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Diabetes ethnopharmacology in rural region: study of a case report and review of literature

Abstract

Recently, there is an ascendant recourse for medicinal plants' utilization as treatment of several chronic diseases, including diabetes. While effective in wound healing, some herbs might present toxic effects at certain doses or when used for long periods. In this study, the frequently used antidiabetic herbs, in a rural region, was reviewed with special focus on their possible toxicological features

Keywords: herbal medicine, toxicological features, diabetes.

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Ghoul Jamal,[1] Bouzenna Hafsia,[2] Jaballah Abir,[2] Ben Nasr Hmed[2,3]
[1]Department of life sciences, Faculty of Sciences of Bizerte, Tunisia
[2]Department of life sciences, Faculty of Sciences of Gafsa, Tunisia
[3]Laboratory of Pharmacology, Medicine Faculty of Sfax, Tunisia

Correspondence: Ben Nasr Hmed, Department of Life Sciences, Faculty of Sciences of Gafsa, Tunisia, Email hmedbnasr@gmail.Com

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Introduction

Diabetes mellitus (DM) is a worldwide chronic disease. Recent data shows that its prevalence reached about 463 million cases, in 2019. The incidence of DM presents important regional disparities, and its etiology includes multiple risk factors such as nutritional habits, age, gender, obesity, physical activity, behavior, and many other factors[1]. DM is mainly characterized by chronic impairment of glucose turnover as a consequence of cellular insensitivity to insulin or the lower levels of its secretion by pancreatic β-cells. DM types and subtypes are defined according to its etiology and clinical findings.[2–4] The disease is usually associated to other pathologies such as Alzheimer,[5] retinopathy,[6] cardiovascular diseases,[7] obesity,[8] and nephropathy.[9] DM management involves both pharmacological and non-pharmacological interventions, in order to reduce the blood levels of glucose through stimulating its cellular uptake and regulating its metabolism.[10]

Phytotherapy is the oldest medical practice throughout the Human history, among which Chinese medicine and Indian ayurveda are the best known. Recently it gains great scientific and clinical interest because of its medical virtue, disponibility for all populations and lower cost. In particular, the anti-diabetic herbarium comprises hundreds of plant species with approved wound healing effects.[11,12] Nonetheless, some plants species might present risk of intoxication that should be considered in order to ensure patients' safety. The variability in plants' distribution and disponibility, and in populations' culture might influence the choice of the used plants and techniques of their preparation as therapeutics. In such view of point, this work discusses the antidiabetic herbarium of a rural region from Tunisia.

Material and methods

Determination of the anti-diabetic herbarium

In order to determine the used medicinal plants to treat diabetes, a questionnaire was administered to diabetic patients belonging to a rural South-Western village (Madjel Belabbes) of Tunisia, from Marsh to April 2021. This region is settled near the Chaanbi mountain which is characterized by high plant's diversity. Among 91 diabetic patients registered at the hospital of the village, 26 DM type 1 and 62 DM type 2 patients were enrolled in this prospective study (two childs and one pregnant woman were excluded from the study). All included participants gave a signed informed consent. Patients' sociodemographic parameters, disease's description and clinical findings are summarized in Table 1 and 2. Participants were asked, by direct interview, about their usage of medicinal plants to treat diabetes (what plant species do you utilize to treat diabetes? How do you prepare the plant for treatment? How do you apply (intake) this plant preparation? How many times do you intake the plant preparation per week? Did you manifest discomfort or signs of intoxication (e.g., vomiting, headache, nausea, fever, etc.) following the intake of the plant's preparation? If yes, what are these signs? Did you have a physical visit because of the developed signs of intoxication?). All related responses did concern the last two months anterior to the questionnaire date. A complete description of the disease's status (type of diabetes, age at diagnosis, associated complications, etc.) was also realized. The hematological and biochemical profiles of patients were retrospectively analyzed using the most recent medical report effectuated within the last two months. Diastolic (PD), systolic (PS) and mean (PM) arterial blood pressures were also registered, for each patient. Chi- square test was used to define significant associations between the studied parameters. To compare mean values of the measured parameters between, one-way ANOVA test followed by LSD test was effectuated. SPSS for Window.17 (IBM corporation) has been used to carry out statistics with fixed confidence interval of 0.95.

Phytochemical characterization of anti-diabetic plants

The content in phenols, flavonoids and tanins were determined for dried fenugreek seeds and leaves of Thynus vularis, Rosmarinus officinalis, Artemisia herba alba and Melissa officinalis following methods described by Bouzenna and golleagues (2021),[13] Aqueous extracts were obtained by 72 hours' water- maceration of the finely grinded parts of plants. Folin- Ciocalteu's reagent was used for total phenolic content measurement. Aluminium chloride (AlCl3) and Vanillin ware respectively utilized to measure flavonoids and condensed tanins contents. Results are expressed as the absorbance of the respective solutions using UV- visible spectrophotometer, respectively at 725 nm, 510 nm and 500 nm, respectively for phenols, flavonoids and condensed tannins.

