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(Review Article)

Diabetes mellitus patient care: An ethnopharmacological study and evaluation of antidiabetic activity invitro and *in vivo* on experimental high-fat diet model

Arar K, [1, 2, *], Ghouini A [3] Imoudache H [4] and Gaci F [5]

[1] *Pharmacognosy Laboratory, Faculty of Medicine, University Blida1, Algeria.*
[2] *Central Pharmacy, Blida University Hospital Center, Algeria.*
[3] Physiology Laboratory, Faculty of Medicine, University Blida1, Algeria.
[4] *Research and Development Center, SAIDAL group, Algiers, Algeria.*
[5] *Laboratory of Phytochemistry and Organic Synthesis, Faculty of Sciences, University of Batna, Algeria.*

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Abstract

Diabetes control in Algeria is necessary for the population's health and the national economy. Indeed, the current challenge is to find practical, safe products containing plant extracts. Diabetes mellitus is a significant health urgency despite the chronic and often silent nature of type 2 diabetes.

This work began with a preliminary ethnopharmacological study with diabetic patients in the province of Blida, followed by a chemical analysis of the selected samples. Finally, an evaluation of the antidiabetic effect of plant extracts administered to animals made diabetic by streptozotocin at low doses. In addition, a demonstration of the harmlessness of the plant extracts studied was carried out by adopting the European Guideline code 423.

Ethnopharmacological data have highlighted four interesting species for their abundance and availability: *Artemisia herba alba, Olea europaea, Marrubium vulgare*, and *Salvia officinalis*.

The results of the phytochemical study show that the species studied contain, in particular, phenolic compounds and flavonoids, substances with a potentially interesting antidiabetic activity demonstrated in vitro by the marked effect of inhibition of intestinal α-glucosidase. The results of animal experiments show an interesting effect on glycemia of extracts of *A. herba alba* and *O. europaea* compared to the diabetic control group and a decrease in fasting blood glucose levels for the groups treated with 300 mg/kg body weight of *A. herba alba* (-61.82%) or *O. europaea* extract (-56.82%) versus reference drug (-54.66%). Consequently, the opportunity is present to provide raw materials in sufficient quantity and quality for possible future valorization in the pharmaceutical and agri-food fields.

Keywords: Type 2 Diabetes; Phytotherapy; Ethnopharmacology; Phytochemistry; Glycemia; Toxicity

1 Introduction

Currently, 642 million individuals worldwide are expected to be living with Diabetes mellitus, and according to a projection, the number will escalate to 800 million by the year 2045 [1]. Algeria is experiencing an increase in the number of patients, and diabetes, like the global prevalence, is constantly increasing; surveys carried out recently indicate that up to 15% of adults aged 25 to 64 have diabetes [2] due to dietary changes, urbanization, sedentary lifestyles, and obesity, usually silent disease without clinical manifestations and underdiagnosed.

* Corresponding author: Arar K.

Building positive health behaviors and maintaining psychological well-being are foundational for achieving diabetes management goals and maximizing quality of life [3]. Essential to achieving these goals are diabetes self-management education and support, medical nutrition therapy, routine physical activity, counseling and treatment to support cessation of tobacco products and vaping, health behavior counseling, and psychosocial care [4].

Herbal and nutritional supplementation is required in managing diabetic patients, a finding shared unanimously by scientists. Recently, diabetologists have come to the evidence that a therapeutic supplement consisting of nutrients and herbs is necessary to optimize diabetes treatment [5].

In treating diabetes, the question remains: What are the most successful methods for diabetes management? No study has fully resolved this issue, nor can a conclusive answer be offered. Diabetes specialists continue to be unsure about advising on herbal supplements, fenugreek seeds, coffee, or other alternatives.

When the first ADA Standards of Care guidelines were published in 1989, nutrition was mentioned in two sentences in an entire 4-page. Even in 2024, the nutrition science for diabetes continues to evolve. At the same time, there has been a change of emphasis from nutrients (macronutrients and micronutrients) to focusing on foods and, more broadly, dietary patterns [6], not yet sufficient precision in herbal supplementation.

Natural products, particularly those of plant origin, represent a significant opportunity for the development of future drugs [7]. This intriguing area of research into plant-based treatments for diabetes management is one that warrants further exploration and study.

Depending on the desired therapeutic effect, traditional use and research have developed plant treatment processes that allow only the molecules of interest to be kept for local, oral, or injectable use.

The use of plants with antidiabetic potential is no exception to this rule. Many investigations have shown great interest in plants as possible sources of new hypoglycemic agents, and many plants have already been examined. More than a thousand plants have been identified as potential antidiabetic drugs. Still, only a few have been evaluated following pharmaceutical and scientific regulations to determine their effectiveness. It is, therefore, essential to know these molecules, potential factors for innovation in antidiabetic products, through the phytochemical characterization of plant extracts and the purification of bioactive compounds before clinical trials.

Diabetes, which constitutes a significant public health issue whose prevalence has increased exponentially over the last 20 years, is a disorder of the assimilation, use, and storage of sugars provided by food [8]. It is due to a relative or absolute deficit in the secretion and/or action of insulin [9]

Classically, we distinguish between T1D, which most often occurs before the age of twenty and represents 5 to 10% of diabetes, and T2D, which frequently appears after 40-50 years and concerns approximately 90-95% of diabetes.

The management of T2D, commonly linked to being overweight, relies on lifestyle and dietary adjustments and may also include the use of ADOs when necessary. Over the past ten years, treatment options have expanded significantly.

In addition to oral treatment, incretinomimetics (GLP1 analogs) are administered subcutaneously to control postprandial blood sugar levels and promote weight loss.

However, the two oral antidiabetics developed more than 50 years ago, biguanides and hypoglycemic sulfonamides, remain the market leaders. Apart from metformin, which reduces hepatic glucose production and food intake and is suitable for overweight or obese subjects, the choice of antidiabetic drugs is problematic [10].

