21 sp), Cyperaceae (19 sp), Juncaceae (18 sp), Rubiaceae (17 sp), Cistaceae (16 sp), Amaryllidaceae (15 sp) and Crassulaceae (14 sp).

Several plants found in the NPSE have been used to treat diabetes. Despite the relatively large number of studies worldwide reporting their biological potential, NPSE species have been little investigated, and species with antidiabetic potential will be the subject of particular attention in the following section. Of the 888 species listed, only 138 plants (15.54 %) from different geographical regions have been selected based on traditional uses and studies into their antidiabetic potential (Table S2). The families with the highest number of species are Asteraceae (21 sp), Lamiaceae (12 sp), Fabaceae (9 sp), Rosaceae (8 sp), Caryophyllaceae (6 sp), Polygalaceae (5 sp) (Figure 3). The Apiaceae, Asparagaceae and Ericaceae contain four species/subspecies, and Boraginaceae, Geraniaceae, Hypericaceae and Fagaceae comprise three (Figure 3). However, the families Brassicaceae, Cistaceae, Amaryllidaceae, Scrophulariaceae, Papaveraceae, Pteridaceae, Caprifoliaceae, Gentianaceae, Urticaceae, Malvaceae, Cupressaceae, Cytinaceae and Pinaceae present only two species with antidiabetic potential. As for the rest, 30 families have only one species, and 42 families have never been traditionally used or studied for their effects on diabetes (Table S2).

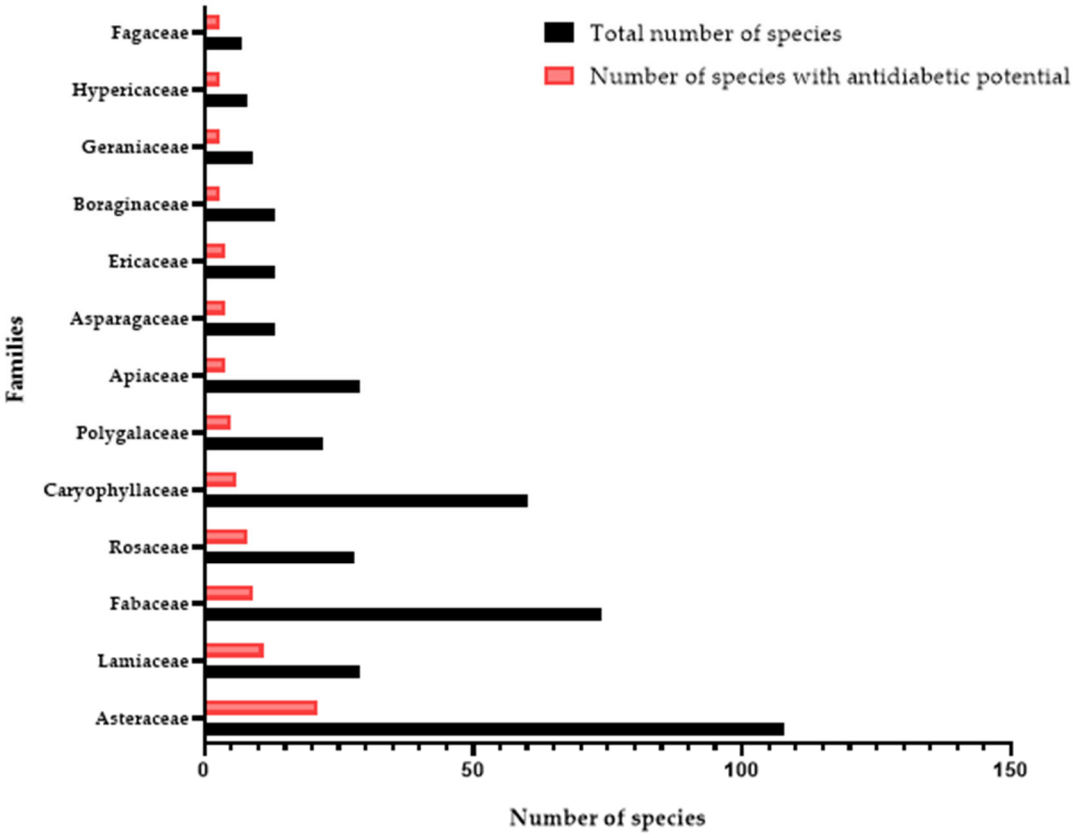

Figure 3. Families containing the highest number of species with antidiabetic potential (out of 888) in NPSE.

The antidiabetic plants belong to fifty-five families (6.20% of the total families of NPSE) and have been reported in the literature for various traditional uses (Supplementary Table S3). The number of

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species for which evidence of traditional use against diabetes had been found was 83 (Supplementary Table S3 and S4). The parts used and the preparation method vary from one plant to another. In most cases, the plant parts were used singularly and sometimes as a combination of two or more parts. However, there are 55 other species whose traditional use has not been revealed. They have, however, been studied for their antidiabetic efficacy (Supplementary Table S4).

3.1.1. Asteraceae

The Asteraceae family has the most significant number of plants with antidiabetic potential. Twenty-one species were selected, or 19.44 % of all Asteraceae species and 2.17 % of all species identified in the NPSE (Tables S1 and S2). The Asteraceae family includes many flowering plants in nearly 1,600 genera, comprising more than 23,000 species [118,119]. The Asteraceae are herbs, shrubs, trees or lianas, with laticifers or resin ducts in some taxa [120,121]. Leaves are simple or compound, spiral or opposite [rarely whorled], and exstipulate. The most distinctive feature of the Asteraceae is their inflorescence structure: the highly compressed inflorescence branch system called a capitulum or flower head, in which all the flowers are attached to a receptacle surrounded by involucral bracts [120,121]. The capitulum forms a pseudanthium, a structure resembling a single large flower. The anthers, which include a tube, and the lower position of the ovary are other features that help to diagnose the family [122]. Modifying the outer floral whorl into pappus bristles, which help disperse the seeds, is also widespread in the family. The fruit is an achene (or "cypsela", an achene derived from an inferior ovary), typically multiple fruits of achenes, with an elongated beak forming between the fruit and the pappus in some taxa. The seeds are exalbuminate [120,121].

Members of the Asteraceae family are distributed worldwide; some of these species are highly aromatic and have already been reported to have medicinal and therapeutic applications. For centuries, they have been used worldwide as traditional medicine against various human ailments, including T2DM, kidney, heart, lung, liver, and skin toothache inflammation, pain, constipation, toothache, throat pain, snake bite, headache, gastrointestinal disorders, diarrhoea, dysentery, tuberculosis, hepatitis, asthma, menopausal and menstrual disorders, stomach ulcers, sores, scabies, filariasis, elephantiasis, night-blindness, impotence, hair fall, jaundice, nose bleeding, allergies, viral infections, cough, bronchitis, different types of cancers, wounds and cuts, and malaria [123–129].

In the NPSE, only 19 of the 55 genera listed have been studied for their antidiabetic potential (Tables S1 and S2). Various biological activities have been reported for these Asteraceae species worldwide [119,124,126–131]. The species *Arctium minus* (Hill) Bernh, *Achillea millefolium*, *Anthemis canescens* (syn. *Matricaria aurea*), *Arnica montana* subsp. Atlantica, *Bellis perennis*, *Bidens frondosa*, *Calendula arvensis*, *Chamaemelum nobile* (syn. *Matricaria chamomilla* or *Matricaria recutita*), *Cichorium intybus, Dittrichia viscosa* subsp. Viscosa (Syn. *Inula viscosa*), *Galinsoga parviflora* (Syn. *Galinsoga quadriradiata*), *Helichrysum stoechas* subsp. *Stoechas* and *Hypochaeris radicata* have been used extensively in traditional medicine to treat diabetes [132–144]. Different parts include flowers, leaves, seeds, stems, and roots. However, no evidence exists of using other species, *Anthemis canescens*, *Bellis perennis, Bidens frondose, Helichrysum stoechas subsp. Stoechas, Lactuca serriola, Onopordum acanthium subsp. Acanthium, Senecio vulgaris, Tanacetum parthenium and Tanacetum vulgare* (Supplementary Table S3 and S4).

3.1.2. Lamiaceae

The Lamiaceae or Labiatae are a family of flowering plants with a cosmopolitan distribution, comprising around 236 genera and an estimated 6,900 to 7,200 species [145]. In continental Portugal, it is represented by 29 genera with 95 different species [109]. They are herbs or shrubs, often aromatic with ethereal oils, with generally 4-sided stems, opposite (or verticillate) leaves, a verticillate or thyrse inflorescence (solitary and axillary flowers in some cases), and zygomorphic (rarely actinomorphic) flowers, usually bilabiate, with a superior ovary, often deeply four-lobed (by the formation of "false septa") with a gynobasic style, the fruit being a schizocarp of usually four nuts or a berry or a drupe [146]. Since antiquity, the family has contained many culinary or flavouring herbs widely used as

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spices, teas, or traditional medicines. Several of its members are also used as sources of essential oils (EO) [147]. They have been reported as a rich source of antidiabetic plants [148].

Based on database analysis, twelve species were selected with antidiabetic potential, representing 37.93% of all Lamiaceae species and 1.13% of all species identified in the NPSE (Tables S1 and S2). Among these species are those traditionally used to treat diabetes, including *Clinopodium nepeta* subsp. *Spruneri* (Syn. *Calamintha officinalis* Moench), *Lavandula stoechas*, *Mentha aquatica*, *Mentha pulegium*, *Mentha suaveolens*, *Origanum vulgare*, *Prunella vulgaris* and *Salvia verbenaca* [149–161]. To our knowledge, there is no record of *Lavandula pedunculata* subsp. *Pedunculata*, *Melissa officinalis*, *Origanum vulgare* subsp. *Virens* and *Thymus mastichina are* being used to treat diabetes in folk medicine (Supplementary Table S3 and S4).

3.1.3. Fabaceae

The Fabaceae (or Leguminosae) are one of the world's twelve flowering plants after the Orchidaceae and Asteraceae, with no fewer than 19,400 species grouped into 740 genera [162]. Thanks to its ability to form root nodules with nitrogen-fixing bacteria [163], this family covers the entire globe in various habitats, with representatives in almost every biome, from deserts to tropical forests [162]. They grow as shrubs, trees and even aquatic plants, have a diverse floral morphology and are adapted to various ecological and climatic conditions. Most species in this family are of significant economic value [164]. Thanks to their nitrogen-fixing behaviour, these plants can produce large quantities of protein, a nutritional source for animal and human consumption [165,166]. They are also considered a good source of fibre, carbohydrates, minerals and vitamins. The Fabaceae members are superior to other dietary supplements due to their low-fat content compared to most cereals [165]— the resistant starch and fibre act as prebiotics for probiotics or beneficial bacteria [166]. Micronutrients are also essential for reducing anaemia risk[166]. Consumption of most Fabaceae species helps moderate blood sugar levels after meals and improves insulin sensitivity. It also positively impacts sight reduction by inducing satiety [167].

In the Serra da Estrela region, nine species had antidiabetic benefits out of 79 species of Fabaceae (12.16%) listed in the area (Table S1, S2), representing 0.93 % of all the species found in the NPSEs. These species comprise *Acacia dealbata*, *Lupinus angustifolius*, *Lupinus luteus*, *Pisum sativum*, *Pterospartum tridentatum*, *Retama sphaerocarpa*, *Robinia pseudoacacia*, *Trifolium pratense* subsp. *Pratense* and *Trifolium repens*. Only the four species (*Pisum sativum, Pterospartum tridentatum, Retama sphaerocarpa and Trifolium pratense subsp. Pratense*) have been registered as being used in traditional medicine in ancient times (Supplementary Table S3). All parts of these plants (leaves, stems, roots and flowers) are traditionally used to combat various ailments. Pollen, bark, gum, seeds, fruit and even cladodes are also used. As far as diabetes is concerned, only the species *Pisum sativum*, *Pterospartum tridentatum*, *Retama sphaerocarpa* and *Trifolium pratense* are recorded as being traditionally used to treat it (Supplementary Table S3 and S4).

3.1.4. Rosaceae

Rosaceae family include species of herbs, shrubs or trees. They are sometimes rhizomatous, climbing or thorny and are cosmopolitan or sub-cosmopolitan [120,168]. They are very diverse, particularly in the northern hemisphere, and are very important from an economic point of view, as they are the source of many cultivated fruits. These species are economically and ecologically beneficial, providing habitat anchorage [169] and timber [170]. Herbaceous species of the Rosaceae grow in temperate forests as understorey plants, in salt or freshwater marshes, in arctic tundra, in old fields, and along roadsides [120,168]. Woody species are pioneer species that play an essential role in the early stages of forest succession. Rosaceae can also be a minor component of mature mixed deciduous forests [120,168]. Their leaves are spiral (rarely opposite), simple or compound, undivided or divided, generally stipulate (lost in some taxa), and the stipules often adnate at the base of the petiole. The inflorescence is variable. The flowers are bisexual (generally), actinomorphic, perigynous or epi perigynous; the receptacle is sometimes enlarged or sunken [120,168]. The fruit is a drupe, pome, hip, follicetum, achenecetum or capsule. The seeds typically have no endosperm [120,168].

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Eight species of Rosaceae are identified in the Serra da Estrela region (Tables S1, S2), including *Agrimonia eupatoria*, *Crataegus monogyna*, *Geum urbanum*, *Potentilla erecta*, *Prunus avium*, *Prunus lusitanica* subsp. *lusitanica*, *Rosa canina* and *Sorbus aucuparia*. These species have traditionally been used to treat diabetes, except for *Prunus lusitanica* subsp. *Lusitanica.*

3.1.5. Caryophyllaceae

The Caryophyllaceae family, commonly known as the rose or carnation family, comprises 104 genera and over 2,000 species. They are annual or perennial herbs or small erect or prostrate shrubs; some species are more prominent or small trees. The species are distributed over almost the entire globe, with the centres of biodiversity being in Europe and Asia's moderate to warm regions [120,171,172]. They are also concentrated in the Mediterranean region, with various habitats and growth forms [171]. The Caryophyllaceae are distinguished by their often-swollen nodes, simple, opposite leaves, an inflorescence of solitary flowers or dichasial cymes, actinomorphic, biseriate flowers, usually pentamerous with distinct, clawed petals, an upper ovary with free or basal distal placentation, and a capsular fruit in which only anthocyanin pigments are present [120,171]. An unusual feature of these families is the stable, long-lasting foam that appears when plant parts are placed in water and shaken [172]. This behaviour is due to saponins, which can be as high as 20% (dry weight) in some species. The most significant quantity of saponins is generally found in the roots or seeds and can vary depending on the growing period, the part of the plant and the season [172].

Corrigiola litoralis, *Corrigiola telephiifolia*, *Paronychia argentea*, *Saponaria officinalis*, and *Stellaria media* are all plants belonging to the Caryophyllaceae family found in the NPSE that have traditionally been used to treat diabetes (except *Spergularia rubra*). The leaves and roots are the most widely used parts of the plants identified (Supplementary Table S3 and S4).

3.1.6. Polygalaceae

The word Polygalaceae, or Milkwort family, comes from a Greek name meaning "much milk", as certain species eaten by cows are thought to increase milk production [120]. This family is almost cosmopolitan (absent only from New Zealand, many islands in the South Pacific, Antarctica and the Arctic), with many genera having a wide distribution [173]. The family has many habits, from rainforest trees to small achlorophyllous grasses, including annual and perennial herbs, lianas and shrubs of various sizes [120,173]. The family comprises 22 genera and between 800 and 1000 species (Forest et al., 2007), characterised by simple, spiral-shaped leaves that are generally exstipulate (modified by a pair of glands or spines in some cases). Their inflorescence is a spike, raceme or panicle. The flowers are bisexual, zygomorphic [rarely almost actinomorphic], hypogynous to perigynous, and subtended by a pair of bracteoles. The fruit is a loculicidal capsule, nut, samara or drupe. The seeds are arillate (with a wattle) and endospermic (proteinaceous) [120].

The species in the Polygalaceae family with antidiabetic potential identified in the NPSE are *Polygonum aviculare*, *Polygonum hydropiper*, *Rumex acetosa* subsp. *acetosa, Rumex crispus* and *Rumex obtusifolius* (Supplementary Table S3). *Polygonum hydropiper* and *Rumex obtusifolius* have never traditionally been used to treat diabetes, but scientific evidence shows they are effective against the disease (Supplementary Table S4).

3.1.7. Other Families

The families Apiaceae (Daucus carota, Eryngium campestre, Foeniculum vulgare, Heracleum sphondylium), Asparagaceae (Muscari comosum, Polygonatum odoratum, Ruscus aculeatus, Urginea maritima) and Ericaceae (Arbutus unedo, Erica scoparia subsp. Scoparia, Vaccinium myrtillus, Vaccinium uliginosum) include four species whose antidiabetic potential has been studied (Supplementary Table S3 and S4). However, only three species have been identified for the families of Boraginaceae, Geraniaceae, Hypericaceae and Fagaceae. The species are Anchusa undulata, Echium plantagineum, Lithodora prostrata, Geranium purpureum, Geranium pyrenaicum subsp.

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Lusitanicum, Geranium robertianum, Castanea sativa, Quercus pyrenaica and Quercus suber (Supplementary Table S3).

The families Amaryllidaceae, Brassicaceae, Caprifoliaceae, Cistaceae, Cupressaceae, Cytinaceae, Gentianaceae, Malvaceae, Papaveraceae, Pinaceae, Scrophulariacea and Urticaceae, each of which is represented by just two species with antidiabetic potential include Allium victorialis, Narcissus pseudonarcissus, Capsella bursa-pastoris, Raphanus raphanistrum subsp. raphanistrum, Lonicera periclymenum, Sambucus nigra, Cistus ladanifer, Cistus salviifolius, Juniperus communis, Juniperus communis subsp. alpina, Cytinus hypocistis, Cytinus hypocistis subsp. hypocistis, Centaurium erythraea, Gentiana lutea subsp. lutea, Malva neglecta, Malva sylvestris, Chelidonium majus, Papaver dubium, Pinus pinaster, Pinus sylvestris, Verbascum sinuatum, Verbascum thapsus, Urtica dioica and Urtica membranacea (Supplementary Table S3).

A single species has been identified in the following families Amaranthaceae (Chenopodium ambrosioides), Betulaceae (Corylus avellana), Buxaceae (Buxus sempervirens), Campanulaceae (Jasione montana var. gracilis), Cannabaceae (Humulus lupulus), Convolvulaceae (Convolvulus arvensis), Cucurbitaceae (Bryonia dioica), Dioscoreaceae (Tamus communis), Dryopteridaceae (Dryopteris dilatata), Juncaceae (Juncus acutus), Lauraceae (Laurus nobilis), Lycopodiaceae (Lycopodium clavatum), Lythraceae (Lythrum salicaria), Moraceae (Ficus carica), Myrtaceae (Eucalyptus globulus), Oleaceae (Olea europaea var. europaea), Oxalidaceae (Oxalis pes-caprae), Phytolaccaceae (Phytolacca americana), Poaceae (Avena sativa), Portulacaceae (Portulaca oleracea), Pteridaceae (Adiantum capillus-veneris L.), Primulaceae (Anagallis arvensis), Rubiaceae (Galium aparine), Simaroubaceae (Ailanthus altissima), Solanaceae (Solanum nigrum), Taxaceae (Taxus baccata), Thymelaeaceae (Daphne gnidium), Ulmaceae (Ulmus glabra), Verbenaceae (Verbena officinalis) and Vitaceae (Vitis vinifera subsp. sylvestris) (Supplementary Table S3 and S4). Finally, no species has been traditionally used or studied for its anti-diabetic potential in the rest of the families listed (42) in the NPSE (Table S2).

3.2. Medicinal Plants with Antidiabetic Potential in NPSE

3.2.1. Asteraceae family

- *Arctium minus* (Hill) Bernh.

Arctium species are known for their pharmacological effects and chemical diversity (Wang et al., 2019). These plants, also known as "burdock", are biennial herbs found in waste ground, streams and roadsides, more rarely in woods and forests, in temperate regions of Europe and Asia, and sporadically in subtropical and tropical regions (Wang et al., 2019). Several Arctium plants have also been reported in folk medicines for T2DM. Among its most investigated members is the species *Arctium minus* (Hill) Bernh (Table 1). Its extracts exert anti-hyperglycaemic properties through various mechanisms. According to İlgün et al. [175], only the leaf extracts (excluding leaf ethyl acetate extract) showed α-amylase inhibition activity at a 1 mg/mL concentration (Table 2). In the α-glucosidase inhibition assay, the dichloromethane extract of the *A. minus* leaf had the highest enzyme inhibition activity, with 87.12% inhibition, compared with the other extracts and with acarbose at a concentration of 1 mg/mL [175]. The hypoglycaemic activity of the crude aqueous extract of the leaves and roots of *A. minus* was also tested in alloxan (ALO)-induced diabetic rats [176].

In this study, the aqueous extract of the leaves caused a 6.2% reduction in blood sugar levels in the rats. The same result was observed with the positive control Glibenclamide. These results are still better than those of the aqueous root extract (5.8%). In any case, these results prove the hypoglycaemic activity of this species [176]. Arctium roots contain inulin, the common name for all linear fructans (insulin-like fructans, ITF), a type of indigestible carbohydrate that is more or less polymerised [177]. It comprises fructose units (2 to 60 units) and a terminal glucose unit. Because of its complex structure, inulin resists breakdown by the digestive enzymes of the small intestine, which are specific to α-glycosidic bonds; the compound is therefore classified as a "non-digestible" oligosaccharide [177]. When inulin remains in the upper gastrointestinal tract, it is fermented by the microbial flora of the colon (or large intestine) to produce short-chain fatty acids (SCFAs), which

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serve as a source of energy for the resident bacteria while exerting numerous other effects on the health of the host. [177]. Inulin promotes the growth (i.e. an increase in the number) of specific health-promoting intestinal micro-organisms, thereby positively modifying the intestinal ecosystem, in addition to inulin-host interaction or immunomodulatory effects [178,179]. In this way, dietary inulin-induced changes to the microbiota could improve type 2 diabetes mellitus [177,180–182]. The intestinal symbiosis supported by supplementation with inulin, among other dietary fibres, provides preventive and/or therapeutic options for many metabolic disorders, including obesity, type 2 diabetes mellitus, cardiometabolic diseases, kidney disease and hyperuricaemia [177].