Data review

In agreement to the questionnaire's results, a search across scientific databases was carried out in order to outline the toxicological patterns

of the frequently used herbs to treat DM. Diabetes, medicinal plant, herb, phytotherapy, intoxication, toxicity, pharmacology, clinical findings, and the plant scientific names, were the used key words in this search.

Results and discussion

The majority of participants in this observational study were undergraduated (88.6 % have primary school levels) and of low income. 52 patients presented familial history of diabetes and 42 ones have associated health's complications (hypertension, obesity, dyslipidemia, anemia, and cardiopathy). 7 patients presented diabetes with two or more associated complications. In exception of three DM type 2 cases, all subjects regularly use their conventional pharmaceutics (Table 1).

Table 1 sociodemographic and physical description of diabetic patients

Age (years)		53.51±16.88
Sex ratio (H : F)		0.96
BMI (Kg.m-2)		25.81±3.87
	Overweight	43.13 % (38)
	Obesity	12.50 % (10)
School level	≤ 6 years	88.60 % (78)
	>6 years	11.36 % (10)
Incomes	low	93.20 % (82)
	Medium	06.80 % (6)
Smoker		10.20 % (9)
Type of diabetes	DM1	29.50 % (26)
	DM 2	70.50 % (62)
Diabetes' duration (years)		8.67±8.64
Familial history of diabetes		59.10 % (52)
Complications	None	52.27 % (46)
	Hypertension	26.14 (23)
	Dyslipidemia	14.77 (12)
	Cardiopathy	05.68 % (5)
	Coagulopathy	01.14 % (1)
	Anemia	01.14 % (1)
	Mutiple complications	07.95 % (7)
Drugs' disponibility	Yes	96.59 % (85)
Non pharmacological treatment	Yes	56.82 % (50)
Phytotherapy	Yes	55.68 % (49)
	Regular (> 3 times / week)	20.41 % (10)
	Irregular (≤ 3 times /week)	79.59 % (39)

A total of twenty-nine plant species were utilized, in different forms, alone or in combination, to treat diabetes and its complications. They belong to different families : Fabaceae (*Trigonella foenum graecum*, *Cicer arietimum*, and *Retama reatam*), Lamiaceae (*Rosmarinus officinalis*, *Thymus vulgaris*, *Melissa officinalis*, *Mentha* sp, *Ajuga chamaepitys* and *Marrubium vulgare*) Rosaceae (*Malus pumula*, *Prunus dulcis*) Rutaceae (*Citrus limon*, *Citrus xsinensis*), Asteraceae (*Artemisia herba alba*), Ephedraceae (*Ephedra alata alenda*), Aparagaceae (*Hyacinthus orientalis*), Lauraceae (*Cinnamomum verum*), Apiaceae (*Foeniculum vulgare*) Saxifragaceae (*Saxifraga* sp), Amaryllidaceae (*Allium sativa*), Myrtaceae (*Syzygium aromaticum*), Oleaceae (*Olea europea*), Cucurbitaceae (*Citrullus colocynthis*), Zingeberaceae (*Curcuma longa*), Cupressaceae (*Tetraclinis articulata*), Theaceae (*Camellia dulci*), Schizandraceae (*Illium verum*), Ranunculaceae (*Nigella sativa*), Verbenaceae (*Vitex agnus castus*), Globulariaceae (*Globularia alypum*) (Figure 1).