The latest generation of antidiabetics causes significant side effects [11], including cases of intolerance, hypersensitivity, drug resistance, and weight gain [12].

Many studies, including the famous United Kingdom Prospective Diabetes Study [13], have shown that current antidiabetic treatments are only imperfectly effective in controlling the blood sugar levels of most T2D patients, or only transiently. The same UKPDS study showed that improving blood sugar control alone, at least with a sulfonamide or insulin, is not enough to improve these patients' cardiovascular prognosis significantly. Given the limitations observed with modern medicine in antidiabetics, searching for new antidiabetic molecules based on plant extracts would be a promising alternative [14].

It is crucial to note that nutritional supplements and herbal products currently lack standardization and regulation. As a result, there is insufficient evidence to support the efficacy of micronutrients and herbal supplements in managing medication-induced diabetes or prediabetes, and their routine use is not advisable. This underscores the urgent need for further research to provide evidence for the use of herbal supplements in glycemic management and to develop new therapies that reduce the frequency, severity, and complications associated with diabetes.

In light of these data and the context of the search for molecules with optimal antidiabetic effect, we propose to test the antihyperglycemic activity in experimental models of type 2 diabetes (with a diet rich in carbohydrates and lipids), which is closest to T2D in humans, model not yet sufficiently developed at present. So, the main objective of our work arising from the problem is the valorization of plant resources to manage type 2 diabetes.

2 Materials and methods

In this study, we adopted an ethnopharmacological approach to identify antidiabetic remedies and select medicinal species that will be the raw materials of the experimental research.

Our study protocol consisted of 3 parts:

- The cornerstone of our study was an ethnopharmacological survey that meticulously selected plant species with a possible antidiabetic power. This was a prospective descriptive study.
- A phytochemical study of the following selected plants: Artemisia herba alba (White Mugwort), Marrubium vulgare (White Horehound), Olea europaea subsp europaea var sylvestris (Oleaster) and Salvia Officinalis (Common Sage)
- An animal experiment on a model of iatrogenic type 2 diabetes, including toxicity tests.

2.1 Study area

A survey was carried out in the province of Blida, located in the north of Algeria, North Africa. We first determined the areas concerned by the traditional use of medicinal plants for therapeutic purposes: Sector EAST Chréa National Park of the ATLAS Blidéen Tifinagh. In semi-arid Mediterranean areas, the soils vary, including Hammam Melouane and Megtaa Lezrag. The plants are harvested whole for the herbaceous and in the form of leafy branches for the woody. They were collected freely or with the population of the region.

2.2 Data collection

The data collection process was meticulous, involving a questionnaire given to recruited patients, which included comprehensive information about the disease and the plants used.

In all patients questioned, we collected the following data:

- Socio-demographic: age, sex, level of education, socio-economic conditions,
- Clinical: medical history, duration of diabetes, notion of familial diabetes, treatment followed, presence or absence of complications,
- Use of plants for diabetes therapy: method of preparation, method of use, side effect or toxicity...

2.3 Statistical treatment of data

A comprehensive descriptive analysis was first carried out according to sex, age, type of diabetes, duration of diabetes, complications of diabetes, and the use of medicinal plants to describe the sample. SPSS 23 software was used for data processing, ensuring a robust statistical treatment of the data.

2.4 Selection and identification of plants

Our study was based on the careful selection and identification of the primary plants used by diabetic patients in the Blida region.

The plant species studied are selected by crossing ethno-pharmacological data with bibliographic data. This approach allowed the selection of plant species with a possible antidiabetic power and is potentially interesting for the pharmaceutical industry in treating type 2 diabetes.

Other criteria were also taken into account, namely the abundance and availability of these plant species in the region to provide raw material in sufficient quantity for possible future valorization in the pharmaceutical and agri-food sectors.

The selected plants are *Artemisia herba alba* (white mugwort), *Marrubium vulgare* (white horehound), *Olea europaea subsp europaea var sylvestris* (Oleastre), and *Salvia Officinalis* (Officinal Sage).

2.5 Samples: origin and authentication

The aerial parts of A. herba alba, M. vulgare, O. europaea, and S. Officinalis leaves were collected in the Blida region. The samples were authenticated by Professor Bouhouhou of the ENSA Herbarium (Algiers); a specimen of each plant was placed there.

Once collected, the samples were dried in the shade. The leaves and aerial parts were then reduced to a powder with a small particle size using a Ciatronic® grinder. The powder obtained was stored at room temperature, away from light and humidity, for analysis.

2.6 Phytochemical study

In this first part, a chemical screening was carried out, allowing a characterization of the main classes of bioactive compounds. The screening of the antidiabetic activity was carried out in vitro by evaluating the inhibitory activity of intestinal alpha-glucosidase by spectrophotometric assay.

2.7 Crude extract of bioactive molecules

The extraction of bioactive molecules from the plants studied was carried out by a first method: extract using distilled water as an extraction solvent due to the use of this aqueous form by local populations; the aqueous extract was obtained by mixing the crushed plant and distilled water with a ratio of 1:10. The mixture is maintained at 60 °C in a reflux apparatus After 30 minutes, the system is cooled, and the extract is recovered after filtration and freeze-drying.

2.8 Phytochemical screening

It was carried out according to the methods of Trease et Evans [15] and Bruneton [16].

2.8.1 Evaluation of the inhibitory activity of intestinal α-glucosidase in-vitro by spectrophotometric assay

The inhibitory activity of α-glucosidase was determined according to the method described by Kee et al. [17]. Absorbance readings were then taken at 405 nm using the spectrophotometer. The inhibitory activity of α-glucosidase was expressed as a percentage of inhibition.