As a result, *A. minus* roots used by diabetic patients can slow the digestion of carbohydrates, reduce absorption and control glucose intolerance [183]. However, controversial results have been obtained by Fereira et al. [184]. In their study, the plant did not control hyperglycaemia in a Goto-Kakizaki (GK) rats model. The plant extract was prepared from a plant sample from a Portuguese herbalist. However, analysis of the plant extract revealed the presence of heavy metals, nickel (Ni) and cadmium (Cd), which could inhibit insulin release and have toxic effects on rats [184]. According to the authors (Table 2), all medicinal plants may contain them, as they can bioaccumulate several heavy metals. These results could be attributed to the different animal models of diabetes, the conditions of experimentation and the different chemotypes investigated [176,184]. Several studies have demonstrated the richness of this plant in bioactive compounds. *Arctium minus* is rich in polysaccharide compounds, flavonoids, phenolic acids and the lignan Arctiin. These chemical compounds are associated with the diverse biological activities observed by the plant (Erdemoglu et al., 2009; Fischer et al., 2018; Guettaf et al., 2022), which are helpful to diabetic patients in reducing oxidative stress and the common low-grade inflammation related to the disease [188,189].

Table 1. NPSE medicinal plants reported constituents to pharmacological use.

Pharmacological Uses	Chemical Constituents
	Asteraceae
Arctium minus (Hill) Bernh	
Antimicrobial, antioxidant, anti-inflammatory, antinociceptive, acetylcholinesterase inhibitory activities, anti-cancer.	**Phenolic acids**: Rosmarinic acid, quinic acid, caffeic acid cynarin, hydroxy cinnamoyl quinic acid. **Flavonoids**: Rutin, isoquercetin, luteolin kaempferol-3-O quercimeritrin, astragalin, arabinose, rhamnose, mannos **Polysaccharides:** Pectic substance, rhamnogalacturonan arabinogalactan, galactan, xylan, xyloglucan, galacturon galactose.
Achillea millefolium	
Anxiolytic, antimicrobial, antioxidant, vasoprotective, vasorelaxant, anti-appetite (orexigenic), anti-tumor, antiulcerogenic, hypotensive, analgesic, modulation of mitochondria respiration, anti-inflammatory, anti-neuroinflammatory, anti-proliferative, antiplatelet, skin-rejuvenating, antinociceptive, hepatoprotective, antiplasmodial, anthelmintic, antispasmodic, anti-cancer, antispermatogenic, for haemorrhoids and dysmenorrhea.	**Phenolic acids:** *Cis* and *trans*-3,5-O-dicaffeoylquinic acid coumaric acid, neochlorogenic acid, ferulic acid, stachyo **Flavonoids**: Resveratrol, morin, myricetin, naringin, nar quercetin, luteolin O-acetylhexoside, apigenin O-acetylh casticin, artemetin, luteolin 7-glucoside, luteolin 4′-O-glu glucoside, apigenin 4′-O-α-glucopyranoside, 5-Hydroxy tetramethoxyflavone, kaempferol, isorhamnetin glycosid cosmosiin, vicenin-2. **Sesquiterpenoids:** paulitin, isopaulitin, psilostachyin C, sintenin, achillicin, 8a-(Angeloyloxy), artabsin 1,4-endop (Tigloyloxy)artabsin 1,4-endoperoxide, 7b-Hydroxy-a-lo Longipin-2-en-1-one (longipinanes), Millefoliumins F an angeloxy-leucodin, achillin, 8α-angeloxy-achillin, desac **Organic acids and phenols:** oxalic, quinic, citric acids, fa and palmitic acids), tocopherols (γ-tocopherol), ascorbic

	salicylic acid, thymol, carvacrol, pyrocatechol, adenine, esters of caprylic-linolenic-undecylenic acid.
Anthemis canescens (syn. *Matricaria aurea*)	
Antioxidant, anti-inflammatory, anti-ulcer, analgesic, antibacterial and anti-cancer.	**Phenolic acids:** *p*-coumaric acid, ferulic acid, shikimic a *p*-aminobenzoic acid, digalloyl-shikimic acid, epicatechi rosmarinic acid, 7,8-dihydroxycoumarin, chlorogenic ac glucopyranosyl sinapate, 5-methoxysalicylic acid. **Flavonoids**: Apigenin, apigenin-7-O-rhamnoglucoside (glucoside, apigenin-7-O-glucoside, 4′-Methoxyapigenin luteolin-6-C-glucoside, quercetin, quercetin-3-D-xylosid rhamnoside, quercetin-3-arabinoside, quercitrin, kaemp kaempferol-3-O-alpha-L-rhamnoside, kaempferol-3-O-a Kaempferide, eriodictyol-7-O-glucoside, baicalin, isovit (saponarin), syringetin-3-O-galactoside, rhamnetin, isor 3-O-rutinoside, isorhamnetin-3-O-glucoside, myricitrin, cyanidin-3-glucoside, myricetin, diosmetin 7-O-rutinosi neohesperidoside, maritimetin-6-O-glucoside, acacetin- acacetin-7-O-rutinoside, naringenin, esculetin, formono eriodictyol. **Others:** Anthocyanins (delphinidin-3-rutinoside), terpe A4), chalcones (Okanin-4′-O-glucoside), coum methylumbelliferone).
Arnica montana	
Antiphlogistic, inotropic, antibiotic, anti-inflammatory, immunomodulatory, antiplatelet, uterotonic, anti-rheumatic, anti-osteoarthritic, antimicrobial, improve circulation, increase respiration, ureotonic, antioxidant, hepatoprotective, insecticidal,	**Phenolic acids:** Chlorogenic acid, 3,5-dicaffeoylquinic a acid **Flavonoids**: Kaempferol 3-O-glucoside, 6-methoxy-kaer hispidulin, quercetin 3-O-glucoside, quercetin 3-O-glucu glucoside, luteolin, apigenin.

hypopigmentation, antihair loss, anticough, antihaemorrhagic and analgesic in febrile conditions.	**Sesquiterpene lactones:** Helenalin,11a,13-dihydohelena **Others:** Carotenoids, diterpenes, arnidiol, 2-pyrrolidine alkaloids (tussilagine and isotussilagine), polyacetylenes (umbelliferone and scopoletin), lignans, dicaffeoyl quini 4,5 dicaffeoyl quinic acids), umbelliferone, scopoletin, o sesquiterpene lactones (2,3-dihydroaromaticin, chamiss
Bellis perennis	
Wound healing, anxiolytic, anti-tumour, antibacterial, anti-fungal, anti-hyperlipidemic, antioxidant, postpartum anti-hemorrhagic, pancreatic lipase inhibitor, and cytotoxic activities.	**Phenolic acids:** Chlorogenic acid, neochlorogenic acid, r caffeoylquinic acids. **Flavonoids:** Isorhamnetin 3-O-*β*-d-galactopyranoside, is acetyl)-galactopyranoside and kaempferol 3-O-*β*-d-gluc **Triterpene saponins:** Perennisosides I-VII, bellidioside A bernardioside A/F/B2, bellissaponin BS6/BA1/BA2, **Anthocyanins:** Cyanidin 3-O-(4 ″-O-(malonyl)-2 ″O-(*β* d glucopyranoside), cyanidin 3-O-(2 ″-O-(*β*-d-glucuronyl)- cyanidin 3-O-(6 ″-O-(malonyl)-2 ″-O-(*β*-d-glucuronyl)-*β*-
Bidens frondosa	
Antibacterial, antioxidant, antidiarrheal, anti-malarial, anti-inflammatory, allelopathic.	**Phenolic acids and their ethers:** Caffeic acid, 4,5-di-O ca methyl ether, isoferuloyl ethyl ester, protocatechuic acid **Flavonoids:** Okanin-4′-O-(6″-O-acetyl-2″-O-caffeoyl-6″- okanin-4′-O-(2″-O-caffeoyl-6″-O-*p*-coumaroyl-*β*-D-gluco methylokanin-4′-O-(6″-O-*p*-coumaroyl-β-D-glucopyrano 4′-O-(6″-O-acetyl-*β*-D-glucopyranoside), 4-O-methyloka O-caffeoyl-*β*-D-glucopyranoside), okanin-4′-O-(6″-O-*p*-c glucopyranoside), okanin-4′-O-(6″-O-acetyl-*β*-D-glucopy coumaroyl-maritimein, (Z)-6″-O-acetylmaritimein, apig O- *β*-D-glucopyranoside, luteolin-7-O-(*β*-dglucopyranos kaempferol-3-O-*β*-D-glucopyranoside, quercetin-3-O-*β*-

	8,3′,4′-trihydroxyflavone-7-O-(6″-O-*p*-coumaroyl)-*β*-D-g hydroxyluteolin-7-O-glucoside, 3″-(3-hydroxy-3-methyl hydroxyluteolin-7-O-*β*-D-glucopyranoside, 8,3′,4′-trihyd glucopyranoside, 3′-hydroxyscutellarein-7-O-(6″-Oproto glucopyranoside, (−)-4′-methoxy-7-O*β*-dglucopyranosyl (−)-4′-methoxy-7-O-(6″-acetyl)-*β*dglucopyranosyl-8,3′-di hesperetin-7-O-*β*-D-glucopyranoside. **Others:** 2′-butoxyethylconiferin, butylconiferin, 2-metho phenol-1-O-*β*-D-glucopyranoside, (1′R,2′R)-guaiacyl gly dglucopyranoside, threo-5-hydroxy3,7-dimethoxypheny hydroxy-3-methoxyphenyl)-3-methoxypropane1,2-diol, methoxyphenyl)propane-1,2-diol, guaiacylglycerol, wilf caffeoylcalleryanin, 1-O-(E)-caffeoyl-*β*-dgentiobiose, dih trimethoxybenzene, vanillin, galacturonic acid, galactos xylose, rhamnose.
Calendula arvensis	
Antibacterial, anti-fungal, antiparasitic, anti-inflammatory, antioxidant, wound healing, antimutagenic, immunomodulatory, and anti-cancer.	**Phenolic acids:** Isomeric form hydroxy ferulic acid hexo acid, 4-O-caffeoylquinic acid, caffeic acid, sinapic acid, s hexoside derivative, caffeoylshikimic acid, 3,4-O-dicaffe feruloyl quinic acid, protocatechuic acid pentoside, quin residue. **Flavonoids:** Quercetin hydrate, quercetin dihexoside, qu quercetin-3-O-neohesperidoside, quercetin-3-omalonylh hexoside, quercetin hexoside I, quercetin 3-O-*β*-D-gluco O-*β*-D-galactopyranoside, apigenin-8-C-pentose-6-chexo 6-C- pentose, apigenin-O-hexosylpentosyl, isorhamnetin **Saponins:** 3-O-(*β*-D-galactopyranosyl-(1⟶3)-*β*-D-glucop 28-O- *β*-D-glucopyranoside, 3*β*-O-(*β*-D-galactopyranosy

glucopyranosyl) oleanolic acid, 3β-O-(β-D-galactopyran
glucopyranosyluronic acid) oleanolic acid-28-O- β-D-glu
galactopyranosyl-(1⟶3)-β-D-glucopyranosyluronic acid
D-fucopyranosyl)-4-alloaromadendrole, arvensoside A,
of arvensoside B, calenduloside D, calenduloside C, 4-O
alloaromadendrole, 4-O-(β -D-fucopyranosyl)-4-alloaron
methylpropanoyl esters, 4-O-(β -D-fucopyranosyl)-4-allo
methyl-2″-butenoyl esters,

Sesquiterpeneglycosides: 3α,7β-dihydroxy-5β,6β-epoxy
β-D-fucopyranoside-2′,4′ -diangelate-3′-acetate), 7β-Hyd
epoxyeudesm-5(15)-ene-11-(O-β-D-ficopyranoside-2′,4′-
3α,7β-Dihydroxy-5β,6β-epoxyeudesm-4(15)-ene-11-(O-β
diangelate-3′-isobutyrate), 3α,7β-dihydroxy -5β, 6β-epox
(O-β-D-fucopyranoside-2′, 4′-diangelate-3′-methylbutyra
dihydroxy-15-acetoxyeudesm-4(5)-ene-11-(O-β-D-fucop
diangelate-3′-acetate).

Carboxylic acids/Fatty acids: Stearic acid, oleic acid, lino
palmitic acid, palmitoleic acid, α-linolenic acid, quinic a
tetracosanoic acid.

Polysaccharides: L-threonic acid, D-(−)-tagatofuranose,
(−)-fructopyranose, D-(−)-psicopyranose, D-(+)-mannopy
galactopyranose, β-D-glucopyranose, D-gluconic acid, g
cellobiose.

Others: Ethyl butyrate, 2-methyl-3-furanthiol, methiona
hexanoate, 2-6-Dimethyl-3 ethyl pyrazine, (E)-2-nonenal
methyl-2-furanaldehyde, citronellol, phenethylacetate, α
and δ-decalactone, Neophytadiene, phytol, α-bisabolol,
stigmasterol, stigmast-5-ene, amyrin, lup-20(29)-en-28-a

	myo-inositol, 1H-benzocyclohepten-9-ol, 1-hexacosanol, aminobutanoic acid, isomer of platynecine derivative, li calendasaponin A, calenduloside G isomer, β-sitosterol.
Chamaemelum nobile (syn. *Anthemis nobilis L. or Chamomilla nobilis*)	
Anti-inflammatory, antioxidant, antinociceptive, antimutagenic, sedative, anxiolytic, antispasmodic, anxiety, depression, sleep quality and insomnia, postoperative gastrointestinal dysfunction, diarrhoea, colic, nausea, vomiting, acute, diuretic, chronic pain, antibacterial, anti-fungal, insecticidal, hypotensive, antiplatelet aggregation, antioxidant, effect in asthma and polycystic ovary, nervous endocrine, cytotoxic, bronchodilator, antispasmodic, carminative, anti-emetic, antispasmodic, cytostatic, anti-oedema sedative properties	**Phenolic acids:** The glucose esters caffeic acid, ferulic ac trans-caffeic acid-glucose ester, trans- and cis- forms of t caffeoylquinic acid, 5-O-caffeoylquinic acid-hexoside, 3, protocatechuic acid, caffeoyl-hexoside-methylglutarate, *p*-coumaroyl-hexoside-methylglutarate 1,3,5-O-Tricaffeo **Flavonoids:** Apigenin, apigenin 6-C-glucose-8-C-glucos glucuronide, apigenin O-glucuronylhexoside, luteolin, l luteolin O-rutinoside, luteolin O-acetylhexoside, luteoli pentosylhexoside, luteolin O-glucuronide, luteolin O-rh quercetin, quercetin 3-O-glucuronide, quercetin 7-O-ma O-acetylhexoside, isorhamnetin O-acetylhexoside, myri anthemoside (apigenin2,3-dihydorycinnamoyl acid 7-O- cosmosioside (apigenin 7-O-β-D-glucose), apiin (apigen apiosylglucoside), chamaemeloside [apigenin 7-O-β-D-g 3″′-methyl-glutarate)], luteolin 7-O-β-D-glucose, quercet kaempferol, kaempferol O-pentosylhexoside, catechins. **Terpenoids and steroids:** α-bisabolol, chamazulene taraxasterol, pseudotaraxasterol, β-sitosterol. **Coumarins:** Herniarin, umbelliferone, scopoletin-7-gluc **Others:** Angelic and tiglic acid esters, anthemic phytosterols, inositol, oxalic acid, quinic acid, malic acid octulosonic acid, betahydroperoxyisonobilin, germacranolide-type sesquiterpene lactones (nobi epoxynobilin, 3-dehydronobilin), amyl and i

	Hydroperoxyisonobilin, alkyl hydroperoxides, *Ci* derivatives, *cis*- and *trans*-dehydromatricariaest polyacetylenes.
Cichorium intybus	
The hepatoprotective, anti-inflammatory, antioxidant, sedative, immunomodulatory effect, cardiovascular, hypolipidemic, gastro-protective, anti-tumour, anti-leukaemic, cytotoxic, antimicrobial, allergenic, antibiotic, anti-cancer, anti hyperuricemia, antiprotozoal, anthelmintic, anti-malarial, sedative.	**Phenolic acids:** Chlorogenic acid, chicoric acid, *p*-couma acid, p-hydroxybenzoic, iso vanillic, gallic acid, 4-amino caffeine, ferulic acid, isoferulic acid, vanillic acid, benzo cumaric, 3,4,5-methoxy-cinnamic, salycilic acid, cinnam quinic acid. **Flavonoids:** Quercetin, quercetin glucuronide, luteolin g catechol, epicatechin, cyanidin-3-O-(6″-malonyl-*β*-gluco 3,5-di-O-(6-O-malonyl-*β*-d-glucoside), delphinidin 3-O-(glucoside)-5-O-*β*-d-glucoside, delphinidin 3-O-*β*-d-gluc *β*-d-glucoside), delphinidin 3,5-di-O-*β*-d-glucoside. **Fatty acids and derivatives**: Lauric acid methyl ester, m palmitoleic methyl ester, palmitic acid methyl ester, met 9,12- linoleic methyl ester, stearic acid methyl ester, met acid methyl ester, 11-eicosenoic acid methyl ester, eicosa hexadecanyl hexadecanoate, n-pentadecanyl octadec-9-e octadec-9-enoate, n-hexadecanyl octadecenoate, n-octad linolenic acid, oleic acid, linoleic acid, palmitic acid. **Sesquiterpene lactones:** Lactucin, 8-deoxylactucin, 11(S deoxylactucin, lactucopicrin, 11(S),13- dihydrolactucopi crepidiaside B, lactuside A, 11(S), 13-dihydrolactucin, la 11(S), 13-dihydro-8-deoxylactucin, 11(S),13-dihydrolactu **Others:** Inulin, coumarin, epigallocatechin gallate.
Dittrichia viscosa subsp. *Viscosa* (Syn. *Inula viscosa*)	

Antiphlogistic, antiviral, anti-fungal, antibacterial, antiseptic, anti-inflammatory, allelopathic potential, fungicidal, nematicidal, antiulcerogenic, antihelmintic, anti-cancer, neuroprotective effects	**Phenolic acids and derivatives:** Caffeic acid, di-o-caffeo acid, protocatechuic acid hexoside, caffeoyl hexose, p-co caffeoylquinic acid, 3-O-caffeoylquinic acid, 4-O-caffeoy Caffeoylquinic acid, caffeic acid phenethyl ester, (Epi)-ro rosmanol, epirosmanol, dicaffeoylshikimic acid, N-caffe dihydroxybenzoic acid. **Flavonoids:** Dihydroquercetin, 3-O-methylquercetin, qu hexoside, quercetin dihexoside, quercetin-3-O-(6″-acetyl rhamnoside, cirsiliol, 3-O-acetylpadmatin, padmatin, ne diosmetin, rhamnetin, hesperetin, hispidulin, catechin, r mangostin, banaxanthone E, epi- granilin, naringenin, is cirsimaritin derivative, genkwanin, rutin, kaempferol-O kaempferol-3-O-(6″-acetyl) hexoside, kaempferol-3-O-(c aromadendrin, naringenin-7-O-hexoside, isorhamnetin O-pentosylhexoside, kaempferol-O-(p-coumaroyl)-hexo (feruloyl)-hexoside, 3,7-dihydroxycoumarin, nepetin, sp dihydroxycoumarin, padmatin isomer 1/2, cinchonain. **Sesquiterpenes:** α- and γ- costic acid isomers, ilicic acid tomentosine/inulviscolide, alantolactone, inulanolide, **Others:** Galloylquinic acid, (Epi)-gallocatechin-3-gallate proanthocyanidin dimer, prodelphinidin B3, malic acid acid, shikimoyl blechnic acid.
Galinsoga parviflora	
Antibacterial, antioxidant, anti-arthritic, antiplatelet, anti-inflammatory, anti-fungal.	Kaempferol, gallic acid, 2,4,5-tricaffeolylglucaric acid, 2, tetracaffeolylglucaric acid, 2,3,4-tricaffeolylaltraric acid, acid, beta-sitosterol-3-O-beta-glucoside, quercetine, beta 3,5,7,3′,4′pentahydroxyflavanone, 4-hydroxybenzoic aci
Helichrysum stoechas	