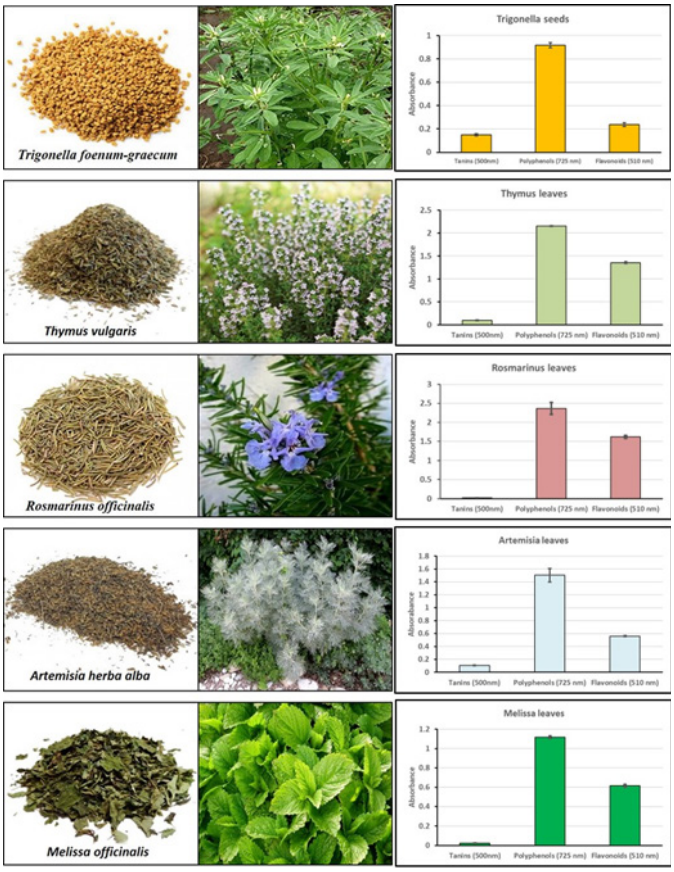

Figure 1 plant species used as antidiabetics and their total contents in tannins, polyphenols and flavonoids (expressed by their absorbance).

The recourse to phytotherapy was observed in 55.68% of cases, among them 20.41% regularly used medicinal herbs. *Trigonella foecum graecum* was the most used antidiabetic plant (71.43 %) irrespectively from the DM type and the presence of associated diseases. *Cinnamomum verum*, *Melissa vulgaris*, *Artemisia herba alba*, *Rosmarinus vulgaris* and *Thymus vulgaris* form a second line to cure diabetes. Other species were less frequently utilized in a discontinuous manner. *T. foecum graecum* seeds were either directly consummed or powdered and suspended in drinking water and used as beverage. *Thymus, Rossmarinus* and *Artemisia* aerial parts are mainly used as tea- infusion or culinary spice. In rare cases, patients did take the water- macerate of the plant's leaves

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Chi- square test revealed significant association between phytotherapy and diabetes' complications ($\chi2 = 4.299$, p=0.036). In particular, diabetes mellitus type 2 patients did intake infusions of Melissa, Thymus and Rosmarinus more frequently when they manifest hypertension ($\chi2=4.299$, p=0.038, $\chi2=8.750$, p=0.015 and $\chi2=8.750$, p=0.015; repectively). Fenugreek was utilized independently from DM type and the presence or not of health's complications. This suggests that Trigonella served only for its antidiabetic properties. Other plants, however, are intended to ameliorate the general health status through preventing or healing associated diseases. The clinical findings revealed significant increase in creatinine content and counts of red and white blood cells in patients auto-medicated by *A. herba alba* in comparaison to those how did not utilize medicinal plants. Most participants (7 per 10) receiving *Melissa officinalis* have a disequilibrated DM type 1 ($\chi2 = 6.521$, p = 0.011) as diagnosed by the augmented levels of glycosylated hemoglobin (HbA-c). In exception of a woman who presented vomiting and nausea immediately following intake of fruits' infusion of *Citrullus colocynthis*, none of patients did experience intoxication signs or discomfort (Table 2).

Table 2 hematological, biochemical and hemodynamic parameters of diabetic patients using or not herbal medicine

	Medicinal herb use		**Frequently used plant species**				
(Number of patients)	No (39)	Yes (49)	Trigonella (35)	Artemisia (12)	Thymus (13)	Rosmarinus (13)	Melissa (10)
Age (yrs)	52.1±17.6	56.4±14.0	55.4±15.6	57.8±14.4	58.0±7.5	56.7±6.0	58.7±8.0
age at diagnosis (yrs)	44.9±17.3	47.7±15.2	47.7±16.6	49.3±18.7	49.9±16.0	48.8±8.6	48.8±8.7
BMI (Kg.m-2)	25.7±3.5	26.1±4.1	25.5±4.3	27.7±3.3	26.9±4.6	26.3±4.4	26.3±3.9
hematology							
RBC (106.mL-1)	4.92±0.46	5.14±0.52	5.06±0.53	5.41±0.63	5.28±0.78	5.06±0.55	5.15±0.23
WBC (103.mL-1)	8.44±1.77	9.23±4.99	9.52±5.62	11.60±5.79 *	8.81±1.56	7.84±1.50	6.90±2.37
PLT (mL-1)	272±67	260±92	251±92	303±96	244±80	229±72	244±63
HGB (g.dL-1)	12.87±1.55	12.99±1.53	12.58±1.51	13.35±1.33	13.40±1.56	13.09±1.44	12.98±0.74
HbAc %	7.13±2.41	8.41±1.48	8.45±1.76	8.55±1.77	8.60±1.92	8.40±1.25	8.09±1.32
biochemistry							
GLUCOSE (mmol.L-1)	11.65±4.98		12.29±4.59	12.75±4.62	13.39±5.05	13.18±4.83	13.09±12.04
CHOLESTEROL (g.dL-1)	4.52±0.83	4.81±1.02	4.67±1.09	4.81±1.03	5.10±1.17	5.18±1.06	5.09±0.48
CREAT (mol.L-1)	92.48±26.72	99.55±28.85	102.5±29.45	149.10±41.16 *	91.0±28.70	83.54±28.76	73.17±8.08
TRIGLYCERIDS (g.dL-1)	1.64±0.65	2.27±1.43 *	2.27±0.97	2.50±1.32	1.86±1.51	2.06±1.64	2.58±1.85
UREA (mol.L-1)	5.45±2.88	5.72±4.80	6.18±2.74	7.46±1.89	5.71±3.20	5.61±3.10	4.12±0.71
AST (IU)	12.13±3.52	20.63±8.07	19.71±8.26	15.50±6.36	24.75±10.01	23.0±9.51	19.6±9.06
ALT (IU)	17.25±5.31	21.67±7.71	20.14±8.19	18.0±7.94	25.25±9.91	23.60±9.34	19.59±6.88
hemodynamic							
PS (mmHg)	12.28±1.21	12.31±1.06	12.17±1.04	12.08±3.35	12.50±1.09	12.31±1.25	12.40±0.97
PD (mmHg)	7.06±1.09	7.06±0.94	7.0±0.97	7.00±1.04	7.25±1.06	7.0±1.15	6.90±0.88
PM (mmHg)	8.80±1.11	8.81±0.95	8.79±1.01	8.70±1.09	9.00±1.04	8.77±1.17	8.74±0.87
FC (bit.min-1)	70.67±2.83	69.73±2.93	70.19±2.97	69.0±2.96	69.8±2.98	69.54±3.04	69.40±2.07