2.9 Hypoglycemic activity

2.9.1 Induction of type 2 diabetes in BALBC mice

The mouse model for T2DM was developed as reported [18] and modified in the laboratory. Animals (4 weeks) were assigned to different diets. To induce T2DM, animals were fed a high-fat diet (HFD) (essential mouse diet 59%, sugar 20%, animal fat 18%, and egg yolk 3%) and received STZ 45 mg/kg intraperitoneally at 6 and 9 weeks of age. Control mice were fed standard chow (Mouse pellet complete feed UAB El-Kseur Bejaia) and received a placebo injection of distilled water. Blood glucose levels were measured twice: after the first injection of STZ and 8 days after administering the second dose, using the Accu-check blood glucose monitoring device. Animals with basal blood glucose levels >200 mg/dl were considered to have developed diabetes [19] and used for experimentation.

2.10 Preparation of extracts

Treatment with 300 mg/kg body weight of aqueous extract of the selected plants. The reference anti-diabetic drug is Glibenclamide. Lot 1: Aqueous extract of *S. officinalis* Lot 2: Aqueous extract of *M. vulgare* Lot 3: Aqueous extract of *O. europaea* Lot 4: Aqueous extract of *A. herba alba*.

2.11 Statistical study

The statistical analysis was performed by Graph PAD Prism Software (version 9.1. San Diego, CA 92108 USA). Results are averaged ± one standard deviation. Statistical analyses were performed: one-way analysis of variance ANOVA and using a student's t-test. The differences were considered significant at the probability level of $p < 0.05$.

2.12 Acute toxicity study in mice

To assess the safety of the plant extracts studied, the acute toxicity class method described in the European Guideline Code 423, a widely recognized standard for assessing acute toxicity, was adopted using animals of one sex per stage, according to mortality. This method is reproducible, uses very few animals compared to other acute toxicity methods, uses predetermined doses, and gives results that allow the classification of substances in the Globally Harmonized Classification System.

Given the common use of the plant species by the population, it's reassuring to note that no toxic effects have been observed. A limit toxicity test, i.e., a single dose of 2000 mg/kg body weight, was used to further confirm the safety of the extracts.

The acute oral toxicity of aqueous and hydro-alcoholic extracts of the aerial part of A. herba alba, M. vulgare, and the leaves of O. europaea subsp and S. Officinalis was evaluated in mice. Our use of the OECD Guideline No. 423 ensures the validity of our methods.

3 Results

In this comprehensive research work, which is part of the valorization of the flora of therapeutic interest used in the treatment of diabetes mellitus, we carried out an ethnopharmacological survey, a phytochemical study, and an experimental protocol on animals made diabetic with an evaluation of the toxicity of the selected plants. To explain the results obtained, we will gradually analyze the different stages of our study.

3.1 Ethnopharmacological survey:

Age. The average age of the study population is 60 years, with an extreme of 16 to 88 years. The majority of people with diabetes belonged to the 60-69 age group. Sex. The series includes 402 women (67%) and 198 men (33%) (sex ratio of 2) M/F = 0.49. The medical history and significant results of the study of diabetic patients in the region using medicinal plants are summarized in Table 1.

Table 1 Summary results of the Ethnopharmacological Survey

Socio-demographic data and medical data					
Age	**Sex**	**Type of Diabetes**	**Balance Glycemic**	**Treatment**	**Complications du diabetes**
16 - 88 years Median: 60 years	Men 33% Women 67%	Type 2: 92% Type 1: 8%	Hb1c superior7%: 51% Hb1c Lower 7%: 28% Not dosed: 21%	Oral antidiabetics (OAD): 46% Insulin: 20% Insulin + OAD: 33% Diet alone: 1%	Macro-angiopathy: 19% Micro-angiopathy: 43% Absence: 30% Not explored: 7%
Medicinal plants and diabetes					
Association Herbal with treatment	**Use**	**Recommended**	**Species And families**	**Parties Vegetables**	**Preparations**
35% of the workforce	Alone: 31% Association: 4%	Word of mouth: 58% Herbalists: 30% Pharmacists: 12%	37 species 23 families Lamiaceae (8 esp.) Fabaceae (3) Apiaceae (3) Asteraceae (2)	Leaves (54%) Stems (15%) Seeds (12%) Fruit (7%) Roots (5%) Gum (5%) Flowers (2%)	Infusion (36%) Decoction (31%) Raw organ (14%) Powder (10%) Maceration (7%) Inhalation (2%)

			Lauraceae (2), Amaranthaceae (2), Others(1)		
Most used species		*Artemisia herba alba*	*Olea europaea*	*Marrubium vulgare*	*Salvia officinalis*
Disorders/combination medical treatment and herbs					
Hypoglycemia	48 %		Digestive disorders	12 %	

The study of the use of medicinal plants by diabetic patients in the region are summarized in Table 1.

3.2 Results of the phytochemical study

3.2.1 Screening phytochimique

Table 2 provides information on the different chemical families contained in the extracts

Table 2 Results of the phytochemical screening

	Plants selected	**Alkaloids**	**Saponosides**	**Anthraquinones**	**Glycosides**	**Phenols**	**Flavonoids**	**Tannins**
		E1	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**
1	*S. Officinalis*	-	+	-	+	+	+	+
2	*M. vulgare*	-	+	-	+	+	+	+
3	*A.herba alba*	-	+	-	+	+	+	+
4	*O. European*	-	+	-	+	+	+	+

E: aqueous extract, +: presence. -: absence.

These results show qualitatively that the selected plants contain various families of naturally active compounds, including phenolic compounds such as flavonoids, tannins and, saponosides, glycosides, and devoid of alkaloids and anthraquinones, except for the leaves of Oleastre, which gave a positive result for anthraquinones.