Antibacterial, anti-proliferative, neuroprotective, anti-inflammatory, antioxidant treatment for urolithiasis.	Neo-chlorogenic acid, chlorogenic acid and crypto-chlo dicaffeoyl quinic acids, isomeric naringenin glucosides, kaempferol, apigenin glucosides, tetrahydroxychalcone- A/B/C, Italipyrone, 20-prenylitalipyrone, Bitalin A (R)-fo helipyrone, 5,7-dihydroxy-3,6,8-trimethoxyflavone, que glucopyranoside, santinol B.
Hypochaeris radicata	
Treatment of jaundice, rheumatism and antibacterial, anti-fungal properties with antioxidant and anti-inflammatory, antihemolytic.	Chicoric acid, hypochoeroside C, hypochoeroside D, an acid, 4-(3,4-dihydroxybenzyl)-2-(3,4-dihydroxyphenyl)t carboxy-O-β-D-glucopyranoside, 4-(3,4-dihydroxybenzy dihydroxyphenyl)tetrahydrofuran-3-carboxy-O-β-D-glu methacrylate, (7S,8R,8′R)-7-(3,4-dihydroxyphenyl)-3′,4′- tetrahydronaphtho [8,8′-c]furan-1(3H)-one, and (7S,8R,8 dihydroxyphenyl)-3′,4′-dihydroxy-8'-(hydroxymethyl)-7 tetrahydronaphthalen-8-carboxylic acid, confertin, scop
Lactuca serriola	
Hepatoprotective, antioxidant, antivenom, allelopathic, sedative, anticonvulsant, antiepileptic, anti-inflammatory, anti-carcinogenic activities	Chlorogenic acid and caffeic acid, quercetin, lactutin, 8- jacquilenin, 11-β-13-dihydrolactucin, deacetoxymatricar leucomisin), loliolide, guaiane ester, the melampolide gl glucoside, protocatechuic acid, 4-hydroxybenzoic acid, l lactucone, lactucic acids, lactucopicrin, sesquiterpene es β-carotene, iron, lupeol, lupeol acetate, oleanans, α-amy
Onopordum acanthium	
Antihypertensive, bactericide, cardiotonic, hemostatic agent, used against hypotonicity, anti-inflammatory, anti-malarial, anti-inflammatory, anti-tumor, cytotoxicity, antipyretic, analgesic, anti-tumor, regeneration, phytotoxic.	**Phenolic acids and derivatives:** Isochlorogenic acid, caf **Flavonoids:** Apigenin, luteolin, scutellarein, nepetin, ch pectolinarigenin, scutellarein 4′-methyl ether, quercetin, apigenin-7-O-rutinoside, apigenin-7-O-β-D-glucuronide

	quercetin-3-O-glucoside, isorhamnetin-3-O-glucoside, ri aconiside. **Others:** pinoresinol, syringaresinol, medioresinol, nitida arctiin, aesculin; aesculetin, 4β,15-dihydro-3-dehydroza 4β,15,11β,13-tetrahydrozaluzanin C, onopordopicrin; ar 11(13)-dehydromelitensin β-hydroxyisobutyrate; acanth amyrin, lupeol; taraxasterol, steroids, heptadecatetraen- (1), tridecadien-(1, 11)-tetrain-(3, 5, 7, 9), heptadecatetra 13), heptadecatetraen-(2, 8, 10, 16)-diin-(4, 6)-ol-(1),), lin stearic, pentadecanoic acids, hentriacontanoic acid, nona acid, arachidic, pentadecanoic acid, margaric acid, myri palmitoleic acid, oleic acid, gadoleic acid, erucic acid, va tocopherol, α-tocotrienol, β-tocopherol, γ-tocopherol, α- propanol, stachydrine, choline, phytin.
Senecio vulgaris	
Antioxidant, cytotoxic, antibacterial and anti-fungal	**Phenolic acids and derivatives:** Caffeic acid, protocatec caffeoylquinic acid (chlorogenic acid), dicaffeoylquinic a acetic acid, vanillic acid, syringic acid, *p*-hydroxy benzer *p*-hydroxycinnamic acid. **Flavonoids:** Quercitin-3-glucoside (Isoquercitrin), querc (quercitrin), kaempferol-3-O-di-deoxyhexoside. **Pyrrolizidine alkaloid:** Retrorsine N-oxide, spartioidine N-oxide, integerrimine N-oxide, senecionine N-oxide, u riddelline, neoplatyphylline, retrorsine, spartioidine, pla integerrimine, senecionine.
Solidago virgaurea	

Antioxidant, anti-inflammatory, analgesic, spasmolytic, antihypertensive, diuretic effects and benefits in other urinary tract conditions, antibacterial, anti-fungal, antiparasitic, cytotoxic and anti-tumor, antimutagenic, cardioprotective, antisenescence effects.	**Phenolic acids and derivatives:** Caffeic acid, chlorogen (neo chlorogenic) acid, 3,5-di-O-caffeoylquinic acid, 3,4 4,5-di-O-caffeoylquinic acid, 3,4,5-tri-O-caffeoylquinic caffeoylquinate, 3-hydroxyphenyl acetic acid, 3,4-dihydr coumaroylquinic acid, homovanilic acid, *p*-coumaric acid rosmarinic acid benzoic acid, 3-hydroxybenzoic acid, 4- dihydroxybenzoic (protocatechuic) acid, salicylic acid, g gallic acid, leiocarposide, 2-methoxybenzyl-2,6-dimetho **Flavonoids:** Quercetin, quercetin-3-O-glucoside (isoq galactoside (hyperoside), quercetin-3-O-rhamnoside (q rutinoside (rutin), quercetin-3-O-arabinopyranoside (av glucoside (astragalin), kaempferol-3-O-rhamnoside (rutinoside (nicotiflorin), kaempferol-3-O-robinobioside rhamnoside (myricitrin), Isorhamnetin-3-O-rutinoside gentiobioside mono-C-glycosylflavones, di-C-glycosyl fl **Others:** Virgaureasaponins 1–6, solidagosaponins X- erythrodiol-3-acetate, α-tocopherol quinone, 2-phyten-1
Sonchus asper	
Antioxidant, anti-inflammatory, antibacterial, insecticidal, and hepatorenal protective, used for treating bronchitis, gastrointestinal infection and cardiac dysfunction, kidney diseases and cancer.	**Phenolic acids and derivatives:** Caffeic acid, 3-couma gallic acid, luteolin, luteolin-7-o, protocatechuic acid, ros vanillic acid. **Flavonoids:** Apigenin, apigenin-7-o, luteolin, pyrocatech **Others:** 11 beta,13-dihydrourospermal A, 15-O-beta-D-g dihydrourospermal A, 15-O-beta-D-glucopyranosylur hydroxyphenylacetyl)]-beta-D-glucopyranosylurosperm methylacetal-15-O-[6'-(p-hydr glucopyranosylurospermal A, asperal, emodin, methyl- 9-oxo-9H-xanthene)-1-carboxylate,

Sonchus oleraceus	
Antioxidant, anti-inflammatory, anti-tumour, antibacterial, anti-fungal, antidepressant, anxiolytic, and antinociceptive effects, used for treating cancer, diarrhoea and enteritis.	**Phenolic acids and derivatives:** Chicorin, caffeic acid g acid, 5-caffeoylquinic acid, *cis*-3′ caffeoylquinic acid, caftaric acid, chicoric acid, 3,4 dicaffeoylquinic acid, dicaffeoylquinic acid (isomer), *cis*-3,5 dicaffeoylquin caffeyolyquinic acid, *cis*-3,4 dicaffeoylquinic acid, 4,5 dic **Flavonoids:** Quercetin-glucoronide-glycosyl, q quercetin glucoside glucoronide, luteolin-glycosy diglucoside, isorhamnetin diglucoside, luteolin, lutec glycoside, quercetin-rutinoside, isorhamnetin rutino acetylglycoside, apigenin glucuronide, apigenin acetylglycoside sesquiterpenes, crepidiaside A. **Others:** 7S,10S- 3,9-dioxo-di-nor-eudesma-4-en-11-oic ac hydroxyldi-nor-eudesma-4-en-11-oic acid.
Tanacetum parthenium	
Antioxidant, anxiolytic, antidepressant, anti-migraine agent, anticoagulant, anti-inflammatory, neuroprotective, antiviral, anti-apoptotic, anti-cancer, antiparasitic, pain reliever.	**Phenolic acids and derivatives:** 4-o-caffeoyl-quinic acid, 3,5-dicaffeoyl-quinic acid, 4,5-dicaffeoyl-quinic acid, ne acid, chlorogenic acid. **Flavonoids:** Kaempferol-3-rutinoside, 6-hydroxykaemp (santin), 6-hydroxykaempferol-3,6-dimethylether dimethylether (axillarin), quercetagenin-3,6,3′-tri quercetagenin-3,6,4′-trimethylether (centaureidin), ap chrysoeriol, luteolin-7-glucoronides, methylq methoxyflavone, costunolide, dihydro-β-cyclopyrethro tanacetol a isomer, nevadensin, parthenolide, casticin, r β-hydroxyanhydroverlotorin, seco-tanapartholide A/B, l
Tanacetum vulgare	

Antioxidant, anti-inflammatory, anti-tumour, antibacterial, antiparasitic, anthelmintic, repellent, insecticidal, antiviral, and anti-fungal.	**Phenolic acids and derivatives:** Caffeoylgluconic ac protocatechuic acid, *p*-hydroxyphenylacetic acid 1-O acid-O-hexoside isomer, syringic acid 4-O-hexos caffeoylquinic) acid, O-caffeoyl hexose, vanillic acid 4- caffeoylgluconic acid isomer, O-caffeoyl hexose isómer, hydroxybenzoic acid-hexoside, 3-p-coumaroylquinic a isomer, O-caffeoyl hexose isomer, quinic acid, chlorogen *p*-coumaric acid, 3-feruloylquinic acid, caffeic acid-O-hexoside, caffeic coumaroylquinic acid, 3-caffeoyl-5-hydroxy-dihydro hydroxyphenylacetic acid, 5-feruloylquinic acid dihydrocaffeoylquinic acid, vanillic acid-4-O-(6-C dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid caffeoylquinic acid, 4,5-dicaffeoylquinic acid, shikimic caffeoylquinic acid, salicylic acid, 3-feruloyl-4-caffeoylq 5-caffeoylquinic acid, caffeic acid-O-(salicyl)-h coumaroylquinic acid, 3-feruloyl-5-caffeoylquinic coumaroylquinic acid, 4-caffeoyl-5-feruloylquinic acid, 3 **Flavonoids:** Apigenin, apigenin-6,8-diC-hexoside, methoxyeriodictyol-O-hexuronide, apigenin-O-hexuron hexuronide, luteolin 7-O-glucoside, 6-hydroxyluteolin- gentiobioside dihexoside (gentiobioside) 6-glucopy luteolin-7-O-neohesperidoside, luteolin-O-caffeoyl acetylhexosidekaempferol 3-O-glucuronide, rutin, q acetylhexoside, quercetin 7-O-hexuronide, kaempferol, l eriodictyol-O-hexuronide, patuletin-O-hexoside, isorhamnetin 3-O-glucoside, naringenin-O-hexuronide, (hesperidin), nepetin-O-hexuronide, hispidulin-O-hex

	hexuronide, chrysoeriol-O-hexuronide, hesperetin-O-h hexuronide, patuletin (6-methoxyquercetin), nepetin methoxykaempferol, naringenin, hispidulin (scute chrysoeriol, hesperetin, Isorhamnetin, jaceosidin (6-hyd ether), quercetagetin-3,6,3′(4′)-trimethyl ether, cirsima 6,7-dimethyl ether), eupatilin, casticin, acacetin. **Sesquiterpene lactones and derivatives:** *α*/*β* thuj ludovicin C, tanacetin/hydroxyraynosin/armefolin, caryophyllene oxide, dehydrosantamarin, caryophyllen palmitamide, oleamide.
	Lamiaceae
Calamintha nepeta subsp. *nepeta (*Syn. *Clinopodium nepeta*)	
Stimulant, tonic, antiseptic, antispasmodic, antioxidant, antimicrobial, anti-inflammatory, anti-ulcer, phytotoxic.	**Phenolic acids and derivatives:** 3-O-Caffeoylquinic acid 5-O-caffeoylquinic acid, rosmarinic acid, quercetin-3- protocatechuic acid, chlorogenic acid, *p*-hydroxyben syringic acid, vanillin, trans-cinnamic acid, couma hexosyljasmonate, caffeic acid hexamer, caffeic acid pent O-(6′-caffeoylhexosyl)jasmonate, acacetin 7-O-[hexosyl(1 → 6″) hexoside. **Flavonoids:** Myricetin, quercetin, luteolin, hesperidin, k O-hexoside, apigenin, luteolin-8-C-(3-hydroxy-3-m hexoside, 6,8-C-dihexosylapigenin, caffeic acid dimer quercetin-3-O-[6″-O-(3-hydroxy-3-methyl-glutaroyl)]hex hexoside, salvianolic acid B, acacetin, acacetin 7-O-[6i 2″)]deoxyhexosyl(1‴ → 6″)hexoside, acacetin 7-O-deoxyh
Lavandula pedunculata	
Anti-inflammatory, antioxidant, antimicrobial.	**Phenolic acids and derivatives:** Salvianolic acid B, ros caffeic acid hexoside, *p*-coumaroyl hexoside, rosmari

	hexoside, sangerinic acid, lithospermic acid A, chlor methoxybenzaldehyde thiosemicarbazone, ferulic acid, *p*-hydroxybenzoic acid, protocatechuic acid, gallic acid. **Flavonoids:** Luteolin-O-hexosyl-O-glucuronide, luteolin-7-O-glucuronide, methylluteolin-O-glucu glucuronide, herniarin, myricetin.
Lavandula stoechas	
Anti-inflammatory, antioxidant, antispasmodic, sedative, antibacterial, anti-fungal, insecticidal, larvicidal, hepatoprotective, renoprotective, and anti-leishmaniasis.	**Phenolic acids and derivatives:** Protocatechuic acid, ch acid, rosmarinic acid, ferulic acid, 7-methoxy coumarin. **Flavonoids:** Flavone di-O-glycosides, flavone 7-O-mon quercetin, pinocembrin, luteolin, vitexin, acacetin, eryth **Others:** Ursolic acid, vergatic acid, oleanolic acid, *α*-amy sitosterol, lupeol, two longipinane derivatives (longipin and longipin-2-ene-7*β*,9*α*-diol-1-one-9-monoacetate), lav
Melissa officinalis	
Anti-proliferative, anti-tumor, antioxidant, antiangiogenic, cardioprotective, anxiolytic antidepressant, antinociceptive, neuroprotective, GABA-T inhibitor, anti-kinetoplastidae, analgesic, hypnotic, anti-Alzheimer, antispasmodic, antiviral, anti-fungal, antibacterial, for premenstrual syndromes.	**Phenolic acids:** Caffeic acid, caftaric acid, chlorogenic a acid, *p*-Coumaric acid, rosmarinic acid. **Flavonoids:** Apigenin, cynaroside, daidzein, hyperoside kaempherol, luteolin, myricetin, quercetin, quercetrol, r **Triterpenes:** Betulinic acid, oleanolic acid, ursolic acid, ichigoside F1, 3*β*,16*β*,23-trihydroxy-13,28-epoxyurs-11-e glucopyranoside, 3,23-Disulfate ester of 2*α*,3β,19*α*,23-tet oicacid, 3,23-Disulfate ester of 2*α*,3*β*,19*α*,23-tetrahydrox O-*β*-D-glucopyranoside, 3,23-Disulfate ester of2*α*,3*β*,23, en-28-oicacid, 3,23-disulfate ester of 3*β*-23,29-trihydroxy 3,23-disulfate ester of 2*α*,3*β*-23,29-tetrahydroxyolean-12- ester of 2*α*,3*β*,19 *α*,23-tetrahydroxyurs-12-en-28-oic acid, melissioside B, melissioside C.

Mentha aquatica	
Antioxidant, anxiolytic, anti-inflammatory, hepatoprotective, antimicrobial, anti-cancer.	**Phenolic acids**: Rosmarinic acid, caffeic acid. **Flavonoids:** Luteolin-7-O-rutinoid, Eriodictyol-O-rutinc rutinoside, hesperetin-7-O- rutinoside, luteolin glucosid diglucuronide, eriocitrin, apigenin-7-O-*β*-D-diglucuroni glucuronide, narirutin, apigenin-7-O-rutinoside, apigen hesperidin, catechin. **Others:** methyl ester palmitic acid, methyl ester linoleni linolenic acid, neophytadiene, phytol, viridiflorol, rotun triterpene, 3-O-benzoyltormentic acid, tormentic acid, 1- acid, 3-epiursolic acid, hyptadienic acid, 3-epi-maslinic a ursolic acid, *β*-sitosterol, oleanolic acid, pomolic acid, m hydroxyursolic acid, pomolic acid, hyptadienic acid, 1-O enadecanoyl-3-O-palmitoleoyl-sn-glycerol, 1-O-oleoyl-2 palmitoleoyl-sn-glycerol, 1, 3-O-dioleoyl-2-O-eicosanoyl linoleoyl-2-O-palmitoleoyl-sn-glycerol, corosolic acid, as acid, formic acid, lactic acid, quinic acid, salicylic acid, s glucose, sucrose, alanine, aspartic acid, glycine, isoleuci phenylalanine, threonine, valine.
Mentha pulegium	
Insecticidal, nematicidal, allelopathic, antioxidant, antimicrobial, antiviral, antileishmanial, anti-tumour, anti-cancer, anti-hemolytic, antihypertensive, anti-inflammatory, burn wound healing, cardioprotective, stomachic, astringent, emmenagogue, decongestant, antispasmodic, antiseptic, depurative, digestive, anti-rheumatic, anti-arthritic, hepatotoxicity.	**Phenolic acids:** Gallic acid, chlorogenic acid, caffeic acid protocatechuic acid, *p*-Hydroxybenzoic acid, syringic ac acid, ferulic acids, *p*-coumaric acid, chlorogenic acid, ros **Flavonoids:** Epicatechin, catechin, apigenin, salvige isorhamnetin, quercetagetin-3,6-dimethylether, kaem rutinoside, hesperidin, thymonin, jaceosidin, pec sorbifolin, pedalitin, diosmin, luteolin, apigenin, naring vicenin-2, gallocatechin isomer 1.

	Others: Alterporriol, atropisomer, altersolanol, stemphy nin, macrosporin, salvianolic acid, Lithospermic acid, ja
Mentha suaveolens	
Antioxidant, antimicrobial, antimutagenic, analgesic, anti-inflammatory, insecticidal, anti-cancer, antithermal skin-aging effect.	**Phenolic acids:** Cinnamic acid, chlorogenic acid, rosm methyl coumarate, ferulic acid, *p*-coumaric acid, gallic a hydroxybenzoic acid, 3-dihydroxybenzoic acid, vanillic a acid 2-O-*β*-glucoside, *trans*-cinnamic acid, *p*-methyl cou **Flavonoids:** Hesperidin, rutin, quercetin, naringen apigenin.
Origanum vulgare L.	
Antibacterial, anti-fungal, antiviral, antiparasitic, antioxidant, anti-inflammatory, antitumoral, beneficial activity on skin disorders, effects on melanin production, on human sperm mobility, anti-Alzheimer, energy producer, stomach booster, nervous system reliever, laxative, reducing the general weakness of the body, anti-cancer, relief of migraine pain, for external use by rubbing in place of fractures and numbness of body parts, toothache, disinfection, antidiarrhoea, anticonvulsant, expectorant, nourishing, menstrual regulator, anti-urinary tract infection, treatment of sexual dysfunction, colic, sinusitis, relaxing, cardiorespiratory booster, nervous system booster, treatment of blockages, hepatoprotective.	**Phenolic acids:** Rosmarinic acid, chlorogenic acid, ci syringic acid, benzoic acid, vanillic acid, *galo*-cou protocatechuic acid, 4-hydroxybenzoic acid, p-coumari acid, *trans*-cinnamic acid, 2,4-dihydroxybenzoic acid, ph **Flavonoids:** Quercetin, apigenin, kaempferol, naringen acid B, llithospermic acid B, amburosides A, luteolin, apigenin 7-O-glucuronide, (−)-epigallocatechin, (+)-cate **Others:** Thymoquinone, thymol, carvacrol, demethylber acid, calleryanin 3,4-dihydroxybenzoate, calleryanin 3-h methoxybenzoate, gastrodin 3,4-dihydroxybenzoate.
Prunella vulgaris	
Anti-tumour, anti-inflammation, immunoregulation, antiviral, antioxidant, anti-osteoporosis, anti-depression, hypotensive, hypolipemic, cardioprotective, anti-dementia, anti-amnesia.	**Phenolic acids:** p-coumaric acid, caffeic acid, rosmarini **Flavonoids:** Kaempferol, luteolin, delphinidin, quer galactoside, homoorinet, cinaroside, quercetin-3-O-*β*-D O-*β*-D-glucoside.

	Steroids and derivatives: Beta-sitosterol, spinasterol, st I, poriferasterol monoglucoside, morin, ducosterol, (diene-3-e, Stigmast-7-en-3β-ol. **Triterpenes:** Oleanolic acid, ursolic acid, vulgarsaponi methyl ursolate, methyl, maslinate, pravuloside A/B, pal tetracosanoic acid, stearic acid, 6,9-octodecadienoic acic oleic acid, peanut oleic acid, moringoic acid, lauric aci acid, palmitic acid, myristic acid, and linoleic acid. **Coumarins:** Umbelliferon, scopoletin, esculetin.
Salvia verbenaca	
Antibacterial, antioxidant, anti-cancer, antiparasitic, insecticidal, antihemolytic.	**Phenolic acids:** *p*-Hydroxybenzoic acid, *p*-coumaric aci acid, caffeic acid, ferulic acid, 3-O- and 4-O-caffeoylquin **Flavonoids:** Naringenin, cirsiliol, luteolin, apigeni genkwanin. **Others:** Palmitic acid, stearic acid, linolenic acid, arachic acid, palmitoleic acid, arachidic acid, verbena dehydroroyleanone, cryptanol, sitosterol, campesterc microstegiol, stigmasterol, carnosic acids, methyl carnos
Thymus mastichina	
Antibacterial, anti-fungal, antioxidant, anti-cancer, antiviral, insecticidal, insect repellent, anti-Alzheimer, anti-inflammatory.	**Phenolic acids:** Rosmarinic acid, hydroxycinn methoxysalicylic acid, caffeic acid, chlorogenic aci salvianolic acid A/K isomer. **Flavonoids:** Quercetin glucoside, 6-hydroxylute luteolin glucoside, 6- hydroxyapigenin7-Ogluco Oglucoside, naringenin, luteolin, carnosol, apigenin, k hexuronide, sakuranetin, sterubin. **Others:** Oleanolic acid, ursolic acid, xanthophyll lutein,

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- *Achillea millefolium* L.