According to Asadi and colleagues (2019), the intake of *Melissa officinalis* improves the control of diabetes by metformin and leads to HbAc reduction.[23] Since most patients using *M. officinalis* are treated by insuline, it is suggested that this plant synergistically acts with metformin but not insuline, fact that explains our observed results. Several studies proved the beneficial effect of medicinal plants, including *Trigonella foenum graecum,*[23] *Artemisia herba alba,*[18,21] *Rosmarinus offiicinalis,*[25–27] Thymus,[29,30] and Melissa[31] in ameliorating the diabetic status. Specifically, great consensus is brought back for the antidiabetic activity of fenugreek that was reviewed elsewhere in EMIJ.[32] Their richness in various chemicals permits different mechanisms of action to lower blood sugar's concentration such as, stimulating insulin secretion, inhibiting amylase, glucosidase and phospho-fructokinases, and facilitating glucose uptake by cells.[27–35] Substances contained in medicinal herbs', essentially polyphenols and flavonoids, are also known to repress oxidative stress that mediates cellular damages and forms a cross- link mechanism for developing associated health disorders.[25] Obviously, most of these herbs are considered as generally safe and can improve many types of metabolic disorders. They can be used as alternative or adjunct for conventional therapy.

Clinical and experimental studies approved the synergism between fenugreek and metformin in reestablishing glycaemia and lipids' profile in diabetes. This encourages its intake as dietetic supplement to manage the disease and its associated.[36–38]

In raison of the frequent use of medicinal herbs and unawareness of the general population about their effectiveness, safe doses and toxicological features, some sporadic intoxications have been observed. Ouzir and colleagues (2016) reviewed these properties for fenugreek and found that its LD50 in experimental animals exceeds 3.5 $g.kg^{-1}$ of body weight. This toxicity considerably varies depending on the extraction's procedure. Clinically, there was only transient nausea, stomach discomfort and diarrhea that were noticed following long-

terme intake of 25 g per day of fenugreek's seeds. Chronic exposure of mice or rats to higher doses of Trigonella extracts resulted in multi-systemic disturbances including convulsion and loss of implantation.[39] Similarly, bare intoxication symptoms have been observed using *Rosmarinus officinalis,*[40,41] *Thymus vulgaris,*[42] *Artemisia herba alba*[43] and *Melissa officinalis,*[44] in animals exposed to very high doses. Other medicinal plants found in this census such as Cinnamon,[45,46] Globularia[47] and *Citrullus colocynthis,*[48,49] showed great potential to counteract diabetes. Obviously, they did present toxicity related to the reproductive system and fertility, when administered at high doses to experimental animals.[50,52]

Conclusion

In this observational study we found 29 plant species that are used to treat diabetes mellitus and its associated pathologies, like hypertension. Such medical virtue is scientifically approved. However, efficacious and safe quantities that patient should intake are still unknown. Experimental models revealed reproductive and fertility related intoxication symptoms at very high doses.[39,50–52] Some allergic reactions to specific vegetal products did also manifest following intake of these herbs. According to experimental findings reported in the literature, it is suggested to avoid auto-medication using herbal medicine for allergic patients and pregnant women. Further prospective toxicological studies are envisaged to better clarify real pharmacological and toxicological patterns of these phyto-therapeutics.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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