3.3 Determination of total polyphenols

3.3.1 Evaluation of the in-vitro antidiabetic activity of selected plants and Total polyphenol levels

The in-vitro antidiabetic activity evaluation of the selected plants was a Crucial step, validating their potential for diabetes treatment. The results of the in-vitro antidiabetic activities of the selected plants are shown in Table 42.

Table 3 Total polyphenol levels and percentage of inhibition of α Glucosidase from aqueous plant extracts studied

Scientific name	**Total polyphenol (Eq mg AG / g E)**	**Inhibition α - Glucosidase (%)**
S. officinalis	151	62
M. vulgare	140	58
A. herba alba	96	15
O. europeae	88	12

The four plants studied showed antidiabetic activity in vitro (inhibitory activity of the alpha-glucosidase enzyme). this result confirms the in vitro antidiabetic activity attributed to these plant species.

3.4 Results of antidiabetic activity

3.4.1 Effect on Blood Glucose

Blood glucose levels measured in normal and experimental Balb/C mice before and after 21 days of treatment are shown in the figure below.

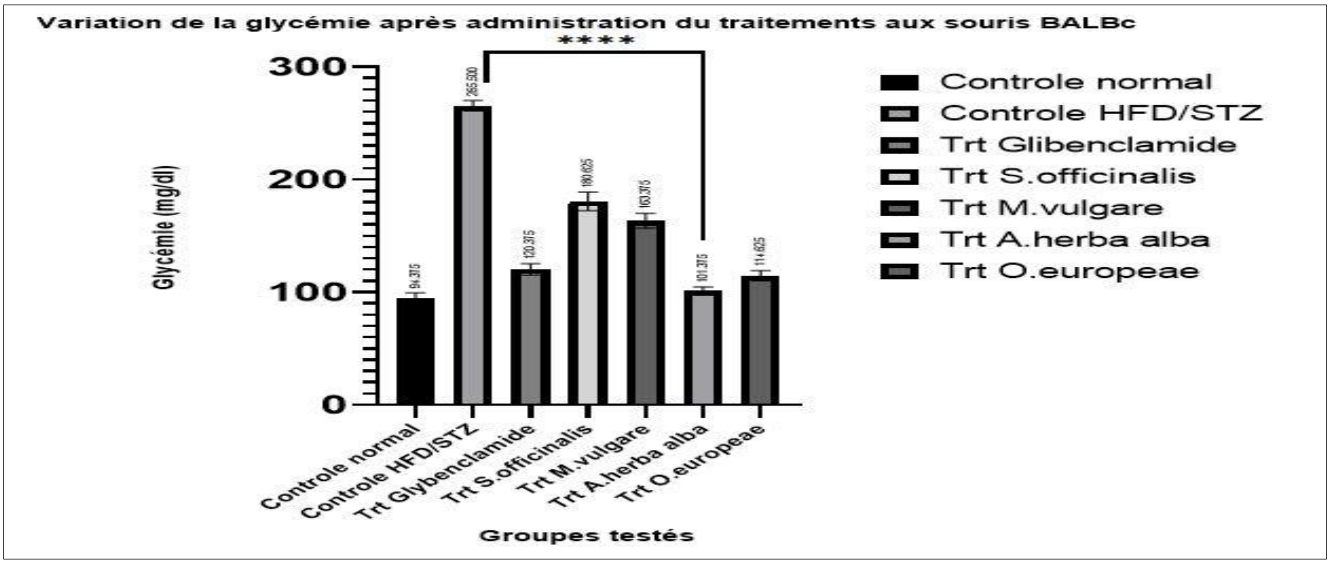

Figure 1 Effect of the extract on blood glucose (mg/dl) in mice

Blood glucose levels in control mice did not change and remained within the normal glycemic range throughout the study (80 mg-100 mg/dl).

The results show a significant difference in blood glucose levels between the untreated group and the healthy control group, confirming the development of type 2 diabetes after a second injection of STZ at 45 mg/kg and the high-fat diet after 40 days.

A decrease in blood glucose levels was observed after treatment of diabetic mice with doses of 300 mg/kg body weight and the reference drug Glibenclamide.

The results show a significant difference in blood glucose levels between the group treated with A.herba alba and O. europaea extract and the control group. There was a noticeable decrease in fasting blood glucose levels for the groups treated with 300 mg/kg body weight of A.herba alba extract (-61.82%) and (-56.82%) O. europaea extract, which is superior to the reference drug (-54.66%). This promising result offers hope for the potential of these plant extracts in managing diabetes.

3.5 Effect on weight

Animal weights measured in normal and experimental Balb/C mice before and after 21 days of treatment:

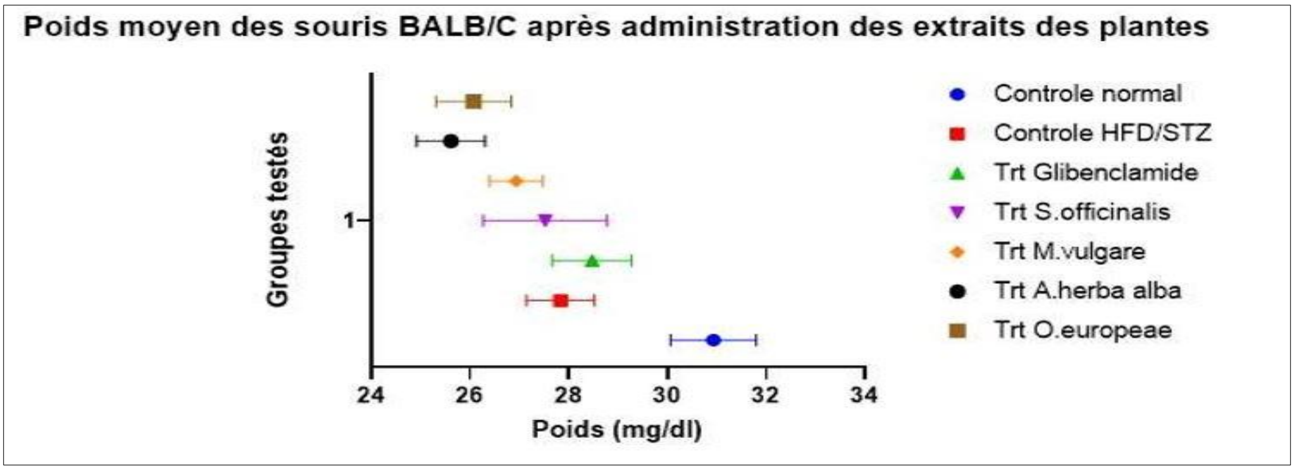

Figure 2 Weight of BALB/C mice under plant extracts

Effect on lipid balance (total lipids, triglycerides and cholesterol)

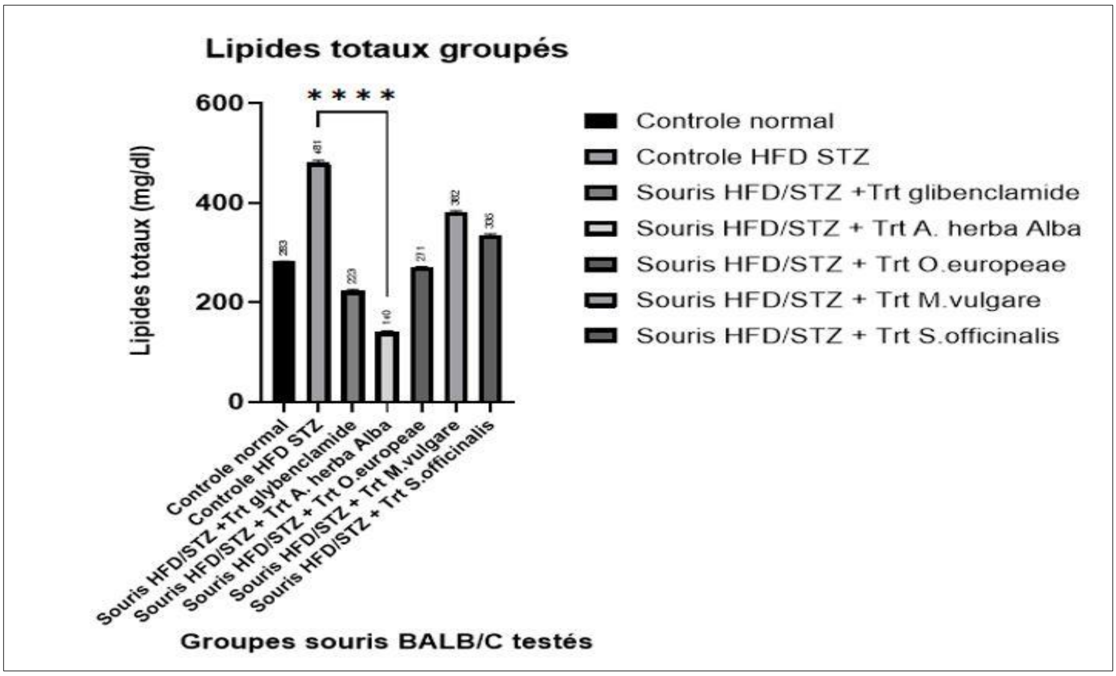

Figure 3 Total lipid levels under the effect of plant extracts

After treatment of mice with the plant extracts studied, the dosage of lipid parameters shows that the level of total lipids is significantly lowered ($P < 0.0001$) under the effect of the administration of the A. herba Alba extract compared to the HFD STZ control.

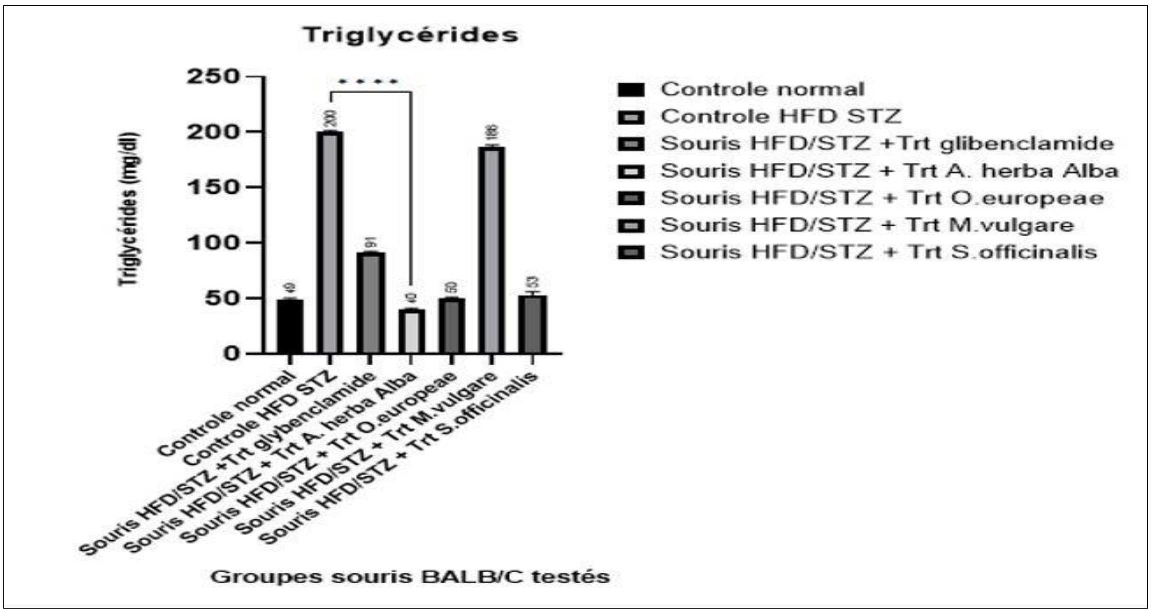

Figure 4 TG levels under the effect of plant extracts

After treatment of mice with the plant extracts studied, the dosage of lipid parameters shows that the triglyceride level is significantly lowered ($P < 0.0001$) following the administration of the A. herba alba extract compared with the HFD STZ control.