The *Achillea* genus is well known for its use in preventing diabetes (Table 2). Most of the research has been carried out on *Achillea millefolium* L. Yarrow, a perennial plant native to the temperate regions of Europe and Asia. Humans have used it for over 3,000 years [218]. It's commonly known as yarrow (milefólio or erva-carpinteira) and is widespread in mountain meadows, pathways, crop fields and home gardens [128]. In the study by Rezaei et al. [408], the effect of a hydroalcoholic extract of this plant at 25 mg/kg/day and 100 mg/kg/day was evaluated on streptozotocin (STZ)-induced diabetic rats. The results showed that this extract had a beneficial effect on serum glucose, lipids and liver enzymes compared with the metformin-treated groups and controls. These effects were also more pronounced at 100 mg/kg/day than at 25 mg/kg/day [408]. According to Rezaei et al. [408], STZ caused a considerable increase in serum liver enzyme levels, while treatment with metformin or *A. millefolium* extract significantly attenuated these elevations.

Similar results were reported in a study by Coskun et al. [409] on the protective effect of Achillea on abnormal lipid profiles. Mustafa et al. (2012) evaluated the hypoglycaemic and hypolipidemic effects of the extract of *A. millefolium* in ALO-induced diabetic rats [410]. They reported that the extracts at dose levels of 250 and 500 mg/kg body weight (BW) showed a significant decrease in blood glucose level, TG (Triglycerides), VLDL (Very Low-Density Lipoprotein), cholesterol, SGOT (Serum Glutamic-Oxaloacetic Transaminase Test), SGPT (Serum Glutamic Pyruvic Transaminase test), and ALP (Alkaline Phosphatase) in diabetic rats. Nematy et al. (2017) reported that the plant had dose-dependent positive effects on appetite in rats [411]. According to Rezaei et al. (2020), the flavonoids present in *A. millefolium* can block serotonin receptors and increase plasma ghrelin content [408], as well as appetite [411,412]. Therefore, this plant has antioxidant properties and can used to improve the complications of oxidative stress conditions such as T2DM [413]. This extract could act as a hypoglycaemic factor and reduce intestinal glucose absorption thanks to its pharmacological properties (Table 1). According to Karimi et al. (2021), treatment with *A. millefolium* could protect renal tissue against the complications of diabetes by increasing Bax (Bcl-2-associated X protein) mRNA levels. This study indicates that hydroalcoholic extracts of the plant not only improve renal function through their antioxidant activity and modulate certain biochemical factors in diabetic rats [414].

Another study by Chávez-Silva et al. (2018) suggests that the hydroethanolic extract of *A. millefolium* probably induces its antidiabetic function via the PPARγ (activating peroxisome proliferator-activated receptors) / GLUT4 pathway, improving sensitivity to insulin and promoting the expression of glucose metabolism genes, such as GLUT4, which allow glucose to be transported into the cell, resulting in its reduction in the blood [415]. On the other hand, Zolghadri et al. (2014) reported that ethanolic extract of *A. millefolium* significantly decreased the expression of IL-1β and iNOS (inducible Nitric Oxyde Synthase) genes against the cytotoxic effect induced by STZ on pancreatic β cells, and those increasing insulinemia [416]. Furthermore, as a result, it was persistent throughout the experiments in the oral glucose tolerance test and the STZ diabetic model; this suggests another mode of function that participates as an extrapancreatic contribution, which could induce insulin sensitisation [415]. According to Chávez-Silva et al. (2018), these results could be related to PPARγ activation, which there is evidence decreases inflammatory cytokines [IL-6, TNF-α (Tumour Necrosis Factor), IL-1β, IL-10, IL-12 and gelatinase B]. It decreases iNOs and scavenger receptor A gene expression [415].

Table 2. Medicinal plants in NPSE for diabetes management with scientific validation of the claimed anti-diabetic effects (*in vitro*).

Target	Part used/Extraction	C
	Asteraceae	
Arctium minus (Hill) Bernh		
A-GLU/A-AMY	1mg/ml of MeOH, CH2Cl2, EtOAc, and BuOH extracts of leaves (L), flowers (F) and roots (R).	AGLU-LMeOHext = 3.32 ± AGLU-LCH2Cl2-ext = 87.1 5.57. AGLU-LEtOAc-ext = na, AI AGLU- LBuOH-ext = 24.49 AGLU-LAqua-ext = 15.51 ± AGLU-FMeOHext = na, AM AGLU-FCH2Cl2-ext = 21.68 AGLU-FEtOAc-ext = 40.69 AGLU- FBuOH-ext = 6.40 ± AGLU-FAqua-ext = 13.32 ± AGLU-RMeOHext = na, AM AGLU-RCH2Cl2-ext = 68.0 AGLU-REtOAc-ext = 36.11 AGLU- FBuOH-ext = na, AI AGLU-RAqua-ext = 30.40 ±
Achillea millefolium		
A-GLU	Hydromethanolic extract of aerial parts.	AI 55% inhibition at 1.6 mg
A-GLU	Hydroethanolic extract of aerial parts.	The extract promoted the α
INS secretion and calcium mobilization		mg/ml concerning control.
PPARγ and GLUT4 expression analysis.		and GLUT4 (two-fold) relat 0.05). Finally, it significantl compared with the control.

Arnica montana		
A-AMY	Methanolic extract fractions (dried cell biomass of seeds germinated).	All fractions inhibited α-am
Bellis perennis		
Quantification of GLUT4 translocation. Glucose Transport Assay	- A mixture of flowers and leaves (EXT4404) ethanolic extracts. - Ethanolic extract of flowers alone (EXT4407). - Ethanolic extract was prepared from flowers collected from a local area.	Both extracts had a clear do being slightly more effecti had no effect at 0.25 r concentration only increase are effective inducers of GL
A-GLU/A-AMY	Methanol: water (80:20%, v/v) extract of flowers.	IC50A-AMY: 8.48 ± 0.07 mg ± 0.01 mg/ml of dried flowe
Bidens frondosa		
A-GLU/A-AMY	Ethanolic extracts (80%) of aerial parts.	IC50A-GLU = 0.41 mg/mL enzyme strongly (64.29–75. activity.
Cichorium intybus		
A-AMY	Aqueous extracts of aerial parts.	IC50A-AMY= 136.13 ± 8.09
Insulinotropic investigations (IC1) Insulin sensitizing investigations (IC2) Hepatocyte culture and glycogenolysis test (IC3) Evaluation of glucose 6-phosphatase activity (IC4)	Caffeic, ferulic acids and Chicoric acid (CAE, extracted from aqueous extract).	Caffeic acid mainly promot Ferulic acid elicits a clear in hepatic glycogenolysis. CA uptake without affecting l compounds implicates hep to chlorogenic acid, an inhi
Glucose uptake assay. β-cell culture and measurement of INS secretion. Rat pancreatic islet experiments.	Caffeic acid, chlorogenic acid (CGA), and chicoric acid (CAE).	CRA and CGA increased gl effect only observed in the p of INS.

		Both CRA and CGA stimul cells and rat islets of Lange observed in the presence of
Study of G6Pase and PEPCK expression (IC5).	Three di-O-caffeoylquinic acids (CQA) were extracted from chicory roots methanolic extract.	CQA suppressed hepatic hepatoma cells by reducing
Gene expression of PI3K and MAPK pathways		Activation of PI3K and MA gene expression. Promoted
Cellular bioenergetics (IC6).		and cellular metabolism b and proton leak.
Differentiation induction of embryonal carcinoma stem cells into INS-producing cells (IC7)	Methanolic extracts (100%) of leaves.	The extract efficiently indu into clusters similar to panc cellular and functional char
A-GLU/A-AMY	Aqueous methanolic extracts (80% methanol, 19% H2O, 1% HCl; v/v/v) of the plant.	IC50A-AMY: 18.3 ± 0.7 mg/
Glucose uptake test.	- Natural chicoric acid extract (NCRAE): Hydroethanolic extract (70:30). - Synthetic Chicoric and Chlorogenic Acids Mixture (SCCAM) contains the two major compounds of NCRAE, in proportion to 70% of synthetic L-chicoric acid (CRA) and 30% of synthetic chlorogenic acid (CGA).	Adding NCRAE increased agrees with our previous r µg/mL, the SCCAM soluti with a value close to the NC
Glucose uptake test and lipid accumulation assays.	Methanolic extract (CME) and CME/DT (detannification).	CME and CME/DT exhibite adipocytes with a dose-de
PTP1B Inhibition study.		profile in the presence of P and Genistein) substantiate CME inhibited the differe failed to show glucose uptal exhibited by CME/DT is exa

		assay, mRNA and protein e behaviour of CME and CM
Glucose uptake assay.	12, 8-guaianolide sesquiterpene lactones isolated from butan-1-ol and ethyl acetate fractions of roots extract	The compounds significar hyperglycemic HepG2 cell
Dittrichia viscosa subsp. *Viscosa* (Syn. *Inula viscosa*)		
A-GLU/A-AMY	Methanol: water (80:20%, v/v) extract of leaves.	IC50A-AMY: 1.381 ± 0.085 r mg/mL.
A-GLU/A-AMY	Methanol (MeOH), ethyl acetate (EtOAc) and chloroform (CHL) extracts of leaves.	IC50A-GLU-EtOAc: 29.9 ± 1 0.387% IC50A-GLU-MeOH: 22.3 ± 1 1.623% IC50A-GLU-Chlo: 39.8 ± 0.7
A-GLU/A-AMY	Tomentosin is extracted and purified from dichloromethane and ethanolic extract.	IC50A-GLU-26.61 ± 0.236 µ
Glucose uptake assay (IC8). Study of aP2 and PPARg2 gene expression.	7-O-Methylaromadendrin (MAD) extracted from methanolic extract of the aerial part of the plant.	MAD significantly stimulat MAD increased the P2a and MAD stimulated the reactiv phosphorylation of PI3K-(A induced, INS-resistant Hep
Galinsoga parviflora		
A-GLU/A-AMY	Aqueous extracts of leaves.	At 2.5mg/mL IA% (A-GLU)
A-GLU	Two compounds, Galinsosides A (1) and B (2), flavanone glucosides extracted from methanolic extract of whole plant.	IC50A-GLU (1): 286 ± 0.68 µ
Helichrysum stoechas		
A-GLU/DPP-4	Methanol extracts of aerial parts.	IC50A-GLU: 481.01 µg/mL,

Hypochaeris radicata		
A-GLU/A-AMY	Aqueous extracts of leaves. HR1: Extract fresh plant materials; HR2: Extract plant materials after blanching; HR3: Blanching water extract.	IC50A-GLU-HR1: 79.4 ± 1.7 μg/mL; IC50A-GLU-HR3: 8 IC50A-AMY-HR1: 41.9 ± 1.4 μg/mL; IC50A-AMY-HR3:
Lactuca serriola		
A-GLU	4-hydroxybenzoic acid (1), protocatechuic acid (2), kaempferol (3), quercetin (4), lactuside A (5), luteolin-7-O-β-D-glucoside (6) are extracted from methanolic extracts of the leaves.	IC50A-GLU-(1): 810.31 ± 1.0 μM; IC50A-GLU-(3): 39.72 ± μM; IC50A-GLU-(5): 468.98 161.29±0.31 μM.
Senecio vulgaris		
A-AMY	Methanol extract (MeOH = 1 mg/ml), Dichloromethane extract (DCM1 = 100 and DCM2 = 50 μg/ml).	MeOH-IA%: 82.46 ± 0.0041 DCM2- IA%: 59.05 ± 0.0001
ALDO	Methanol extracts of aerial parts.	IA%: 42.00% at 1mg/mL.
Solidago virgaurea		
A-GLU/A-AMY	Conc-ASE (Concentrated extract obtained after accelerated solvent extraction) Conc-LE (Concentrated extract obtained after Laser extraction).	Conc-ASE = IC50A-GLU: 9. μg/mL. Conc-LE = IC50A-GLU : 8.7 μg/mL.
Sonchus oleraceus		
Glucose uptake assay (IC13) Analysis of p-AMPK/Akt/GSK3-β expression in cells.	Hydroethanolic extract (90%) of the leaves (SOL).	The glucose uptake in HepG was significantly increased than that treated with insul extracts for 24 h, the p-AMI significantly increased by a respectively, compared wit
Tanacetum parthenium		

ra-ALDO/AGEs	Methanolic extract (70%) (ME) Ferulic acid (FA), Apigenin (API), Luteolin-7-O-glucoside (LUG), Luteolin (LUT), Chrysosplenol (CHR), Kaempferol (KAE), Santin (SAN) were extracted and purified from the methanolic extract.	ME: ra-ALDO-IA% (61.1 μg/mL), IC50-AGEs (163.71 FA: IC50-ra-ALDO (3.20 ± μg/mL). API: IC50-ra-ALDO (1.97 ± LUG: IC50-ra-ALDO (1.31 ± 0.12 μg/mL). LUT: IC50-ra-ALDO (1.76 μg/mL). CHR: IC50-ra-ALDO (1.92 ± KAE: IC50-ra-ALDO (1.11 ± SAN: IC50-ra-ALDO (NA),
A-GLU/A-AMY	Ethanolic extract of aerial parts. Extraction by Accelerated solvent extraction (ASE), Microwave−assisted extraction (MAE), Maceration (MAC), Soxhlet (SOX) and Ultrasound−assisted extraction (UAE).	ASE: IC50A-GLU (1.63 ± 0.0 extracts), IC50A-AMY (0.51 MAE: IC50A-GLU (1.64 ± AMY (0.53 ± 0.05 mmol AC MAC: IC50A-GLU (1.65 ± AMY (0.52 ± 0.02 mmol AC SOX: IC50A-GLU (1.67 ± AMY (0.51 ± 0.03 mmol AC UAE: IC50A-GLU (1.64 ± AMY (0.56 ± 0.01 mmol AC
Tanacetum vulgare		
A-GLU/A-AMY	Hexan, hydroethanolic and infusion of flowers (HEXF, HETF, INFF), Stems (HEXS, HETS, INFS) and Aerial parts (HEXAP, HETAP, INFAP).	HEXF: IC50A-GLU (10.4 (ACAE)/g extracts), IC50A extract). HETF: IC50A-GLU (10.77 ± AMY (0.33 ± 0.01 mmol AC

		INFF: IC50A-GLU (3.57 ± AMY (0.07 ± 0.01 mmol AC HEXS: IC50A-GLU (10.60 ± AMY (0.50 ± 0.02 mmol AC HETS: IC50A-GLU (7.54 ± AMY (0.33 ± 0.02 mmol AC INFS: IC50A-GLU (4.00 ± AMY (0.10 ± 0.01 mmol AC HEXAP: IC50A-GLU (10.56 AMY (0.48 ± 0.03 mmol AC HETAP: IC50A-GLU (8.67 AMY (0.35 ± 0.03 mmol AC INFAP: IC50A-GLU (4.26 ± AMY (0.09 ± 0.01 mmol AC
	Lamiaceae	
Calamintha nepeta subsp. *Nepeta* (Syn. *Clinopodium nepeta*)		
A-GLU/A-AMY	Methanolic extract (80%) of leaves.	At 10 mg/ml IA% (A-GLU) 0.94%
A-AMY	Methyl alcohol: water (7:3) extract fractionated with ethyl acetate (AcOEt), dichloromethane (DCM), and n-butanol (BuOH).	IC50A-AMY of DCM, AcO
A-AMY	Methanolic extract (ME), essential oil (EO), and aqueous extract (AQ).	IC50A-AMY-ME: 24.46 m IC50A-AMY-AQ: 115.47 mg
Lavandula pedunculata		
A-GLU/A-AMY	Aqueous extract of flowering tops.	IC50A-AMY: 0.44 ± 0.05 mg
Intestinal Glucose Absorption *in vitro*		The extract inhibited the int ± 4.01 μg/mL) in a concentr
Lavandula stoechas		

A-GLU/A-AMY	Aqueous extract of aerial parts.	IC50A-AMY: 0.485 ± 0.13 m
Intestinal Glucose Absorption assay, *In situ*.		The extract lowered intestin mg/kg.
A-GLU/A-AMY	EO of aerial parts.	IC50A-AMY: 3.00 ± 0.008 m
Glucose production assay (IC9)	Ethyl acetate (EE) and n-butanol (BE) fractions are prepared from an aqueous extract of aerial parts.	EE and BE at low doses
Glucose uptake assay (IC10)		hepatic gluconeogenesis in
Effects on PEPCK and G6Pase gene expression.		expression of PEPCK and extracts increased the IN
Effects on AKT activation and GLUT4 expression.		effectively than metformin expression of lipoprotein
Transcriptome analyses		myotubes at low doses. EE and stimulated the activati C2C12 cell lines.
A-GLU	Ursolic acid extracted from Methanol (ME), ethanol (ET), methanol-dichloromethane (1: 1, v/v) (MDI), acetone (AC), ethyl acetate (EA), diethyl ether (DEE), and chloroform extracts (CHL).	IC50A-GLU-ME: 49.86 ± 0.3 mg/mL, IC50A-GLU-MDI: 24.63 ± 0.13 mg/mL, IC50A GLU-DEE: 23.60 ± 1.04 m mg/mL.
A-GLU	EO of flowering leaves.	IC50A-AMY: 106.73 ± 3.27 μg/mL.
Melissa officinalis		
Anti-glycation assay.	Aqueous extract of leaves (AQ). Rosmarinic acid (RA), melitric acid A (MA), salviaic acid A (SA), caffeic acid (CA).	IC50-AQ: 0.24 mg/mL, IC50 IC50-SA: 0.16 mM, IC50-CA
A-GLU/A-AMY	Aqueous extract of leaves	IA%: 83.9%, A-AMY: No ac
A-AMY	Lemon balm-based extract with 50% RA	IA%: 50%

Uptake inhibition of glucose (UIG) and fructose (UIF) (IC12)	Methanolic and aqueous extract of leaves.	UIG%: <25%, UIF: No activ
Glucose consumption (IC8)	EO (A, B and C compagnies)	EO-A: 63.64 ± 11.46%, EO-E
Gene expressions analysis of p-AMPK, AMPK, p-ACC, ACC, PPAR, CEBPα, and SREBP1 proteins.		The Western blot data sugg adenosine monophosphate carboxylase pathway can b
Mentha aquatica		
A-AMY	Hydroethanolic extract (70%) of the leaves.	IC50A-AMY: 229.50 ± 4.1 µ
A-AMY	Methanolic (ME) and aqueous extracts (AQ) of the leaves.	IA%-ME: 61.7 ± 5.5%, IA%-
Uptake inhibition of glucose (UIG) and fructose (UIF) (IC12)	Methanolic and aqueous extract of leaves.	UIG%: <25%, UIF: No activ
Mentha pulegium		
A-GLU/A-AMY	Methanolic and aqueous extract of leaves.	IC50A-GLU-ME: 20.38 µg/m IC50A-AMY-ME: 23.11µg/m
A-GLU/A-AMY	Ethyl acetate fraction of aerial part.	IC50A-GLU: 61.85±1.69 µg/
Mentha suaveolens		
A-GLU/A-AMY	EO of the aerial part.	IC50A-GLU: 141.16 ± 0.2 µg
Origanum vulgare		
A-AMY	Clonal oregano shoots ethanolic extracts (50%) (O-1, O-9, O-11Y, O-11M, O-12, O-17, OK-17, O-23, O-24, O-26, GO-19-1).	The strongest anti-amylase which had an AI index val 57% inhibition of enzyme a extracts tested had AI index these experiments, an AI approximately 33% α-amyl
ALDO		

Docking studies of ALDO inhibitory activity (EB).	Caffeic acid (CA), rosmarinic acid (RO), lithospermic acid B (LTO), 12-hydroxy jasmonic acid 12-O-β-glucopyranoside (HDG), p-menth-3-ene-1,2-diol 1-O-β-glucopyranoside (MDG) isolated from the polar extracts of aerial parts.	ALDO-CA: 8 ± 4.6 %, ALDO ALDO-HDG: 77 ± 1.4 %, AL EB-CA: −7.68 kcal/mol, kcal/mol, EB-HDG: −14.58 k
A-GLU/A-AMY	Aqueous and ethanolic (12%) extract of plant clonal lines.	At 1000 μg/mL: A-GLU (93.
Analysis of PPARγ- and δ-mediated transactivation, a test of adipogenic potential, INS-stimulated glucose uptake, Neutral red assay.	*Origanum vulgare* ssp. *vulgare* (1): Hexane (Hex), dichloromethane (DCM), and ethyl acetate (EtOAc) extracts of the aerial part. *Origanum vulgare* ssp. *hirtum* (2): dichloromethane (DCM), methanol (MeOH) extracts of the aerial part.	(1): Hex ext = Activatio differentiation (NA), INS-s endothelial cells (NA), Viab DCM ext = Activation of t (NA), INS-stimulated GLU- (-), Viability of macrophage EtOAc ext = Activation of (NA), INS-stimulated GLU- (NA), Viability of macropha (2): DCM ext = Activation o (NA), INS-stimulated GLU- (NA), Viability of macropha MeOH ext = Activation of th (NA), INS-stimulated GLU- (NA), Viability of macropha
DPP-IV/PTP1B	Methanolic extracts of leaves: Commercial oregano extract (E1) and Greenhouse-grown oregano extract (E2). Chemical fractionation by flash chromatography system (fractions FA to FI).	DPP-IV-IC50: (E1) = 28.4 ± 6 FA>500 μM GAE, FB = 206. = 317.4 ± 60.7 μM GAE, FE = GAE, FG = NA, FH = NA, F