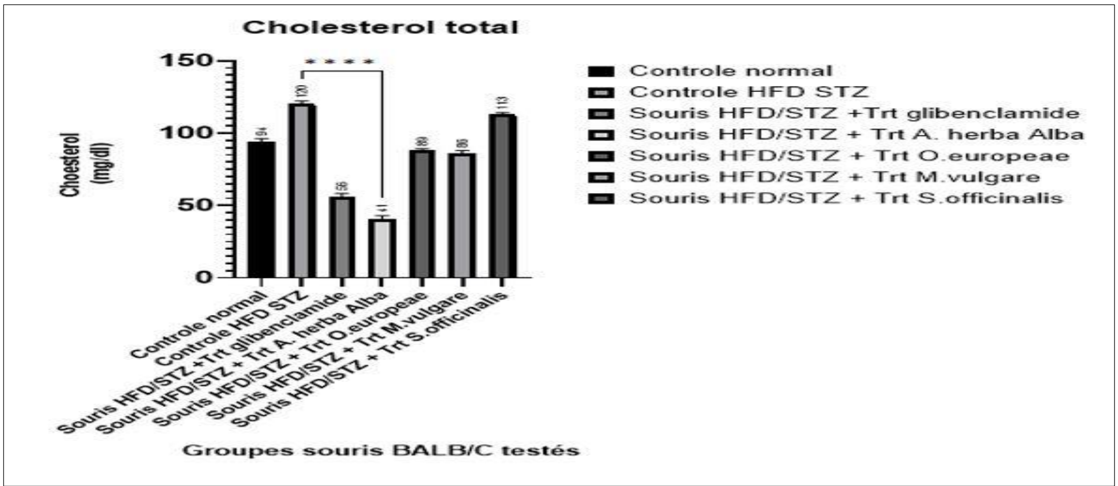

Figure 5 Total cholesterol levels under the effect of plant extracts

According to the results obtained in this study, it is indicated that the aqueous extracts of A. herba alba, O.europaea, and M.vulgare possess an intense hypocholesterolemic activity (significant statistical test with $p < 0.0001$) and a relatively average activity for S. officinalis ($p = 0.0064$).

3.6 Acute toxicity study in mice

An acute toxicity study is a qualitative and quantitative analysis of the alteration of vital functions after a single substance administration within a few minutes to a few days (2 to 4 weeks). It is the first test on a new compound intended to be used as a drug.

3.7 The result of the test limit of 2000 mg/kg

The different batches are placed under observation for 14 days, during which time signs of toxicity and mortality are looked for.

No mortality was recorded in mice receiving aqueous and hydroalcoholic extracts of the aerial part of A. herba alba, M. vulgare, and the leaves of O. europaea and S. Officinalis. - The results of the assessment of the acute oral toxicity of the extracts show that the lethal dose 50 of the plant extracts tested is more significant than 2000 mg/kg body weight and that according to the GHS (Globally Harmonized Classification System) classification, category five substances are very low in toxicity, providing further reassurance.

4 Discussion

In this section, we will analyze the various stages of our study. We conducted an ethnopharmacological survey, phytochemical research, an experimental protocol, and the selected plants' toxicity.

4.1 Ethnopharmacological survey

To enhance our understanding of populations' knowledge regarding the research, preparation, and use of traditional medicinal remedies, we adopted a transdisciplinary approach that includes an ethnopharmacological survey. This approach may involve ethnobotany initially, as both disciplines focus on the interrelationships between people and their environment, particularly medicinal plants. [20].

Ethnopharmacology has significantly contributed to the discovery of active substances in modern medicine. Many active ingredients, such as anticancer drugs (vincristine, vinblastine, taxol), analgesics (morphine, aspirin), antimalarials (quinine, artemisinin), and psychotropic drugs (reserpine, mescaline), derive from traditional medicinal knowledge. Identifying these substances stems from observing the effectiveness of various plants in different pharmacopeias and their use in conventional medicine [21].

Thus, ethnobotany and ethnopharmacology are essential to preserving a written record of the pharmacopeias of traditional medicines whose transmission is based on oral tradition.

Considering the survey among people with diabetes in the Blida region, we listed 37 plant species divided into 23 botanical families. This survey allowed us to distinguish the most used families, in particular, for managing diabetes. These are the families of Lamiaceae, Fabaceae, Apiaceae, and Asteraceae.

Our study made us notice that 35% of people with diabetes questioned use plants with a female predominance, which correlates with the study [22].

Our study indicates that socio-economic status is not a significant factor in the use of herbal medicine. Despite the low cost of these products, being diabetic does not appear to influence the use of medicinal plants either.

Indeed, the Algerian pharmacopeia is described as traditional because, unlike Western pharmacopeias, which were formalized in forms or codices, it was not written but has been perpetuated to the present day by passing from generation to generation among healers and herbalists through oral transmission of knowledge and the practice of medical art

4.2 Phytochemical screening

Epidemiological data on polyphenols' properties indicate a relationship between consuming a diet rich in polyphenols and preventing certain diseases such as cardiovascular diseases, atherosclerosis, allergies, diabetes mellitus, and cancer [23].

Similarly, many studies have been conducted to evaluate the antidiabetic potential of phenolic compounds and extracts. Polyphenols reduce fasting and postprandial hyperglycemia by inhibiting the intestinal flora's disaccharidases (α-amylase and α-glucosidase) [24].

This supports our results concerning S. officinalis and Marrubium vulgare, demonstrating the highest inhibition percentages of α-glucosidase.

These species would be interesting for lowering hyperglycemia and could be the subject of a food supplement formulation recommended after meals.

This result is consistent with the work carried out by the team of Khacheba et al. from the University of Sétif, who demonstrated that among eighteen medicinal plants tested, S. officinalis (highlands region) is the species that showed the most potent inhibitory activity of the digestive enzyme after Cistus Sp.

On the other hand, O. europaea and A. herba alba allowed a decrease in fasting blood sugar in mice treated with their extracts but resulted in a weak inhibition effect on α-glucosidase; this is related to the nature of the phenolic compounds contained in these plants and their mechanism of action which would be likely to modulate or improve glucose transport in muscle cells and adipose tissue. It is noted that glucose absorption in skeletal muscles and adipose tissue contributes to maintaining low blood sugar levels, a hypothesis supported by Khacheba I et al. [25].

The selected plants appear to be very promising, for their abundance (they are available in sufficient quantity to provide raw material for possible use by the pharmaceutical industry), their adaptation to the semi-arid climate of Algeria (endemic plants), their safety that has been demonstrated and their high use in traditional therapy by local populations.

Our results and conclusions are consistent with Anhê FF et al. [26].

Indeed, finding new, safe, and economical health products in the form of plant extracts, mainly from abundant and low-value raw materials, is a real challenge nowadays, especially in sustainable development.

Furthermore, Oleaster, Mugwort, White Horehound, and Common Sage are plants that have been used for a long time in traditional Algerians, Maghreb, and international medicines (among others, as antidiabetics). The importance of this consumption, particularly in Algeria and around the world, by diabetic patients has led to an increase in scientific work aimed at determining the real impact of consumption, in the short and long term, on glycemic balance and overall health. Their effects on a human scale are far from true in the absence of clinical studies. Indeed, clinical studies on homeostasis and glycemic balance are not yet sufficiently numerous.

4.3 Animal Testing (Induced Diabetes)

We were interested in evaluating its role in glycoregulation to determine its antidiabetic action and justify its use for both its effectiveness and safety.

It is known that several medicinal plants have antidiabetic potentialities, and the mechanisms by which this effect is induced are varied.

- Inhibition of intestinal α-glucosidases: decreased intestinal glucose absorption
- Pharmacological target of GLUT-4: for intracellular glucose transport
- pharmacological target of PTP1B, proteins that intervene at the level of the receptor and its substrates.

Our study showed the efficacy of the oleaster in lowering blood glucose levels in diabetic animals and is consistent with the data published by Arab et al [27].

The mechanism incriminated by this author could combine an improvement in insulin secretion, an increase in glucose transport at the peripheral level, a reduction in the elevation of GTP in the serum, or an increase in the use of glucose at the mitochondrial level [28].

Knowing that antidiabetic medicinal plants can offer a broad answer to the complex problem of diabetes mellitus and its complications and therapeutic perspectives for better management, they can, therefore, play a role as a dietary adjuvant as a preventive measure, or increase the effectiveness of oral antidiabetic agents to delay the onset of comorbidities associated with this disabling pathology.

Our results corroborate the many teams involved in this type of work [29, 30].

Numerous clinical trials now, including meta-analyses, show a significant interest in phenolic compounds in glycemic control [31].

Suppose sage and horehound extracts have shown potent in vitro activity but a weak effect on blood glucose. In that case, this may be related to the bioavailability of the main constituents, which is only partially known [32].

A randomized, double-blind clinical trial with Olea europaea versus placebo found that a titrated leaf extract increased insulin sensitivity [33], highlighting the different modes of action of herbal medicines in the control, particularly for type 2 diabetes.

In addition, previous studies have investigated the effect of plant extracts on a model of alloxan-induced diabetes, characterized by the disruption of several biochemical parameters, with insulin deficiency responsible for a significant increase in triglyceride levels and total cholesterol in diabetic mice[34].

It is well known that insulin plays an essential role in lipid metabolism, intervening at several levels. In adipose tissue, it inhibits the action of hormone-sensitive lipase, promoting fat storage in adipocytes and reducing the release of free fatty acids into the circulation. As a direct effect, it slows down the hepatic production of VLDL. In addition, insulin is a potent activator of lipoprotein lipase, thus promoting the catabolism of triglyceride-rich lipoproteins (Chylomicrons, VLDL). Insulin facilitates LDL catabolism by acting directly on LDL receptors. Insulin is also involved in HDL metabolism by activating LCAT, reducing PLTP activity, and modulating the action of hepatic lipase. Because of the significant role of insulin in lipid metabolism, it is easy to understand that any situation in which the action of insulin is altered, such as insulin resistance and diabetes, is accompanied by lipid abnormalities that are often significant [34].

However, few documents describe the effect of extracts from selected plants on a model of T2D induced by a high-fat diet and low doses of streptozotocin on lipid profile.

According to the results obtained in our experiment, it appears that the aqueous extracts of A. herba alba, O. europaea, and M. vulgare have a high cholesterol-lowering activity (significant statistical test with $p < 0.0001$) and a relatively average activity for S. Officinalis, $p = 0.0064$).