		PTP1B-IA: (E1)/(E2) = NA, 1.3 ± 1.0 %, FD = NA, FE = 3 FH = NA, FI = NA.
A-GLU/A-AMY	(1): EO of *O. vulgare* subsp. *Hirtum.* (2): EO of *O. vulgare* subsp. *Vulgare.*	IC50A-AMY (1): 0.14 ± 0.00 0.03 mmol ACEs/g. IC50A-AMY (2): 0.13 ± 0.00 0.91 mmol ACEs/g.
A-GLU/A-AMY	Methanolic extract (80%) of leaves.	A-GLU-IA = 58.41 ± 1.97 %,
A-GLU	Aqueous acetonitrile (50%) of powder leaves.	IC50A-GLU = 0.35 ± 0.03 µg
AGEs assay		Cells treated with extract le
Glucose uptake assay (IC13).		showed significantly enha
The mRNA and protein expression of PEPCK, SREBP-1c, GLUT2, CYP2E1 (IC14).		INS-treated cells. The extract decreased the protein expression of PE inhibited the expression of of GLUT2.
A-GLU/A-AMY/LIPA	Ethanolic extracts (80% v/v).	IC50A-AMY = 44.71 ± 0.86 µ IC50-LIPA = 922.35 ± 30.99
Prunella vulgaris		
Study of Glucose Production (IC15).	Methanolic extract of arial part (PVA). Rosmarinic and caffeic acids were extracted from solid residue PVA by organic solvent, representing about 26% and 0.3% w/w of total extract.	The PVA lowered gl (glycogenolysis), dihy (gluconeogenesis). None of mRNA expression, which I decreased by INS, increase
The mRNA expression analysis of G6Pase, GLUK, CALM, PEPCK and GK (IC16).		

		other treatments. Both co mRNA expression; PVA dic
ra-ALDO / hu-ALDO / AGEs assay	Aqueous extract (AQE) partitioned sequentially with n-hexane (HEX), methylene chloride (CH2Cl2), ethyl acetate (EtOAc), n-butanol (BuOH) and water (H2O). Compounds (C1 to C6) isolated from AQE fractionation.	ra-ALDO: AQE-IA = 36.1 CH2Cl2-IA= 32.49 ± 0.54 % 2.99 ± 0.10 μg/mL), BuOH-IA NA, C2 = NA, C3-IC50 = 8. C5-IC50 = 3.20 ± 0.55 μM, C hu-ALDO: C1 = NA, C2 = N C5-IC50 = 12.58 ± 0.32 μM, C AGEs assay: AQE-IA = 2 CH2Cl2-IA = 54.03 ± 1.00 % = 68.31 ± 1.06 % (IC50 = 40.47 ± 0.68 %, H2O-IA = 30 NA, C3 = NA, C4 = 20.67 ± 33.16 ± 0.54 μg/mL), C6-IA μg/mL).
Cas-3 activity and activation of the apoptotic signaling pathway (IC16) analysis (Bax/Bcl-2, Fas/FasL, phospho-JNK, phospho-ERK, phospho-p38, NF-κB binding activity, phosphorylated-IκB, TNF-α, IL-6).	Aqueous extract (AQE).	AQE administration signifi 1 cell death and LDH activi 3 activity.
A-GLU/A-AMY	Hydroethanolic extract of inflorescence (PV) contained RA (4.5%), CA (9.8%) and pCA (11.6%).	IC50A-GLU-PV: 90.9 μg/ml IC50A-GLU-CA: 4.7 μg/ml, IC50A-GLU-RA: 11.6 μg/m
NPMDA	Active coumpouds tested (Kaempferol, luteolin, delphinidin, quercetin, beta-sitosterol, spinasterol,	The sterols and flavonoids signalling pathway, AGE

	stigmasterol, vulgaxanthin-I, poriferasterol monoglucoside, stigmast-7-enol, morin)	pathway, and PI3K-Akt pa INS.
A-GLU	Hydroethanolic extract (75%) (HE) partitioned sequentially with Petroleum ether (PE), Ethyl acetate (EtOAc), n-butanol (BuOH), and water (H2O) fractions. Compounds Caffeic acid (C1), Isoquercitrin (C2) and Rosmarinic acid (C3) isolated from AQE fractionation.	HE-IC50 = 130.46 ± 4.33 µg/ EtOAc-IC50 = 69.13 ± 2.86 µ µg/mL, H2O-IC50 = 191.88 µg/mL, C2-IC50 = 85.52 ± 2. µg/mL.
	Salvia verbenaca	
A-GLU/A-AMY	Methanolic extract (85%) (ME) and decoction (DE) of the aerial part.	IC50A-GLU-ME: 50.5 ± 1.40 0.08 µg/ml. IC50A-GLU-DE: 313.7 ± 1.3
	Thymus mastichina	
A-GLU/A-AMY	Essential oil.	IC50A-GLU = 100 ± 0.0 µg/

ACC: Acetyl-CoA carboxylase, **ADIP**: Adiponectin **AGEs:** Advanced glycation end products inhibition assay, **AI:** Amylase inhibition, **Akt:** adenosine 5-monophosphate-activated protein kinase, **aP2**: Adipocyte-specific fatty acid binding protein; **A-AMY:** Alpha amylase, **A-GLU:** **Bcl-2**: Marker linked to germinal center B cells, **CALM:** Calmodulin, **cas-3**: Caspase, **CEBP*α*:** Transcription factor CCAAT/enhancer binding Energy binding (kcal/mol), **ERK:** Extracellular Signal-Regulated Kinases, **GAPDH:** Glyceraldehyde-3-phosphate dehydrogenase, **GLUT4:** **G6Pase**: Glucose-6-phosphatase, **hIR:** Human insulin receptor, **Hu-ALDO:** human recombinant aldose reductase, **IL-1β**: Beta 1 Interleukin kinase, **JNK:** c-Jun N-terminal cinase, **LEP:** Leptin, **LPL:** Lipoprotein lipase**, NA:** Not actif, **NF-κB:** Nuclear factor-kappa B, **NPMDA:** Netwo The potential action targets were (IL-6 and INS), and the signalling pathways were (the AGE-RAGE signalling pathway, TNF signalling pathw pathway)**, PEPCK**: phosphoenolpyruvate carboxykinase, **PI3K**: phosphatidylinositol 3-kinase, **PKB**: Protein kinase B, **PPAR:** Activating p Peroxisome proliferator-activated receptor g2, **PTP1B:** Protein tyrosine phosphatase 1B, **P38:** mitogen-activated protein kinases, **ra-ALDO**: R Element-binding Protein, **TNF-*α*:** Tumor necrosis factor, ***In vitro* Cellular models studied. IC1:** Rat insulinoma-derived INS-1 β-cells, **IC2:** L rats fed *ad lib*, **IC4:** Microsomal fractions of hepatic cells, **IC5:** H4IIE cells (Rat hepatoma cell line), **IC6:** Changes in mitochondrial respirati carcinoma cell line), **IC8:** 3T3-L1 (Murine preadipocyte cell line), **IC9:** HepG2 (Human hepatocellular liver carcinoma) and differentiated 3T3 H4IIE cells, **IC11:** Palmitate induced INS resistance model in C2C12 cells (Immortalized mouse myoblast cell line), **IC12:** Human colorecta HepG2 cells, **IC14:** HepG2 and E47 cells (Cellosaurus Hep G2-E47), **IC15:** Rat hepatocytes, **IC16:** Fao Cells differentiated derivatives of the c Reuber H35 rat hepatoma, **IC17:** INS-1 cells (INS-1 832/13 Rat Insulinoma Cell Line), **IC18:** The pRB-deficient mouse embryonic fibroblasts (M cells (CRL1830), mouse hepatoma from BW7756 tumours in C57L mice, Murine monocyte/macrophage cell line RAW264.7, The human hybri

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- *Anthemis canescens* var. *aurea*

The native range of *Anthemis canescens* var. *aurea* (syn. *Matricaria aurea*), also known as corn chamomile, is Mediterranean to the northwest of India and the Arabian Peninsula. It is annual and grows primarily in the subtropical biome [117]. Several scientific studies have examined these effects, notably Ismail et al. [222]. A T2DM rat model was used, along with identification of chemical components by LC-MS/MS (Liquid Chromatography coupled to tandem Mass Spectrometry), enzyme activity assays, gene expression analyses by q-RTPCR, network pharmacology analyses and molecular docking simulations were also carried out in an attempt to elucidate the molecular mechanism(s) of this plant's antidiabetic effects [222]. The results showed that only the polar hydroethanol extract of *M. aurea* exhibited remarkable antidiabetic activity. In addition, it improved dyslipidaemia, insulin resistance status, ALT (Alanine transaminase) and AST (Aspartate aminotransferase) levels [222].

LC-MS/MS analysis of the hydroethanol extract identified 62 compounds, including the popular flavonoids of chamomile, apigenin and luteolin, other flavonoids and their glycosides, coumarin derivatives and phenolic acids (Table 1). According to the authors [222], the 46 compounds selected were linked to 364 candidate T2DM targets. Network analysis enabled them to identify 123 pivotal proteins, including insulin signalling and metabolic proteins: IRS1 (Insulin receptor substrate 1), IRS2 (Insulin receptor substrate 2), PIK3R1 (Phosphoinositide-3-kinase regulatory subunit 1), AKT1 (AKT Serine/Threonine Kinase 1), AKT2 (AKT Serine/Threonine Kinase 2), MAPK1 (Mitogen-Activated Protein Kinase 1), MAPK3 (Mitogen-activated protein kinase 3) and PCK1 (Phosphoenolpyruvate carboxykinase 1), inflammatory proteins TNF and IL1B (Interleukin-1Beta), antioxidant enzymes: CAT (Catalase) and SOD (Superoxide dismutase), and others [222]. Subsequent filtering enabled them to identify 40 crucial principal targets (major hubs) of *M. aurea* in treating T2DM. Functional enrichment analyses of the candidate targets revealed that the plant targets were mainly involved in the inflammatory, energy-sensing/endocrine/metabolic, and oxidative stress modules. According to Ismail et al. (2022), the hydroethanol extract of *M. aurea* is capable of significantly increasing PIK3R1 and decreasing IL1B, PCK1 (Phosphoenolpyruvate carboxykinase 1) and MIR29A (microRNA 29a human gene) according to q-RTPCR gene expression analysis [222]. Based on experimental and computational analysis, this study revealed that *M. aurea* exerted antidiabetic action via simultaneous modulation of multiple targets and pathways, including inflammatory, energy-sensing/endocrine/metabolic, and oxidative stress pathways [222].

- *Bellis perennis* L. and *Bidens frondose*

The *Bellis* genus comprises around twenty species of small annual or perennial herbs found mainly in the Mediterranean region. *Bellis perennis* L. (common daisy) is widely distributed in Portugal continental and used in folk medicine (Supplementary Table S3). Many of its pharmaceutical functions derive from the antioxidant characteristics of its contents and its quantity of phenolic compounds. All parts of this plant have been studied, and several chemical compounds have been characterised. In a study by Haselgrübler et al. (2018), the effect of its ethanolic extracts (50%) revealed significant efficacy in inducing GLUT4 translocation in the *in vitro* cell system applied using a screening assay based on fluorescence microscopy [419]. The extracts also reduced blood glucose levels in chicken embryos (*in ovo*), confirming the plant activity in a living organism.

According to the results of high-performance liquid chromatography (HPLC), the numerous polyphenolic compounds identified and quantified, including apigenin glycosides, quercitrin and chlorogenic acid (Table 1), potentially contribute to stimulating the transfer of GLUT4 from the cytosolic zone to the plasma membrane, leading to decreased blood glucose levels [419]. Moreover, it was shown in the study by Nowicka and Wojdyło (2019) that the methanolic extract (50%) has a high content of triterpenoids, carotenoids and flavonols, with the ability to inhibit α-amylase and α-glucosidase (Table 1). The species *Bidens frondosa* also displayed promising results in diabetes [420]. The acute hypoglycaemic activity of its ethanolic extract (80%) was studied in normoglycaemic, glucose-loaded and STZ-induced diabetic rats [421]. The subacute antidiabetic effect was studied in an 8-day experiment. The extract showed a promising and significant hypoglycaemic impact in all the *in vivo* models tested [421]. The acute antidiabetic effect was 42% at 500 mg/kg. The α-glucosidase

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and α-amylase inhibitory activity of the extract was also determined and showed strong inhibition of the α-glucosidase enzyme (75.22% at 2 mg/mL) [421] (Table 2).

- *Chamaemelum nobile*

Roman chamomile, as *Chamaemelum nobile* (syn. *Anthemis nobilis* L. or *Chamomilla nobilis*), is an ornamental plant known as a medicinal plant since the Middle Ages [251]. It is native to Southwest Europe (France, Spain and Portugal) but is present all over Europe, North Africa and Southwest Asia [251]. The plant is cultivated mainly in England, Belgium, France, Germany, Hungary, Poland, Bulgaria, Egypt and Argentina. Pharmacological studies have revealed a wide range of biological properties and a broad phytochemical diversity (Table 1).

Among these studies, Eddouks et al. (2005) carried out a single study on the plant against diabetes. A single dose and daily oral administration (20 mg/kg BW) for 15 days tested the aqueous extract of the aerial part of Roman chamomille on blood glucose concentrations and basal insulin levels in normal and STZ-induced diabetic rats [462]. Single oral administration of the aqueous extract reduced blood glucose levels from 6.0 ± 0.3 mmol/l to 4.9 ± 0.09 mmol/l ($P < 0.05$) 6 hours after administration in normal rats and from 21.1 ± 1.3 mmol/l to 14.5 ± 0.9 mmol/l ($P < 0.001$) in streptozotocin-induced diabetic rats [462]. In addition, blood glucose levels decreased from 6.1 ± 0.06 mmol/l to 4.6 ± 0.17 mmol/l and from 21.1 ± 1.31 mmol/l to 13.7 ± 0.90 mmol/l in normal and STZ diabetic rats, respectively, after 15 days of treatment [462]. Basal plasma insulin concentrations remained unchanged after treatment in normal and STZ diabetic rats.

According to the authors, the mechanism of this pharmacological activity may be independent of insulin secretion [462]. It can exert hypoglycaemic activity in the gastrointestinal tract by slowing digestion and reducing carbohydrate absorption rate [462]. Another study conducted on the compound chamaemeloside, an apigenin glycoside containing a hydroxymethylglutaric acid (HMG) fraction extracted from this plant [463], showed that it did not affect glucose uptake in cultured L6 muscle cells but reduced plasma glucose levels in SwissWebster mice by 19.2% and 31.9% at doses of 125 and 250 mg/kg, respectively. Chamaemeloside only exerted effect after 4 hours of i.p. (intraperitoneal) administration [463]. The effect on interpretandial blood glucose levels in normal rats and oral glucose tolerance was also studied. The results showed that inter-prandial blood glucose levels were unaffected, but that chamaemeloside significantly improved glucose tolerance 4 hours after administration [463].

According to Witherup et al. (1995), chamaemeloside may influence glucose homeostasis via multiple mechanisms, including the release of HMG acid from chamaemeloside and its modulation of insulin secretion [463,464]. A clinical study was also conducted on the hypoglycemic effect of Roman chamomile [465]. Twenty-six pre-diabetic volunteers (21 men and five women; mean age: 50.5 ± 8.5 years) were selected for an 8-week study of supplementation with mixed plant extracts combining a hot water extract of *Anthemis nobilis* (synonym of Roman chamomile), *Crataegus oxyacantha* (hawthorn berry), *Houttuynia cordata* (dokudami), and *Vitis vinifera* at a dose of 1200 mg [465]. The results showed that the mixture reduced abnormal glucose levels and the risk of developing diabetes. The underlying mechanism of action can be attributed to stimulating peripheral energy utilisation, particularly in muscle and adipose tissue [465].

- *Cichorium intybus* L.

Plants in the *Cichorium* genus are particularly valuable for their exceptional therapeutic and medicinal properties (Table 1). It includes plants from the dandelion tribe in the sunflower family, with 10 to 12 species, four to six of which are wild species. They are herbaceous perennials, typically Mediterranean, native to Europe, western Asia and North America. Among its species is *Cichorium intybus* L. (Asteraceae), commonly known as chicory, widely cultivated in many countries worldwide for its many traditional uses and as an edible food. Indeed, it has been included in Chinese Pharmacopoeia for its many beneficial effects on various ailments, from wounds to diabetes (Supplementary Table S3).

In the study by Pushparaj et al. (2007), the hypoglycaemic and hypolipidaemic properties of an ethanolic extract of *C. intybus* were tested on Sprague-Dawley rats treated with STZ (Table 3). The oral glucose tolerance test (OGTT) (a dose of 125 mg plant extract/kg BW) showed a potent

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hypoglycaemic effect. In addition, daily administration of the extract (125 mg/kg) for 14 days to diabetic rats reduced serum glucose by 20%, triglycerides by 91% and total cholesterol by 16% [466]. However, there was no change in serum insulin levels, ruling out the possibility that the extract induces insulin secretion by pancreatic *β*-cells.

This effect on pancreatic *β*-cells was also demonstrated in the study by Ghamarian et al. (2012). Aqueous chicory seed extract prevented BW loss and reduced fasting blood glucose levels in a four-week trial in rats (Table 3). Chicory appears to have both short-term (around 2 hours) and long-term (28 days) effects on T2DM and is a natural food supplement for slowing the progression of diabetes [467]. The ethanolic extract of chicory seeds containing 9.6% caffeoylquinic acids improved blood sugar levels, reduced the atherogenic index and increased blood antioxidant status during a 28-day treatment on Wistar rats (WR) [468].

In another study by Petrović et al. (2024), a polyherbal mixture composed of *Centaurium erythraea* aerial parts, *Cichorium intybus* roots and *Potentilla erecta* rhizomes was tested to determine its potential toxicity *in vivo* and its effect on diabetic complications [469]. The results showed that treatment with the decoction had no toxic effect. Its antidiabetic activity was high *in vitro* and *in vivo* studies (Tables 2 and 3). Fourteen days of treatment with the decoction (15 g/kg) completely normalised the blood glucose levels of diabetic animals, whereas treatment with insulin and glimepiride only slightly lowered glycaemic values [469]. In addition, the lipid status of the treated animals and the levels of AST, ALT, ALP, creatinine, urea and MDA (malondialdehyde) were completely normalised [469]. In addition, the polyherbal mixture completely restored histopathological changes in the liver, kidneys and the four *Cornu ammonis* regions of the hippocampus. According to the authors, the ameliorative effect of the treatment was essentially due to bioactive compounds [469]. They are known for their hepatoprotective activities and ability to lower serum transaminases, ALP and MDA [470,471], with even greater success than glimepiride [472,473].

On the other hand, treatment with the polyherbal mixture increased hepatic glycogen deposition via *β*-cell regeneration by the various compounds present in the preparation [469]. Indeed, hydroxybenzoic acid, one of the bioactive compounds in the tested polyherbal mixture, can regenerate *β*-cells and normal serum insulin and hepatic glycogen levels [474]. In addition, the hepatoprotective activity observed can also be explained by the high antioxidant activity of the mixture [469], which boosts antioxidant defence enzymes via the expression of Nrf2/cytochrome P450 2E1 (CYP2E1), reduces inflammation via the inactivation of MAPK/NF-κB (Nuclear factor-kappa B) signalling pathways and reduces apoptosis via regulation of B-cell lymphoma 2 (Bcl-2)/protein kinase B (AKT)/CAT expression [475].

Furthermore, caffeic acid in the herbal mixture decreases the level of MDA in the kidney and visibly reduces renal epithelial damage in the diabetic animal model [469]. At the same time, rutin administration regulates renal function and reduces the degree of renal tissue damage in induced nephropathy by down-regulating TGF*β*-1 (Transforming growth factor beta 1) and fibronectin expression [471,476]. Epicatechin also reduces lipid peroxidation in kidneys due to benzo rings and aromatic compounds that can bind hydroxyl radicals in tissues [477]. Hyperoside in treating diabetic nephropathy regulates blood urea and creatinine levels. It reduces renal tissue damage by suppressing the expression of fibronectin, collagen IV and tissue inhibitors of metalloproteinase 1 (TIMP-1) while promoting the expression of matrix metalloproteinases 9 and 2 (MMP-9 and MMP-2) [478]. It also prevents further podocyte apoptosis in the glomerulus following diabetes, allowing the regeneration of damaged tissue via the miR-499-5p/APC (Anaphase-promoting complex) axis [479]. In addition, isoquercetin possesses nephroprotective capacity through its hypoglycaemic, hypolipidaemic [480,481] and hepatoprotective activities, similar to sulphonylureas [481]. In addition, caffeic acid regulates lipid status and blood glucose. It attenuates oxidative damage in blood cells, liver cells and kidney tissue [471] by upregulating nuclear erythroid-related factor 2 (NRF2) and downregulating NF-κB [482]. Caffeoylquinic or chlorogenic acids (CQAs), abundant intermediates of lignin biosynthesis in chicory, have also been reported to improve human glucose metabolism (Table 3).

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According to the study by Palatini Jackson et al. (2017), the three di-O-caffeoylquinic acids extracted from chicory suppressed hepatic glucose production in H4IIE rat hepatoma cells by reducing the expression of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), two key enzymes that regulate hepatic gluconeogenesis [424]. Direct comparisons between CQAs and their metabolites (3-caffeoylquinic, caffeic and quinic acids) revealed that the caffeic acid component alone was responsible for the effects observed [424]. Further analysis suggested that activation of the PI3K (Phosphoinositide 3-kinases) and MAPK pathways to control gene expression was common in caffeoylquinic and caffeic acids (Table 1). These compounds promoted increased mitochondrial respiration and cellular metabolism, inducing oxidative phosphorylation and proton leakage [424].

In the study by Azay-Milhau et al. (2013), the anti-hyperglycaemic effect of three hydroxycinnamic acids present in the roots of *C. intybus* was also tested (Table 1). *In vitro* experiments were carried out to compare the results of two hydroxycinnamic acids, caffeic and ferulic acids, with those obtained with chicoric acid extracted (CAE) (50 and 100 µg/mL) on the three main tissues involved in blood sugar regulation (pancreas, muscle and liver) [422].