Some studies have shown that compounds such as flavonols (quercetin, kaempferol), present in extracts, improve insulin sensitivity and dyslipidemia. Herbal medicines, due to bioactive compounds, especially flavonoids, have been shown to decrease complications of diabetes mellitus, especially those associated with T2D [35]. The result was also highlighted by Pareira et al. [36]

The antidiabetogenic and cytoprotective effects of flavonoid extracts from Ranunculus repens L. and quercetin have been studied in alloxane-induced diabetes in albino Wistar rats. These phenolic compounds have been shown to have the cytoprotective potential of β cells and an antidiabetogenic capacity in alloxan diabetes that unbalances the redox status of pancreatic cells in favor of oxidative stress. The activity of these flavonoids reveals a significantly positive effect on insulin secretion of β cells and blood sugar levels. This action is due to the antioxidant and cytoprotective power of phenolic compounds carried on β cells poisoned by alloxane, resulting in a reduction in the production of MDA, thus preventing lipoperoxidation and normalization of the cytosolic level of antioxidant systems (SOD, CAT and GSH). These effects are likely to maintain a cellular redox status in equilibrium after administration of alloxane in combination with flavonoids, avoiding multiple complications [37].

A significant decrease in total lipids was found by analyzing the results obtained with daily administration of the extracts in all the groups tested, including those treated with Glibenclamide. In addition, untreated diabetic mice had the highest triglyceride (TG) levels (200.3 mg/dl). The TG levels in animals treated with A. herba alba extracts are 40.16 mg/dl and 50.23 mg/dl for O. europaea, close to the rate of the control group (49.1 mg/dl). In comparison, the level presented by animals treated with Glibenclamide is higher than that of animals treated with these extracts ($P < 0.001$); our results are consistent with those of EIdi A et al. [164], who showed an antidiabetic effect of an extract of olive leaves (Olea europaea L.) in normal diabetic and streptozotocin-induced rats. Oral administration of olive leaf extract for 14 days significantly decreased blood glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, aspartate aminotransferase, and alanine aminotransferase, while it increased serum insulin in diabetic rats but not in normal rats. A comparison was made between the action of olive leaf extract and Glibenclamide. The antidiabetic effect of the extract was more effective than that seen with Glibenclamide. In addition, the works of Al-Shamaony L et al. [38] and [39] confirm our results.

Regarding the weight of mice, we noted a significant decrease in the body weight of untreated diabetic animals (27.6 g) compared to normal animals (30.9 g), which generally gained weight. This difference could be explained by a difference in insulin sensitivity between the two batches. On the other hand, we found no difference in weight between the two groups of animals treated with plant extracts, unlike normal animals put on a hyper-fat diet, which showed weight gain with a significant difference at $P < 0.0001$, confirming the role of the selected plants in weight stabilization.

In short, all the effects we have mentioned in this work are most likely due mainly to the phenolic and flavonoid acids contained in the extracts of the selected plants. In addition, several studies have demonstrated the potential health benefits of natural phenolic compounds and flavonoids in treating obesity and diabetes and show increased bioavailability and proven action on multiple target molecules [40].

4.4 Toxicity study

A renewed interest in phytotherapy in recent years has made it possible to deepen the analysis of its therapeutic efficacy and especially its toxicological aspect [41]. This last aspect remains in the background compared to the progress of phytotherapy. Indeed, several studies carried out on traditional herbal treatments have reported toxicity or interaction problems that can cause therapeutic failures or accidents [42]. On the other hand, the toxic principles of plants are little known, mainly because of their natural complexity. Like "conventional medicines," medicinal plants must obey strict cultivation, control, and dispensing rules.

Therefore, for the safe use of medicinal plants, it is necessary to ensure their safety. However, unintentional contamination is possible (by another plant, heavy metals, pathogenic micro-organisms, or agrochemical residues), and failure to comply with the appropriate dose or drug interaction [43].

Our toxicological study was conducted to determine the toxicological parameters of four medicinal plants' aqueous and hydro-alcoholic extracts. The test was conducted at a dose of 2000 mg/kg [44]; acute toxicity tests conducted by OECD Protocol 423 in mice [45] have confirmed that aqueous and hydroalcoholic extracts of A. herba alba, M. vulgare, and leaves of O. europaea and S. officinalis are devoid of toxicity, as revealed by Clarke et al. whose in vitro tests have shown promising results with an essential oil that has undergone a toxicological evaluation to evaluate its effect and estimate the toxic dose on living organisms.

Substances with an oral LD50 of 1000 mg/kg are considered safe or low toxicity.

The LD50 observed is an LD50 > 2000 mg/kg for the aqueous and hydroalcoholic extracts of the four plants studied. As a result, all extracts belong, under these toxicity threshold conditions, to Category 5 of the World System of Classification of Chemicals [46].

5 Conclusion

This work supports the traditional use of the selected species, *Artemisia herba alba*, *Olea europaea*, *Marrubium vulgare*, and *Salvia officinalis*, in diabetes management.

This work confirms the ethnopharmacological and phytochemical knowledge, which refers to the study of the medicinal properties of plants based on the practices and beliefs of a particular culture, of local plants in the Blida region and emphasizes the role of phenolic compounds in regulating and normalizing glycemic disorders.

In addition, and to effectively combat the harmful effects of diabetes, such as oxidative stress, lipoperoxidation, and the formation of advanced glycation end products AGE, a thorough knowledge of the impact of bioactive compounds of antidiabetic medicinal plants on free radicals should be promoted.

In terms of safety of use, medicinal plants must, like drugs, obey strict standard rules to which only the specialist in phytotherapy can respond. This necessarily implies the regulation of the profession. In short, as recommended by WHO, the validation and rationalization of the use of herbal drugs as a traditional remedy in the treatment of diabetes mellitus should go through the evaluation of their efficacy, safety, and standardization of their use. It could constitute a promising and complementary means of treating diabetes mellitus and be introduced into the conventional care system, offering new hope in the fight against this disease.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest

Statement of ethical approval

The competent authorities approved All procedures and protocols to ensure compliance with ethical standards.

International and institutional ethical guidelines for animal experimentation were respected, and ethical approval for animal studies was obtained from the scientific council study of the Blida Faculty of Medicine.

Statement of informed consent

The study on patients was conducted following ethical guidelines and principles and after informed consent of people with diabetes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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