In vivo experiments were performed on WR given a daily intraperitoneal injection of CAE (3, 15 or 30 mg/kg) for four days (Table 3). An intraperitoneal glucose tolerance test (1 g/kg) was performed on the fourth day. The results showed that the three compounds used could induce an original response. Caffeic acid mainly reduces hepatic glycogenolysis [422]. Ferulic acid caused a marked increase in insulin release and a reduction in hepatic glycogenolysis. However, this compound also inhibited muscle glucose uptake. CAE increased insulin release and glucose uptake without affecting hepatic glycogenolysis (Table 3). The study showed that none of these compounds involved hepatic G6Pase, unlike chlorogenic acid, which is known to inhibit the enzyme and can reduce glucose production by hepatocytes [422]. These results underline that CAE can lower blood glucose levels without affecting the liver. The *in vivo* experiments provide evidence that daily i.p. administration of CAE improves i.p. glucose tolerance in a dose-dependent manner and mainly via an insulin sensitization effect [422].

Table 3. Medicinal plants in NPSE for diabetes management with scientific validation of the claimed anti-diabetic effects (*in vivo*).

Part Used/Extract tested	Model/Parameters studies	Intervention and Duration	Observations
		Asteraceae	
Arctium minus (Hill) Bernh			
R/DEC	Male diabetic GK (Goto-kakizak) rats.	125 g/L DR *ad libitum* / 4 weeks.	The DEC led to a GK rats' occasi significantly affect glycemic control; effects. The DEC decreased several respiratory activity.
R/L/AQ	ALLO-induced diabetic rats. Measurement of biochemical parameters (**B1**)	RAQ (500 mg/kg) and LAQ (200 mg/kg) OG / 21 days.	RAQ was reduced by 34.6 ± 5.8%, and
Achillea millefolium			
NI/HET	STZ-induced diabetic rats. Measurement of biochemical parameters (**B2**)	25 mg/kg/day and 100 mg/kg/day OG / 28 days.	Compared to Metformin, the HET hepatic enzymes with a dose-depende
NI/AQ/MET	OGTT	250 and 500 mg·kg−1 BW DR / 18h.	The AQ/MET at dose levels of 250 an decrease in BG level, TGL, VLDL, c diabetic rats.
	ALLO-induced diabetic rats. Measurement of biochemical parameters (**B3)**	250 and 500 mg/kg BW DR / 14 days.	

AP/HET (70%)	OGTT	100 mg/kg 0, 0.5, 1, 1.5, 2 and 3 h	The HET showed significant glucose tests and in acute experimental T2DM a
	STZ-induced diabetic mice.	33, 100 and 330 mg/kg 1, 3, 5, and 7 h	dependent manner.
AP/HET	STZ-induced diabetic rats.	100 mg/ kg/ day	The HET significantly reduced the exp
	Measurement of biochemical parameters (**B4**) and IL-1β/ iNOS gene expression.	i.p. / 14 days	The serum INS levels in the HET group decreased significantly. The HET e iNOS genes, which may have a protect
NI/HET	STZ-induced diabetic rats.	250 mg/kg	The results indicated that the HET imp
	Measurement of biochemical parameters (**B5**) Analysis of oxidative stress-related factors (**O1**).	NI / 21 days	activity and modulates some biochemi
Anthemis canescens (syn. *Matricaria aurea*)			
ET/EA/DCM/HEX	STZ-induced diabetic rats.	ETH1= 100 mg/kg, ETH2=200 mg/kg EA1= 100 mg/kg, EA2=200 mg/kg DCM1= 100 mg/kg, DCM2=200 mg/kg HEX1=100 mg/kg, HEX2=200 mg/kg OG / 4 weeks.	Treatment with either ETH1/2 ex
	Measurement of biochemical parameters (**B6)**.		ameliorated INS resistance, hyper
	Oxidative stress and antioxidant markers in the liver (**O2**)		significantly affecting fasting INS lev increased liver protection from injury a a significant decrease in ALT and AST
Bellis perennis			

L/F/ EXT4404/EXT4407/HMET	Avian embryos in the first two-thirds of embryonic development (lasting 21 days) Hens egg test-chorioallantoic membrane (HET-CAM) assay.	EXT4404 (300 mg/L), EXT4407 (300 mg/L), HMET (300 mg/L).	All three extracts resulted in a compara h and 30% after 2 h) and were statistica The three extracts significantly reduc comparable efficacy (~12% after 1 and
Bidens frondosa			
AP/ET (80%)	OGTT Healthy and STZ-induced diabetic rats. Measurement of biochemical parameters (**B1**)	250 and 500 mg/kg BW OG / 7 days	ET exhibited weak to moderate hypogl at the tested doses. In OGTT, higher d inhibitory activities. The ET lowered weight of the animals was not changed
Chamaemelum nobile (syn. *Anthemis nobilis* L. or *Chamomilla nobilis*)			
AP/AQ	STZ-induced diabetic rats. Measurement of biochemical parameters (**B7**)	20 mg/kg BW OG / 15 days.	Single oral administration of AQ re diabetic rats. BG levels were decreas respectively, after 15 days of treatment
Cichorium intybus			
R/AQ	ALLO-induced diabetic rat Measurement of physiological and biochemical parameters (**P1**)	2.5, 5, 10, and 15 g DPM/kg OG / 2 weeks	Treatment with 10 g/kg of the herbal m values compared to the diabetic control concentration (15 g/kg) completely rest in experimental groups. The lipid stat ALT, ALP, CRE, URE and MDA were mixture completely restored the his kidneys and hippocampus.

WP/ET (80%)	STZ-induced diabetic rats (Male Sprague–Dawley rats) OGTT Measurement of biochemical parameters (**B8**)	125 mg of plant extract/kg BW OG / 14 days	Daily administration of ET (125 mg/kg BG by 20%, TG by 91%, and tTC by 16
R / AQ	STZ- niacinamide (NIA/STZ) induced diabetic rats Measurement of biochemical parameters (**B9**) OGTT	125 mg/kg BW i. p. injections / 28 days.	The extract prevented body-weight loss and TG, TC and HbA1c levels decreas the chicory-treated groups. Unlike la concentrations were higher, and the normal in chicory-treated early-stage d
AP / CAE	Healthy rats. OGTT Measurement of biochemical parameters (**B10**)	3, 15 or 30 mg/ kg i. p. injections / 4 days.	The CAE can decrease BG without administrations of CAE improve i.p. manner, mainly via an INS sensitising
S / CQA-ET	Healthy rats. High-fructose diets Measurement of physiological and biochemical parameters (**P2**) Antioxidant status of rats (**O3**)	Diet with CQA-ET FEE / 28 days	The CQA-ET was found to decreas observed in the control rats' group an Both dietary supplements reduced the substances in kidney and heart tissue c
NCRAE, SCCAM	STZ-induced diabetic rats OGTT Measurement of biochemical parameters (**B11**).	15 mg/kg i. p. injections / 7 days.	Both NCRAE and SCCAM can improv after a subchronic administration of se decreases the basal HYG after six days

Dittrichia viscosa subsp. *iscosa* (Syn. *Inula viscosa*)			
L / AuNPs	High-fat diet (HFD)/STZ-induced diabetes in rats Measurement of biochemical parameters (**B12**)	2.5 mg/kg i. p. injections / 21 days.	Treatment with AuNP significantly lov and the activity of hepatic PEPCK in group. The AuNPs synthesised can diabetes in rats by reducing hepat expression and activity of the hepatic I
AP / AQ	Normal and STZ-induced diabetes rats Measurement of biochemical parameters (**B13**)	20 mg/kg OG / for 2 weeks.	A significant reduction in BG levels 2 single oral administration. Repeated reduced BG levels after 4 days of treat In diabetic rats, a significant reduction single oral administration. Repeated oral administration reduced TC and TG levels was observed after a in both normal and diabetic rats. Plasm unchanged after 15 days of repeate diabetic rats.
Galinsoga parviflora			
WP / HET 80%	STZ-induced diabetic rats. Measurement of biochemical parameters (**B13**)	400 mg/kg BW NI	The extract reduced the BG level equiv rats.
Lactuca serriola			
L / AQ	STZ-induced diabetic rats. OGTT Measurement of biochemical parameters (**B14**)	200 and 500 mg/kg BW OG / NI	Both doses of extracts restored β -cell f INS secretion.

Onopordum acanthium			
L / MET	STZ-induced diabetic rats Measurement of biochemical parameters (**B15**)	200 and 400 mg/kg OG / 8 days	Administration of extracts significantly marked enhancement of pancreatic isl level and BW loss. Extract treatment su cell score in myocardial tissue with an
Solidago virgaurea			
AP / HE	ALLO-induced diabetic rat. Measurement of physiological and biochemical parameters (**P3**)	250 mg/kg BW OG 15 days	Extract significantly reduced BG level, pancreatic MDA level, as well as incr pancreatic SOD, and CAT activities ir diabetic rats.
Sonchus asper			
NI / ME	STZ-induced diabetic rats. Measurement of physiological and biochemical parameters (**P4**)	200 mg/kg 21 days	The ME improve the activity of the anti cholesterol profile of the diabetic r significantly lower in treatment than th
Sonchus oleraceus			
WP / ME	STZ-induced diabetic rats. OGTT Antioxidant status of rats (**O4)**	75, 150, 300 mg/Kg 14 days	The Me (150 mg/Kg) treatment exhib measurement of stress markers in administration showed a significant peroxide levels, coupled with a substa
L / HET (90%)	STZ-induced diabetes in rats		

	Measurement of physiological and biochemical parameters (**P5**)	100, 200, 400 mg/kg/day BW 6 weeks	HET significantly increased both SOD a reduction of MDA levels in the liv induced liver function and pathologica 6 weeks showed significantly decrease HET decreased MyD88, TGF-β, and TL
L / HET (90%)	HFD/STZ-induced diabetes in rats OGTT Measurement of physiological and biochemical parameters (**P6**)	100, 200, 400 mg/kg/day BW 6 weeks	In DTR treated by HET (400 mg/kg/day reduced by 43%, 22%, and 16%, respe that daily feeding of DTR decreased p 23%. DTR with HET at 400 mg/kg/day fibrous expansion without sep inflam administration of HET exhibited a prot induced by STZ, which was also corro colour observed in HET-administered
L / ET (80%)	ALLO-induced diabetic rat. Measurement of physiological and biochemical parameters (**P7**)	100, 200, and 300 mg/kg BW 56 days	The treatment of SOE 200 and 300 m dramatically decreased BG, total lipid, improved liver and kidney functions. T treatment of SOE 300 mg/kg significan
		Lamiaceae	
Lavandula pedunculata			
FTO / AQ	Healthy Rats Acute OGTT and Chronic OGTT for plant mixtures Measurement of biochemical parameters (**B13**).	1 g/kg BW NI	Acute and chronic oral administration (30 min) and the area under the curve as the positive control Metformin.
Lavandula stoechas			
AP / EO	ALLO-induced diabetic rat.	50 mg/kg BW	

	Measurement of biochemical parameters (**B16**).	i. p. injections / 15 days.	Subacute EO administration prevented alloxan-induced increase in hepatic an EO treatment corrected the BG l lipoperoxidation and decreased (−SH) enzyme depletion. Induced by allo significantly protected against hepa disturbance of lipid metabolic paramet
AP / EO	ALLO-induced diabetic rat Measurement of physiological and biochemical parameters (**P8**)	50 mg and 160 mg/kg BW i. p. injections / 15 days	EO treatment protects against decrease weights, testosterone level, and sperm against oxidative damage to DTR's ma
R / ET (70%)	ALLO-induced diabetic rat. Measurement of biochemical parameters (**B13**).	50, 100, and 150 mg/kg BW i. p. injections / NI	The extract significantly reduced BG manner.
NI / EO	STZ-induced diabetic rats. Wound healing test Measurement of physiological and biochemical parameters (**P9**)	0.05 ml DDR / 21 days	The percentage of healing was highest Microscopic examination of the bio healing on Days 7 and 14. Reduced m hair follicle and adipose tissue develo group on Day 7. On Day 14, the T2DM- hair follicles.
AP / AQ	ALLO-induced diabetic rat OGTT Measurement of biochemical parameters (**B13**).	150 mg/kg OG / NI	Oral extract administration reduced H normal and diabetic rats.
Melissa officinalis			

EO	db/db mice Measurement of biochemical parameters (**B17**). OGTT	0.0125 mg EO/d FEE / 6 weeks	Mice administered EO for 6 weeks sho < 0·05) and TG concentrations, improv OGTT, and significantly higher serum were significantly upregulated, where down-regulated in the livers of the EO
L / ET	HFD C57BL/6 mice Measurement of biochemical parameters (**B18**).	200 mg/kg/day FEE / 6 weeks	The DTR revealed significantly redu decrease versus vehicle). The extract showed no significant effec It significantly decreased the HFD-ind the HFD-provoked rise in fasting plas by 59% and plasma TAG gain by 66% plasma levels of LDL/VLDL-c (32% de decrease). The extract treatment led t 56%.
NI / EO	STZ-induced diabetic rats. Measurement of biochemical parameters (**B1**).	0.01, 0.02 and 0.04 mg/day FEE / 4 weeks	EO at both high doses restored gly compared to untreated diabetic anima
L / HAE	ALLO-induced diabetic rat. Measurement of biochemical parameters (**B19).**	20, 100 or 500 mg/Kg BW OG / 4 weeks	There was a significant decrease in bloo with HAE. An increase in HDL levels
L / HE-EA (ALS-L1023)	HFD C57BL/6 mice Measurement of physiological and biochemical parameters (**P10**)	HFD supplemented with 0.4% (w/w) ALS-L1023 (HFD-ALS)	Administration of ALS-L1023 to high-f in BW gain, VFM, and VAS withou improved HYG, HYIN, BG and INIT a in OMI. ALS-L1023 decreased hepatic

	OGTT and IPITT	FEE / 12 weeks	expression of PPARα target genes re livers.
L / HE / EA	Otsuka Long-Evans Tokushima fatty (OLETF) rats Measurement of physiological and biochemical parameters (**P111**)	HFD with 0.4% or 0.8% (w/w) of extract FEE / 4 weeks	The EAE administration resulted in a also markedly inhibited HYG and HY impaired in OLETF rats. There was a c muscle of the ORAT after treatment w and skeletal muscle increases the expr (AMPKα2, ACOX, MCAD, and VLCA inflammation, including the infiltratio mast cells, and attenuated the expres CD68).
Mentha aquatica			
L / AQ	STZ-induced diabetic rats. Measurement of physiological and biochemical parameters (**P12**)	50 mg, 100mg and 150mg OG / 90 days.	FBG and HbA1c levels decreased in DT significantly increased. The levels of T HDL were significantly increased. The ALB of DTR were significantly inc CREA were decreased in DTR. TBA decreased in DTR. The activities of CA in DTR. DTR at a dose of 100 mg/kg bw intertubular vessels, and tubular ep changes in the kidney.
Mentha pulegium			
AP / AQ	STZ-induced diabetic rats. OGTT	20 mg/kg BW	The AQE caused a significant rec morphometric analysis and histologica

	Measurement of physiological and biochemical parameters (**P13**)	OG / 15 days	liver have shown the beneficial effe According to OGTT, the AQE has imp
AP / AQ	STZ-induced diabetic rats. Measurement of biochemical parameters (**B20).**	20 mg/kg BW OG / 15 days	The AQE alleviated hyperlipidemia in the TC levels without affecting the T increasing activity on plasma HDL-c le
Mentha suaveolens			
AP / AQ	STZ-induced diabetic rats. OGTT Measurement of physiological and biochemical parameters (**P14**)	20 mg/kg BW OG / 15 days	The AQE decrease the BG, TC and TG The AQE treatment was demonstrat pancreas histopathological tissues.
Origanum vulgare L.			
L / AQ	STZ-induced diabetic rats. Measurement of biochemical parameters (**B4).**	20 mg/kg OG / 2 weeks	The AQE produced a significant decre were normalised from the fourth day a of AQE. No changes in basal plasma I treatment in either normal or DTR.
L / AQ	STZ-induced diabetic rats Measurement of biochemical parameters (**B21**).	20 mg/kg OG / 6 weeks	Administration of AQE significantly d in DTR.
L / ME / AQ	STZ-induced diabetic rats. Measurement of physiological and biochemical parameters (**P15**)	5 mg/kg per day i. p. injections / 10 days	ME reduced diabetes incidence and p scavenged reactive oxygen and nitrog upregulate antioxidant enzymes. I inflammatory response mediated by inflammatory T helper 2 and T regulato pathways and transcription factors.

L / EtOAc	STZ-induced diabetic rats. Measurement of physiological and biochemical parameters (**P16**)	2 mg/mouse OG / 10 days	EtOAc treatment significantly prese diabetes incidence in DTR. Beside macrophages, EtOAc reduced the r CD4+CD25+ T cells. EtOAc affected t helper 17 (Th17) cells by downregulati and RORγT.
L / AQ	ALLO-induced diabetic rat. Measurement of biochemical parameters (**B22**)**.**	150 mg/kg, 300 mg/kg BW 300 mg/ kg Equal mixture (150 mg chamomile + 150 mg oregano) OG / 6 weeks	Treatment with higher or lower doses weight gain, hypoglycemic effect, decr levels. Restoration of the renal profile HDL-C and the reversal of Bax and Bcl- mixture showing synergistic activity o low doses of 150 mg/kg.
L / HE	Glucose-induced-diabetic zebrafish Measurement of biochemical parameters (**B23**)**.**	10 µg/L FEE / 24H	The BG level, TC and TG were signi treated.
L / INF	ALLO-induced diabetic rat. Measurement of biochemical parameters (**B10**)**.**	55 mL OG / 40 days	The INF reduced BG levels after the f diabetic CGr. The INF appears to stimu
Prunella vulgaris			
WP / AQ	db/db mice HCF/HFD	100 mg, 200mg/kg/day	

	Measurement of physiological and biochemical parameters (**P17**).	DR / 8 weeks	AQE treatment markedly lowered B restored by treatment with AQE. The A c, MDA and TGFβ1 and increased HI vascular relaxation of aortic rings by dose-dependent manner. AQE treatr expressions of ICAM-1, VCAM-1, ET- eNOS in aortic was increased by AQE
Fr / HE / TAP	STZ-induced diabetic rats. Measurement of physiological and biochemical parameters (**P18**).	50 mg/kg, 100mg/kg, 200 mg/kg of TAP OG / 6 weeks	The BW and the levels of BG, FMN, I serum decreased significantly compa dependent manner. The activity of significantly compared with the STZ g DTR showed a significant increase in S cells. Histopathological examination al on pancreatic β cells.
HFOR / HE / AQ	Male CD-1 (ICR) mice / FFF OGTT and IPITT Measurement of physiological and biochemical parameters (**P19**).	8.02 g/kg OG / 10 weeks	HEE could improve glucose intoleranc provokes an increase in peripheral an FAs level, enhanced GLUK activity a antioxidant activity. Hepatic histopath administration markedly decreased fat
IF / PV(HE) / CARF / CA / RA	ALLO-induced diabetic rat model.	50, 100, 150 mg/kg	CARF reduced BG levels and impr reduced HbA1c levels more significan

	Measurement of physiological and biochemical parameters (**P20**).	i.p. injections / 8 weeks	CA or RA. CARF had significantly incr hyperalgesia and tactile allodynia more equivalent amounts of CA or RA. Th restoration of the lipid peroxide levels.
WP / AQ	Male Sprague-Dawley (SD) STZ-induced diabetic rats.	100 mg, 300mg/kg/day	In DTR, AQE significantly decreased CRE. AQE reduced the PAS positiv
	Measurement of physiological and biochemical parameters (**P21**).	DR / 8 weeks	membrane thickening in the glomeruli

ACOX: Acyl-CoA oxidase, **ALB:** Albumin, **ALLO**: Alloxan, **ALP:** Alkaline Phosphatase, **ALT:** Alanine aminotransferase, **AMPKα2**: AMP-ac parts, **AQ:** Aqueous extract, **AST:** Aspartate aminotransferase, **AuNPs:** Gold particles of dried leaf aqueous extract, **BG:** Blood glucose, **BUN CAE:** Chicoric acid extracted and purified from water extract, **CARF:** Caffeic acid-rich fraction, **CAT:** Catalase, **CGr**: Control group, **CQA-ET** chicory seeds (9.6% of CQA), **CRA:** L-chicoric acid, **CRE:** Creatinine, **CGA:** Chlorogenic acid, **DCM:** Dichloromethane extract, **DDR:** Daily **DTR:** Diabetic treated rats, **EA:** Ethyl Acetate extract, **EO:** Essential oil, ET: Ethanol extract, **EXT4404:** Mixture of flowers and leaves ethanolic **FBG**: Fasting blood glucose, **FC:** Food consumption, **FEE:** Feeding, **FFF:** fed with a fructose/fat-rich combination diet**, FI**: Food intake, **FPIL**: F plants, **GK1**: Hepatic glucokinase, **GLIB:** Glibenclamide, **GLUT4**: Glucose transporter type 4, **GLUK**: Glucokinase, **GLY:** glycogen, **GPx:** Glut **HAE:** Hydroalcoholic extract, **HbA1c:** Glycosylated haemoglobin, **HFD:** High cholesterol food, **HDL-c**: High-density lipoprotein cholestero **HFD:** High fat diet, **HFOR:** Ethanolic extract of herbal formulation composed of *R. dioscorea*, *L. barbarum*, *P. vulgaris* and hawthorn in a ratio of 6 from flowers collected locally, **HYG**: hyperglycemia**, HYIN**: Hyperinsulinemia**, IL-6:** Interleukin 6, **INS:** Insulin, **INIT**: Insulin tolerance, **IPITT** dehydrogenase, **LDL-c:** Low-density lipoprotein cholesterol, **LIA**: lipid accumulation, **ME:** Methanolic extract, **MCAD:** Medium-chain a **NCRAE:** Natural chicoric acid extract (from hydroethanolic extract 70%), **NI:** Not indicated, **NO:** Nitric oxide, **OG:** Oral gavage, **OGTT:** Ora Obese rats, **PAL:** Phosphatase alkaline, **PASS**: Periodic Acid Schiff, **PEPCK**: Phosphoenolpyruvate carboxykinase, **PV**: *Prunella vulgaris*, **RA:** Ro Synthetic Chicoric and Chlorogenic Acids Mixture containing the two major compounds of NCRAE, in proportion of 70% of synthetic L-chicor Glutamic-oxaloacetic transaminase, **SGPT**: Serum Glutamate Pyruvate Transaminase, **SOD:** Superoxide dismutase, **STZ:** Streptozine, **TAG** *vulgaris* hydroethanolic extract (75%), **TC:** Serum total cholesterol, **TG:** Triglycerides, **TGF-β**: Transforming growth factor beta, **TLR4:** Toll-L **URE:** Plasma urea, **VAS:** Visceral adipocyte size, **VFM:** Visceral fat mass, **VLCAD:** Very long-chain acyl-CoA dehydrogenase, **VLDL:** Very-lo

Biochemical parameters studied. B1: Assessment of the body weight (BW) and blood glucose (BG) levels; **B2**: Assessment of levels, **B3:** Assessment of the BW, BG, TC, TG, VLDL levels, SGOT, SGPT and ALP activities, **B4:** Assessment of the BW, BG and

HDL-c, TG and LDL-c levels, **B6:** Assessment of fasting BG and INS. Systemic insulin resistance was estimated using the h
resistance (HOMA-IR). Study the triglyceride and glucose (TyG) index, insulin sensitivity and the secretory capacity of the p
profile and liver injury markers TC, TG, HDL-c, LDL-c, ALT, and AST, **B7:** Assessment of BG levels and basal plasma INS co
glucose, TG, TC, and INS levels, **B9:** Assessment of the BW, fasting BG, intraperitoneal glucose tolerance test (IPGTT), HbA1c,
and INS levels, **B10:** Assessment of BG and INS levels, **B11:** Assessment of the BW, food intake (FI) and plasma/urinary gluco
gene expression and activity of phosphoenolpyruvate carboxykinase (PEPCK), **B13**: Assessment of BW, BG, TG, and TC level
and LDL-c levels. IR-HOMA and HOMA-B (β-cell function) were evaluated using the homeostatic model assessment (HOMA) in
analysis, histopathological study and immunohistochemical analysis, **B16:** Assessment of BG, biochemical determination of pro
activities (SOD, CAT) in the liver and the kidney homogenates. Assessment of liver function (AST, ALT, PAL, LDH). Assessm
analyses). Determination of metabolic parameters (TC, LDL-c, HDL-c and TG concentrations), **B17:** Assessment of BG, INS l
adipocyte GLUT4, PPAR-γ, PPAR-α, SREBP-1c, G6Pase, PEPCK expression analysis, **B18:** Assessment of BG, TAG, FAs and LI
TC, TG, LDL and HDL contents, **B20:** Assessment of TC, TG and HDL-c levels, **B21:** Assessment of BG, INS, liver and muscle gl
AMY, **B22:** Assessment of BG, INS, HbA1c, TC, TG, HDL-C, VLDL-c, LDL-c, URE, CRE, UA, TPRO and AMY, **B23:** Assessmen

Antioxidant status parameters studied. O1: Analysis of oxidative stress-related factors in renal tissue: MDA level, SOD and
measurement of Bcl-2-associated X protein (BAX) expression, **O2:** Assessment of the level of MDA, reduced glutathione (GSH)

O3: Analysis of oxidative stress-related factors: GPx, SOD, Serum antioxidant capacity [hydrophilic substances, lipophilic su
Substances) in Heart, kidney and liver tissues, **O4:** Titration of markers of oxidative stress in treated rats (MDA and Hydroge
and biochemical parameters studied. **P1:** Assessment of the BW, BG level, TC, HDL, TG, AST, ALT, ALP, CRE, and URE. Su
analysis, **P2:** Determination of diet intake, BW, the mass of selected organs of rats; indices of gut functioning of rats; basic bioch
HDL-c, TG, Atherogenic index), **P3:** Assessment of BG, INS, serum lipid profile, Tumor necrosis factor-α (TNF- α), liver glyc
Histopathological study of pancreatic tissue, SOD, CAT, and MDA levels in pancreatic tissue was also assessed, **P4:** Assessmen
concentration of the supernatant from pancreatic tissue. Determination of lipid peroxidation enzymes, glutathione-S-transferas
peroxidation (TBARS), CAT, and SOD activities, **P5:** Assessment of BG, SOD, GSH activities, MDA, GLY levels, histological an
of the levels of IL-1β and TNF-α and gene expression of NF-κB, TNF-α, IL-1β, p-TLR4, MyD88, and TGF-β analysis in the live
TC, HDL, LDL, GLY levels, immunohistochemistry of the liver tissues and analysis of p-AMPK/Akt/GSK3-β expression in liver
levels, activities of liver enzymes, including (ALT) and (AST), as well as the serum total bilirubin (TB), total protein, and seru
MDA levels, GSH, SOD, CAT and GST activities and histological analyses of the pancreatic tissue samples, **P8:** Evaluation o

(count, motility, viability, morphology, production). Assessment of plasma glucose, relative body and reproductive or
butyrylcholinesterase activities. Biochemical determination of protein, -SH groups, MDA and antioxidant enzyme activitie
epididymis, and sperm, **P9:** Assessment of BG levels, BW. Macroscopic and microscopic data analysis, **P10**: Assessment of BW, FI
insulin sensitivity check index) and HOMA-IR values were determined. Histological Analysis (quantification of the visceral a
P11: Assessment of BG, INS levels, TAG, FAs and body weight. Histology (quantification of the epididymal adipocytes size, ex
and gastrocnemius muscle tissues), immunohistochemistry (detection of INS and CD68), and real-time polymerase chain reactio
URE, CRE, ALB, INS, HDL-c, ALB, URE, CRE levels. Determination of antioxidant enzyme activities (SOD, CAT, GPx, GST) and
MDA contents), **P13**: Assessment of BG, the histological sections and morphometric analysis, **P14**: Assessment of BG, TC,
examination of pancreas and liver, **P15:** Assessment of BG, INS, Metabolic parameters (Glutathione S-transferase) and leuco
pancreatic-infiltrating mononuclear cells and immunofluorescence analysis. Determination of cytokine and nitrite levels. Histol
Determination of antioxidant enzyme activity (Catalase activity, Glutathione peroxidase (GSHPx), Glutathione reductase), **P1**
composition and cytokine production and histopathological examination of pancreas, **P17:** Assessment of BG level, BW, ur
(sodium, potassium, and chloride), systolic blood pressure (SBP), INS levels, transforming growth factor-beta1 (TGF-β1) and to
blood urea nitrogen (BUN), total bilirubin, TPRO, albumin (ALB), globulin, glutamic oxaloacetic transaminase (GOT),
dehydrogenase (LDH), AMY, and MDA levels in plasma. Histological and Immuno-histological Examinations, **P18:** Measureme
(NO), nitric oxide synthase (NOS), MDA and SOD. Histopathological studies of rat pancreatic islet cells and expression of SO
of BG, HOMA-IR index, hepatic glucokinase activity, hepatic glycogen content, serum lipid profile (TC, TG, LDL-c, HDL-c con
antioxidant capacity [T-AOC], SOD, MDA) and histological examination of liver, **P20:** Assessment of BG level, BW, INS level,
plate latency test, tail flick latency test, Von Frey filaments test), measurement of lipid peroxidation and serum catalase (CAT)
creatinine (CRE). Immunohistochemistry and Western blot analysis of the kidneys.

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3.2.2. Lamiaceae Family

- *Lavandula stoechas*

Lavandula Stoechas L. is widely recognised for its pharmacological properties [347]. It is one of the best-known and most economically valued plants and was probably the first species to be used for its EO. The genus comprises around 39 species, numerous hybrids and almost 400 registered cultivars [520]. Phytochemical studies of its many co-products have revealed the presence of a variety of bioactive compounds (Table 1). This plant is frequently used in traditional medicine to treat various conditions, including inflammation, neurological disorders, microbial infections, etc. [347,521–523]. It is the subject of much attention from diabetes scientists, and numerous *in vitro*, animal and clinical studies have been carried out on its use (Table 3).

Elrherabi et al. (2023) evaluated the antihyperglycaemic impact of the aqueous extract of *L. stoechas* and attempted to explore its mechanisms. The researchers used a OGTT on normal and diabetic WR, administering 150 mg/kg of extract. Hyperglycaemia induced by sucrose and starch was reduced under the effect of the plant in normal and diabetic rats. The extract also caused a decrease in intestinal glucose absorption *in situ* at 250 mg/kg. As a result, the aqueous extract would have clear antihyperglycaemic effects attributed to inhibiting intestinal glucose absorption and key enzymes in monosaccharide digestion, such as α-amylase and α-glucosidase [441]. Indeed, the IC50 equals 0.485 ± 0.13 mg/mL and 168 ± 40.10 µg/mL, respectively, for amylase and glucosidase [441]. In addition, the antidiabetic potential of lavender essential oil and its main compounds was also investigated by measuring their inhibitory activity towards the two digestive enzymes [350]. Camphor (76.92 ± 2.43 µg/mL) and fenchone (69.03 ± 2.31 µg/mL) showed the best inhibitory activities for the α-amylase and α-glucosidase tests, respectively. The essential oil had an IC50 equal to 98.54 µg/mL. Interestingly, all the elements in this study had higher activities than acarbose, whatever the test adopted [350].

The study by Kulabas et al. (2018) aimed to elucidate the potential ameliorative effects of aqueous extracts of *L. stoechas* on insulin resistance and inflammation patterns using multi-targeted *in vitro* approaches and also to elucidate the mechanism of action by analysing transcriptional and metabolic responses [442]. The anti-insulin-resistant effects of ethyl acetate (EE) and butanol (BE) extracts prepared from the aqueous extract were assessed on the palmitate-induced insulin resistance model of H4IIE (Rat hepatoma cell line), C2C12 (Immortalized mouse myoblast cell line) and 3T3L1 (Murine adipocytes) cells using several metabolic parameters. Specifically, whole genome transcriptome analysis was performed using microarrays on over 55,000 genes in control, insulin and EE (25 µg/mL) treated H4IIE cells. Both extracts at low doses (25-50 µg/mL) significantly decreased hepatic gluconeogenesis in the H4IIE cell line by suppressing PEPCK and G6Pase expression [442]. In C2C12 myotubes, both extracts increased insulin-stimulated glucose uptake more effectively than metformin. Both extracts decreased isoproterenol-induced lipolysis in the 3T3L1 cell line. In addition, they also effectively increased lipoprotein lipase protein expression in insulin-resistant myotubes at low doses. EE increased PPARγ protein levels and stimulated AKT activation in insulin-resistant H4IIE and C2C12 cell lines [442].

The results obtained from biochemical analyses, mRNA/protein studies and whole genome transcriptome analyses were complementary. They supported the hypothesis that EE may be biologically active against insulin resistance and act via inhibition of hepatic gluconeogenesis and activation of AKT. According to the study data, *L. stoechas* EE contains phytochemicals that may be effective in the treatment/prevention of insulin resistance and inflammation [442].

In the study by Sebai et al. (2013), EO of *L. stoechas* (LSEO), collected in the Ain-Draham region (northwest Tunisia), were tested for their protective effects against ALO-induced diabetes and oxidative stress in rats [495]. Antidiabetic and antioxidant activities were assessed after subacute intraperitoneal injection of LSEO (50 mg/kg BW, i.p.) to rats for 15 days. They found that the EO significantly protected against increased blood glucose and decreased antioxidant enzyme activities induced by ALO treatment. Subacute treatment with EO induced a decrease in lipoperoxidation and an increase in antioxidant enzyme activities. These results suggest that LSEO protect against diabetes

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and oxidative stress induced by ALO treatment. These effects are partly due to its powerful antioxidant properties [495].

On the other hand, two other studies blended lavender with other plants to study their joint efficacy against diabetes. The first was by Sebai et al. [496], who sought to assess the protective effect of *Rosmarinus officinalis* EO (ROEO) and *L. stoechas* EO (LSEO) against ALO-induced reproductive damage and oxidative stress in diabetic male rats. The results showed that treatment with ROEO and LSEO protected against ALO-induced decreases in BW gain, relative reproductive organ weights, testosterone levels and sperm quality. They also showed that administration of ALO was accompanied by a state of oxidative stress assessed by an increase in levels of MDA and hydrogen peroxide (H_2O_2), as well as by a decrease in the sulphydril group (-SH) content and antioxidant enzyme activities such as SOD, CAT and glutathione peroxidase (GPx) in the testes, epididymis and spermatozoa [496]. More importantly, treatment with ROEO and LSEO significantly protected against oxidative damage to male reproductive organs in ALO-induced diabetic rats. The study's results suggest that ROEO and LSEO potentially protect against ALO-induced damage to reproductive function and oxidative stress in male rats. According to the authors, the beneficial effect of ROEO and LSEO could be linked, in part, to their antioxidant properties [496].

In the other study by Mustafa et al. [497], hydroalcoholic extracts of *L. stoechas, Curcuma longa*, *Aegle marmelos* and *Glycyrrhiza glabra* and their polyherbal preparation (PHP) were tested for their antihyperglycaemic potential in ALO-induced diabetic mice. The plant extracts tested significantly reduced the blood glucose concentration of the diabetes-induced mice dose-dependently. According to the authors, the medicinal plants studied all or mixed PHP had antihyperglycaemic activity, possibly due to bioactive phytoconstituents in the plants. However, more extensive studies are needed to identify, isolate and characterise the bioactive phytoconstituents responsible for the antihyperglycaemic activity of the medicinal plants studied [497].

- *Melissa officinalis*

Melissa officinalis, or lemon balm, is a medicinal plant native to southern Europe and the southern Mediterranean, northern Africa and western Asia [524]. It is a bushy, herbaceous perennial commonly cultivated in herb and border gardens for its distinctive lemon-fragrant leaves. Numerous studies have described its therapeutic and pharmacological benefits thanks to its wealth of bioactive compounds (Table 1). It is particularly known for managing hyperlipidaemia, diabetes and other metabolic syndromes [524,525].

Numerous studies have described the antidiabetic potential of this plant (Tables 2 and 3). In cell models, *M. officinalis* extracts stimulated the expression of PPARα target genes involved in fatty acid β-oxidation and lipolysis [447]. Lemon balm EO significantly activated the AMPK/ACC (acetyl-CoA carboxylase) pathway. Activation of AMPK allows cells to take up more glucose from the environment and down-regulate ACC, thereby inhibiting lipid accumulation in adipocytes. The effect of EO on the expression of key transcription factors, such as C/EBPR (CCAAT-enhancer-binding protein R), SREBP1 (Sterol regulatory element-binding transcription factor 1) and PPARγ, was assessed using Western blotting analysis [447]. Compared with untreated adipocytes, the presence of lemon balm EO during adipogenic differentiation caused an increase in the expression levels of SREBP1 and C/EBPR but not PPARγ. Although increased expression levels of SREBP1 and C/EBPR should increase lipid accumulation in cells, activated ACC proteins can inhibit lipid synthesis [447].

Finally, the Western blot data confirm and explain why lemon balm EO caused adipocytes to use more glucose but inhibited lipid accumulation [447]. These results are supported by those obtained *in vivo*. Mice given EO (0.0125 mg/d) for six weeks showed a significant reduction in glycaemia, TG concentrations, improved glucose tolerance and significantly higher serum insulin levels than the control group. In addition, of all the glucose metabolism-related genes studied, hepatic glucokinase and GLUT4 and adipocyte GLUT4, PPARγ, PPARα and SREBP-1c expression were significantly upregulated. In contrast, G6Pase and PEPCK were down-regulated in the livers of the EO-treated group [447].

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Another study was conducted on the hydroalcoholic extract of lemon balm (ALS-L1023) to examine its effect on the regulation of hepatic lipid accumulation, obesity and insulin resistance and determine whether its mechanism of action involves PPARα [503]. Indeed, excessive lipid accumulation in non-adipose tissue is thought to be responsible for developing insulin resistance. Activating the PPARα receptor would reduce weight gain and improve insulin sensitivity in obese mice [526,527]. In this study, the administration of ALS-L1023 (food supplemented with 0.4% (w/w)) to obese mice (induced by a high-fat diet) resulted in a reduction in weight gain, visceral fat mass and visceral adipocyte size without any change in food consumption profiles [503].

ALS-L1023 improved hyperglycaemia, hyperinsulinaemia, glucose and insulin tolerance, and normalised insulin-positive β-cell surface area in obese mice [503]. ALS-L1023 decreased hepatic lipid accumulation and concomitantly increased the expression of PPARα target genes responsible for fatty acid β-oxidation in the liver [503]. Higher phosphorylated protein kinase B (*p*Akt)/Akt ratios and lower expression of gluconeogenesis genes were also observed in the livers of ALS-L1023-treated mice. According to the authors, ALS-L1023 may inhibit obesity and improve insulin sensitivity in part by inhibiting hepatic lipid accumulation via hepatic PPARα activation [503].

In a similar study by Shin et al. (2021), the administration of ALS-L1023 (HFD with 0.4% or 0.8% (w/w)) for four weeks to Otsuka Long-Evans Tokushima fatty (OLETF) rats resulted in a reduction in BW with no change in food intake [504]. The extract also markedly inhibited hyperglycaemia and hypoinsulinaemia and restored β-cell mass, severely impaired in rats. A reduction in lipid accumulation in the liver and skeletal muscle of obese rats was observed after treatment with ALS-L1023 [504]. In parallel, the expression levels of fatty acid oxidising enzymes [AMPKα2, ACOX (Acyl-CoA Oxidase), MCAD (Medium-chain acyl-coenzyme A dehydrogenase) and VLCAD (Very Long Chain Acyl-CoA Dehydrogenase Deficiency)] increased in liver and skeletal muscle after ALS-L1023 treatment. In addition, ALS-L1023 attenuated pancreatic inflammation, including infiltration of CD68-positive macrophages and mast cells, and attenuated the expression of inflammatory factors (IL-6 and CD68) [504].

- *Mentha sp.*

The mint family includes 25 species in Europe, Africa, America and Australia [528,529]. These are the herbs most widely used in traditional medicine for nutritional and medical purposes since ancient times (Supplementary Table S3). Because of their ability to grow rapidly, invade and tolerate a wide range of agro-climatic conditions, they are now cultivated and distributed worldwide. Their therapeutic benefits derive mainly from their chemical composition, which has many properties (Table 1). In addition to these medicinal effects, mint and its various species are also known for their antidiabetic value (Tables 2 and 3).

The effect of oral administration of the aqueous extract of the three plants *Mentha aquatica, M. pulegium* and *M. suaveolens* was evaluated on the glycemic and lipid profiles of normal and streptozotocin-induced diabetic rats. A dose of 20mg of the aqueous extract of *M. pulegium* and *M. suaveolens* was effective against diabetes. They produced significant hypoglycaemic effects in normal and diabetic rats [506–508]. In addition, a significant influence on glucose tolerance was also observed by the aqueous extract of *M. suaveolens* [508]. Both extracts showed an improvement in TC (total cholesterol) and TG levels, while no significant effect of the *M. suaveolens* extract was observed on serum lipoproteins (HDL and LDL (low-density lipoprotein)] [507,508]. In addition, both plants acted positively on histopathological tissues of the liver and pancreas. Furthermore, in the study by Yellanur et al. (2020). a dose of 100 mg/kg bw/day of *Mentha aquatica* aqueous extract for 90 days significantly reduced levels of fasting glycaemia, HbA1c (glycated hemoglobin test), TC, TG, plasma urea, creatinine, urinary albumin and renal lipid peroxidation, and increased BW, insulin, HDL cholesterol, plasma albumin, urinary urea, urinary creatinine and antioxidant enzyme activities (CAT, SOD, GPx, and GST) [505]. The authors demonstrated that the aqueous extract of *M. aquatica* leaves has antidiabetic activity by stimulating insulin secretion and potential nephroprotective activity by reducing lipid peroxidation and enhancing the scavenging capacity of the antioxidant defence system in the body [505].

- *Origanum vulgare L.*

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Origanum vulgare (oregano) is another of the best-known plants in the Lamiaceae family, traditionally used to control and treat diabetes (Supplementary Table S3). It is an annual, perennial and shrubby plant native to the Mediterranean, Euro-Siberian and Iranian-Siberian regions [530]. The main constituents of oregano are quercetin, apigenin, kaempferol, naringenin, eriodictyol, salvianolic acid B, lithospermic acid B, amburosides A, luteolin, luteolin 7-*O*-glucuronide, apigenin 7-*O*-glucuronide, epigallocatechin, catechin, rutin, etc (Table 1). These compounds have been reported to have several pharmacological activities, including antibacterial, antifungal, antiviral, antiparasitic, antioxidant, anti-inflammatory, antitumour and antidiabetic (Table 1). They hold great promise for the design of new plant-based medicines, and derivatives of these compounds are being produced to assess their pharmacological effects for future use, particularly in the treatment of diabetes [531]. Antidiabetic characteristics have been previously identified in oregano, and it is currently one of the most sought-after plants for treating hyperglycaemia due to its wide accessibility, potency and lack of adverse effects [84].

Oregano can potentially inhibit the enzymatic activity of pancreatic amylase and glucosidase. This property may be part of the mechanism by which oregano may be used in the treatment/prevention of T2DM. According to the results of a study by McCue et al. (2004), extracts of clonal lines of oregano have strong inhibitory activity against porcine pancreatic amylase *in vitro* [451]. The inhibition rate depended on the clonal line and varied from 9% to 57%. This difference was because the clonal lines tested were characterised by a difference in the phenolic distribution of the main components (rosmarinic acid, quercetin, protocatechuic acid and *p*-coumaric acid) [451]. However, the clonal line with the highest rosmarinic acid content (O-11Y with 114.0 μg phenolic/200 μg total phenolic content per extract) showed weak inhibition of α-amylase.

According to McCue et al. (2004), the antidiabetic potential of the different clonal lines involves a synergistic role between rosmarinic acid and other identified (quercetin and *p*-coumaric acid) and unidentified phenolics. Gonçalves et al. (2017) also reported the efficacy of methanolic extracts of oregano obtained in Portugal on the enzymatic inhibition activity of α-glucosidase and α-amylase [339]. The results showed that inhibition was more specific and higher for α-glucosidase than for α-amylase. This observation was particularly linked to the content of phenolic compounds in oregano identified by HPLC. High content of rosmarinic acid (23.53 mg/g dry extract), (-)-epicatechin (4.65 mg/g dry extract), 3,4-dihydroxybenzoic acid (1.97 mg/g dry extract), gallic acid (1.19 mg/g dry extract) and (+)-catechin (1.03 mg/g dry extract) were reported [339]. These results are also consistent with Kwon et al. (2006) study for aqueous and ethanolic extracts (12%). The aqueous extract showed a higher dose-dependent inhibitory activity of α-glucosidase than the ethanolic extracts [444]. It was also related to the phenolic content of each extract. Indeed, the aqueous oregano extracts showed a higher rosmarinic acid content than the ethanolic extract (16.5 vs 3.78 mg/g dry weight, respectively). Rosmarinic acid was then tested and showed an inhibitory activity of 85.1% [444].

Dipeptidyl peptidase IV (DPP-IV) inhibition is another hypoglycaemic target of oregano that may be involved [532]. In the study by Bower et al., 2014 it was shown that the methanolic extract of commercial Greek oregano (28.4 ± 6.3 μM) was a better inhibitor of DPP-IV than greenhouse-grown Greek oregano extract (86.2 ± 18.8 μM) [454]. The chemical fractions designed according to flash chromatography retention time OE and OF from Greek oregano were the most potent inhibitors of DPP-IV (IC50 from 20.3 to 23.3 μM) [454]. As previously indicated, oregano species' phenolic content and distribution are related to the inhibitory activity of αglucosidase and α-amylase; this is also the case for DPP-IV. Of all the greenhouse-grown herbs tested in the study, Greek oregano extracts contained the highest concentration of polyphenols (430.1 ± 17.1 μg of GAE/mg DW). Considering the extract's yield, the total polyphenol concentration for greenhouse-dried Greek oregano herbs was 6452 mg GAE/100 g DW.

According to these studies (Table 1), oregano has numerous active compounds that can act through multiple actions and give rise to synergistic or antagonistic interactions (Table 1). Thus, the utilisation of plant-derived antioxidants with antidiabetic qualities, such as the action of DPP-IV inhibitors, is considered the most effective strategy for maintaining normal β-cell physiology and treating diabetes [533]. One of the advantages of therapies based on DPP-IV inhibition is their

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perceived impact on improving HbA1c, fasting glycaemia and 2-hour postprandial glycaemia [534]. In addition, most studies have reported its beneficial effects on regulating triglycerides (TG), HDL-c and LDL-c [535,536]. The DPP-IV inhibitor has fewer side effects, such as hypoglycaemia, increased BW and gastrointestinal disorders. Glucose tolerance tests in animals have shown improved glucose tolerance and increased insulin secretion thanks to the genetic deletion of DPP-IV. In clinical observations, some DPP4 inhibitors influence enzymatic activity, reducing the baseline value by more than 50% [537].

Another important target in treating diabetes is the peroxisome proliferator-activated receptor (PPAR) γ, a key regulator of adipogenesis and glucose homeostasis. In Christensen *et al.* (2009) study, extracts of common medicinal/food plants, including oregano, were tested in a screening platform comprising a series of bioassays, including PPAR γ, α and δ transactivation, adipocyte differentiation and insulin-stimulated glucose uptake, to identify plants containing potentially interesting PPAR agonists [453]. Hexane (Hex), dichloromethane (DCM) and ethyl acetate (EtOAc) extracts of *Origanum vulgare* ssp. *vulgare*, dichloromethane, and methanol (MeOH) extracts of the aerial parts of *Origanum vulgare* ssp. *hirtum* were tested. According to the study results, all the extracts activated PPAR γ and increased insulin-stimulated glucose uptake. In addition, hexane and methanolic extracts activated PPAR γ and δ. However, they did not affect endothelial cells or adipocyte differentiation [453].

At the cellular level, Yu et al. (2021) evaluated the hypoglycemic effect of leaf extract on HepG2 and HepG2- GFP-CYP2E1 (E47) cells. This work examined the plant's potential for promoting glucose uptake, inhibiting glycosylation and alleviating oxidative stress [399]. The promoter activity, mRNA and protein expression of PEPCK and SREBP-1c, and the expression of CPY2E1 and GLUT2 in the antidiabetic capacity mediated by oregano were analysed in HepG2 and E47 cells. Inhibition of PEPCK activity by the extract will effectively reduce sugar isogenesis and lower blood glucose levels, as it is a key enzyme in gluconeogenesis [399]. Studying the transcriptional and translational levels of SREBP-1c in HepG2 cells is an important step in analysing carbohydrate and lipid metabolism. Indeed, these proteins are highly expressed in most tissues of diabetic mice and humans, including liver, adipose tissue and skeletal muscle. Therefore, inhibition of SREBP-1c promoter activity and mRNA and protein expression in HepG2 cells would indicate that oregano extract could inhibit hepatic lipogenesis *in vitro*. Overexpression of cytochrome P450 2E1 (CYP2E1) indicates the presence of oxidative stress caused by excess glucose in the blood [399]. The use of oregano would, therefore, reduce the oxidative damage associated with insulin resistance and changes in glucose metabolism, particularly the activation of the glucose transporter 2 (GLUT2) function [399].

In vitro tests showed that the extract promoted glucose uptake, inhibited glycosylation and relieved oxidative stress, suggesting that oregano leaf extract has a strong hypoglycaemic capacity [399]. In addition, mechanical analysis also showed that the extract decreased promoter activity and mRNA and protein expression of PEPCK and SREBP-1c. The extract, therefore, inhibited CPY2E1 expression and increased GLUT2 expression [399].

Several studies have demonstrated the efficacy of oregano *in vivo* models (Table 1). In a rat model treated with ALO, oral administration of an infusion of oregano leaves reduced blood glucose levels after the first day of treatment, compared with the diabetic control group [515]. The results showed that the infusion exhibited hypoglycaemic activity, possibly due to the combined effect of rosmarinic acid and other minor compounds [515]. According to Luis et al. (2022), oregano infusion has an antidiabetic effect by stimulating insulin secretion. In the streptozotocin-treated rat model (Table 3), aqueous leaf extract (20 mg/kg) slightly decreased blood glucose levels in normal rats 6 hours after single oral administration and 15 days after repeated daily oral administration [509]. The treatment also caused a significant reduction in blood glucose levels in STZ diabetic rats. Blood glucose levels normalised from the fourth day after treatment. However, this effect was less pronounced two weeks later, and no change was observed in basal plasma insulin concentrations after treatment in normal or STZ diabetic rats, indicating that aqueous oregano extract exhibited a blood glucose lowering activity independently of insulin secretion by pancreatic β cells of Langerhans islets [509].

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Different results were reported in another study by Mohamed and Nassier (2013), who reported that oregano extracts improved glycaemia by enhancing insulin sensitivity. The antihyperglycaemic effect of the same aqueous preparation of oregano leaves at the same dose (20 mg/kg) was tested in STZ-induced diabetic rats. Its oral administration significantly reduced blood glucose levels, glycosylated haemoglobin and pancreatic amylase in STZ diabetic rats compared with the standard drug, Glibenclamide (0.9 mg/kg BW) [510]. Liver weight/BW ratios were also reduced, while kidney weight/BW ratios, urea, uric acid and creatinine levels were partially improved. Oral treatment with the extract reduced serum insulin, liver and muscle glycogen levels and body weight in STZ diabetic rats. This evidence suggests that modulation of insulin secretion and/or action mechanisms may be involved in oregano's antidiabetic effect (Mohamed & Nassier, 2013).

Furthermore, according to Mohamed and Nassier (2013), oregano's hypoglycaemic effect may be mediated by interference with the absorption of dietary carbohydrates in the small intestine or by stimulation of glucose utilisation by peripheral tissues [510]. The results showed that oregano leaves contain phenolic glucosides that help control blood sugar levels and stimulate the β-cells of the pancreas to produce insulin. The reduced HbA1c levels in treated diabetic rats could be due to an improvement in insulin secretion by the remaining pancreatic β cells in diabetic rats, resulting in improved glycaemic control [510]. A decrease in liver and muscle glycogen has also been observed in diabetic rats, possibly attributable to insulin insufficiency and inactivation of the glycogen synthase system in the diabetic. However, after oregano treatment, there was a significant increase in liver and muscle glycogen levels in diabetic rats [510]. According to the authors, the higher liver glycogen levels in treated diabetic rats could be caused by increased insulin levels, which increased glycogenesis and decreased glycogenolysis and gluconeogenesis. Thus, the antihyperglycaemic effect of aqueous oregano extract may protect surviving pancreatic β cells and increase insulin secretion and glycogen storage [510].

In the study by Vujicic et al. (2015), methanolic (ME) and aqueous (AQ) extracts were administered to C57BL/6 mice treated with multiple low doses of STZ for the induction of diabetes (MLDS) (Table 3). According to the study results, prophylactic treatment with the AQ extract had no impact on diabetes induction. On the other hand, ME extract reduced the incidence of diabetes and preserved normal insulin secretion. In addition, it specifically attenuated the pro-inflammatory response mediated by T-helper 17 cells (Th17) [511]. It enhanced anti-inflammatory T helper 2 (Th2) and regulatory T cells by activating specific signalling pathways and transcription factors. Finally, it also preserved *β* cells from apoptosis *in vitro* by blocking caspase 3. Rosmarinic acid, a predominant compound in the ME extract, was also tested and showed only partial protection against the induction of diabetes [511]. According to the authors, through its antioxidant, immunomodulatory and anti-apoptotic properties, oregano protected the mice against the development of diabetes.

In addition, this efficacy could be mediated by the influence of additional chemical compounds [511]. In a comparable efficacy study, the immunomodulatory effect of oregano ethyl acetate extract (EtOAc) was assessed by measuring immune cell proliferation or cytokine secretion [512]. In addition, it was administered intraperitoneally for ten days in male C57BL/6 mice MLDS treated. EtOAc extract suppressed macrophage and lymphocyte function *in vitro*. The *in vivo* oregano treatment significantly preserved pancreatic islets and reduced the incidence of diabetes in mice with MLDS [512]. In addition to the modulatory effect on macrophages, EtOAc reduced the number of total CD4+ T cells and activated CD4+CD25+ T cells. It also affected the number of T helper 1 (Th1) and Th17 cells by downregulating their key transcription factors T-bet and RORγT (RAR-related orphan receptor gamma). Treatment with EtOAc thus protected the mice against the development of hyperglycaemia by reducing the pro-inflammatory macrophage/Th1/Th17 response and shifting the macrophage population to the protective M2 form [512]. The EtOAc extract is reported to exert a wide range of immunomodulatory effects that appear to be useful for attenuating islet-directed inflammation [512], unlike the methanolic extract of oregano tested by Vujicic et al. (2015), which showed very specific effects on IL-17-producing T lymphocytes [511]. According to Vujicic et al. (2016), the possible interaction of EtOAc with TLR4 (Toll-like receptor 4) function would make this extract a possible candidate for the treatment of immunoinflammatory and autoimmune diseases

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such as systemic lupus erythematosus, uveitis, inflammatory bowel disease, arthritis and diabetic nephropathy, which seem to benefit from TLR4 blockade in the preclinical setting [512].

- *Prunella vulgaris*

Around 20 species of *Prunella* are in the world, found in the temperate regions and tropical mountains of Europe and Asia, northwest Africa and North America [538,539]. They are herbaceous perennials that grow mainly in forests, bare mountains, ridges and roadsides. In common with other members of the *Prunella* genus, which is currently attracting great interest due to its important new therapeutic application [539,540]. *Prunella vulgaris* L. (PV) has been used worldwide for centuries as an alternative medicine for various illnesses. (Wang et al., 2019). It is a native plant that grows mainly in the temperate biome, extending from the temperate and subtropical northern hemisphere to Central America [117]. Its dried fruit spikes have been used in folk medicine, particularly in China, for thousands of years to relieve sore throats as an antipyretic and accelerate wound healing (Supplementary Table S3). As a result, it is listed in the Chinese Pharmacopoeia as a commonly used Chinese medicinal material [540,541]. It has also been classified as one of the new Chinese herbal medicines in the list of medicinal and food homologies by the National Health Commission of the People's Republic of China [540,542].

Several pharmacological and/or clinical studies have demonstrated the efficacy of PV, including its antiviral, antibacterial, anti-inflammatory, immunomodulatory, anticancer, antioxidant, hypolipidaemic, antitumour, hypotensive and sedative actions (Table 3). It has great value in terms of application and research into treating hyperglycaemia. Numerous researchers have been attracted to exploring and studying its effects on diabetes (Tables 2 and 3).

Fructosamine (FMN) is a non-enzymatic glycation product that can monitor glucose control [543]. This parameter is correlated with blood glucose levels. It reflects the state of glycaemic control over the last 2-3 weeks, and its increase favours the development of diabetes [517]. These observations were observed in STZ-induced diabetic rats in the study by Zhou et al. (2013). However, after six weeks of treatment with 100 mg/kg and 200 mg/kg of PV triterpene acid, blood glucose and FMN levels were significantly reduced in STZ-induced diabetic rats and improved body weight compared with the control group [517]. These data indicate that PV has a dose-dependent antihyperglycaemic effect. Other parameters were also investigated in this study. An increase in nitric oxide (NO) concentration and nitric oxide synthase (NOS) activity was observed in STZ-induced diabetic rats [517]. The increase in oxygen free radicals is linked to the development of hyperglycemia. In the study, oral administration of Prunella to diabetic rats significantly decreased NO levels and NOS activity. In addition, PV has the effect of increasing the concentration of MDA, serum SOD activity and total SOD mRNA expression in pancreatic islet β-cells, demonstrating that the plant may have an antioxidant capacity to enhance the oxidative stress response to eliminate the increase in free radicals and prevent radical damage [517].

In the study by Raafat *et al.* (2016), PV's caffeic acid-rich fraction (CARF) reduced blood glucose levels and improved oxidative stress *in vivo* [458]. It inhibited alpha-amylase and alpha-glucosidase enzymes and reduced HbA1c levels more significantly than hydroethanolic extract and equivalent amounts of caffeic acid (CA) or rosmarinic acid (RA) (Raafat et al., 2016), indicating that CARF provides continuing glycemic restoration in diabetic animals. For longer durations, it significantly increased serum insulin and improved thermal hyperalgesia and tactile allodynia more significantly than the effects of hydroethanolic extract and equivalent amounts of caffeic acid or rosmarinic acid. In addition, the compounds tested showed potential for restoring lipid peroxide levels. As a result, CARF and the hydroethanolic extract observed an increase in serum insulin, attenuation of alpha-amylase and alpha-glucosidase, and their antioxidant potential could be responsible for their anti-diabetogenic and antinociceptive properties. RP-HPLC and ^{1}H and ^{13}C NMR experiments showed that CARF isolated from PV contained CA (93.4%) and RA (6.6%). According to the authors, the acute and subchronic hypoglycemic activity of CARF was 1.27 and 2.72 folds more effective than Glibenclamide's, respectively. Subchronically, it has significantly improved body weight, indicating its long-term efficacy in T1D (Type 1 Diabetes) amelioration [458].

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According to existing research, diabetic patients are at greater risk of developing atherosclerosis [544,545]. Diabetes mellitus, in both its forms, is an independent risk factor for the accelerated development of atherosclerosis [546]. Diabetes and atherosclerosis appear to be linked by multiple pathogenic mechanisms [544]. Dyslipidemia with high levels of atherogenic LDL, hyperglycaemia, oxidative stress and increased inflammation are possible explanations for this acceleration [546]. *Prunella vulgaris* can improve impaired insulin secretion, vascular dysfunction and metabolic abnormalities and markedly attenuate hyperglycaemia and vascular inflammatory processes in db/db T2DM mice. The study by Hwang et al. (2012) was conducted to determine whether *Prunella vulgaris* could inhibit diabetic atherosclerosis in db/db mice fed a high-fat, high-cholesterol (HFHC) diet [516]. This eight-week regimen increased body weight, blood glucose, and insulin levels to study the relationship between hyperglycaemia, which may also contribute to atherogenesis in db/db mice and the efficacy of PV in treating this dysfunction [516]. According to the authors, treatment with an aqueous extract (100 and 200 mg/kg/day) reduced glycaemia and systolic blood pressure. A clear improvement in renal function markers such as creatinine clearance and blood urea nitrogen was also observed. These results suggest the possible beneficial effects of using PV in treating nephropathy in T2DM [516]. The groups treated with the plant also had a reduction in glucose and lipid levels and body weight, even though food intake did not change. According to the authors, the improvement in diabetic complications by PV is independent of diet. It involves energy consumption and additional factors outside the scope of insulin resistance and hyperlipidaemia and is necessary to mediate the effects of vascular complications on HFHC-db/db mice. In Hwang et al. (2012) study, PV's antioxidant effect also improved diabetic atherosclerosis.

Chronic plant treatment of db/db mice significantly reduced malondialdehyde levels, a naturally occurring reactive species marker of oxidative stress. By improving lipid levels and attenuating oxidative stress, PV could be one of the potential therapeutic strategies for the early management and prevention of coronary heart disease [516]. According to the Hwang et al. (2012) study, NO levels were increased by PV treatment, suggesting an association with vascular dysfunction. Vascular relaxation of the aortic rings induced by acetylcholine or SNP (sodium nitroprusside) was improved by PV in a dose-dependent manner. In addition, PV ameliorated the dysfunction associated with vascular intimal injury and media hypertrophy observed in db/db mice. The aortic expression of ICAM-1 (The intercellular adhesion molecule -1), VCAM-1 (Vascular cell adhesion protein 1), ET-1 (Endothelin 1) and nitrotyrosine was significantly reduced by PV. In addition, eNOS expression in the aorta was remarkably increased by PV treatment [516].

PV also has a significant protective effect against diabetic renal dysfunction, including inflammation and fibrosis, by disrupting TGF-β (Transforming growth factor-beta)/Smad signalling [519]. In human mesangial cells (HMCs), PV pre-treatment attenuated the suppression of TGF-β and Smad-2/4 expression induced by 25 mM high glucose and increased the level of Smad-7 expression. PV significantly reduced connective tissue growth factor (CTGF) and collagen IV, fibrosis biomarkers [519]. In addition, it suppressed inflammatory factors such as intracellular cell adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1). PV inhibited the activation and translocation of NF-κB in high glucose-stimulated HMCs. In addition, PV significantly reduced high glucose-induced ROS dose-dependently [519].

The aim of the study by Jiao et al. (2021) was to investigate the active ingredients, potential targets and signalling pathways of PV and to explore the 'multi-target, multi-pathway' molecular mechanism of Prunella vulgaris L on diabetes mellitus complicated with hypertension (DH) [160]. This work was based on network pharmacology and molecular docking analyses. According to the analysis results, 11 active compounds, 41 key targets and 16 significant signalling pathways were identified from Prunella vulgaris L. The main active components of PV against DH that were discovered were beta-sitosterol, Kaempferol, Spinasterol, Stigmasterol, Delphinidin, Luteolin, Vulgaxanthin-I, Poriferasterol monoglucoside_qt, Stigmast-7-enol, Morin and Quercetin [160]. The potential action targets identified are diverse, including IL-6 and INS (Insulin), MAPK3, ALB (Albumin), AKT1, TNF, etc. The most active signalling pathways are AGE-RAGE (Advanced Glycation Endproducts/ Receptor for AGE), the TNF signalling pathway, the MAPK signalling

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pathway, the PI3K-AKT signalling pathway, etc. PV is involved in biological processes such as cell proliferation, apoptosis and inflammatory response [160]. According to the authors, the main molecular mechanism of *Prunella vulgaris* against DH is via sterols and flavonoids, which play an active role in affecting the TNF signalling pathway, the AGE-RAGE signalling pathway, the MAPK pathway, the PI3K-Akt pathway and targets linked to the IL-6 and INS pathways [160].

4. Conclusions and Perspectives

In this review, we have described the botanical diversity of the NPSEs. We have tried to investigate the traditional, therapeutic and antidiabetic uses and the chemical composition of the various plants found there. It was noted that there are few or non-existent studies of medicinal plants in this region. Therefore, we have tried to collect all the relevant information concerning worldwide traditional and modern medicine in medicinal plants of the NPSEs to enhance their value and explore their therapeutic and chemical potential for possible application in preventing and treating diabetes. It has been noted that several plants used in traditional medicine have not yet been tested for their antidiabetic effects. Therefore, further research is needed on these medicinal plants *in vitro* and *in vivo* antidiabetic effects. Some of them have been tested against diabetes without having had any subsequent traditional use. We found that the two families, *Asteraceae* and *Lamiaceae*, are the two plant groups most present in the Park with the highest number of citations of traditional use against diabetes. Studies of the hypoglycemic potential of members of these two families have revealed numerous remarkable properties against diabetes. Several mechanisms of action have been implicated. However, further research, particularly of a clinical nature, is required. Phytochemical characterisation has shown that these medicinal plants contain numerous bioactive compounds from different chemical groups. Pharmacological studies of these remedies have shown that they have interesting therapeutic effects. Given this information, we need to study the possibilities for successfully integrating the medicinal plants of the NPSEs into a public health framework. Studies should be conducted to develop new antidiabetic drugs based specifically on medicinal plants from the Park and their respective bioactive compounds.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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