



# **The Use and Potential Interactions of Herbal Medicines among Diabetic Patients in Saudi Arabia: A Cross-sectional Study**

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## **Author's contribution**

*The sole author designed, analysed, interpreted and prepared the manuscript.*

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## **ABSTRACT**

**Objectives:** The use of herbal medicines as non-conventional treatment is popular, especially in developing countries where people suffering from chronic diseases as diabetes mellitus are more likely to use herbal medicines along with conventional medicines. However, their simultaneous use may concur serious drug interactions and may therefore result in a serious outcome. The present study was designed to identify the most commonly used herbal medicines and conventional anti-diabetic medications among Saudi population.

**Methods:** A cross-sectional survey was developed and piloted. Data were retrieved and manually entered in Excel 2016. Frequencies and percentages were utilized to perform descriptive analysis. The study was approved by the Scientific and Research Committee of the main hospital taking part in the study.

**Results:** A total of 347 responses were recorded (69.4% response rate). 54% of participants were male, 53% were between the age of 41 and 64 years, and 35.5% had no formal education. Black tea, Peppermint, ginger, green tea, olive oil, and black seed were among the frequently mentioned herbal medicines. Black tea was used by the majority of patients (80%) while peppermint and ginger were used by more than half of patients, i.e., (56.5%) and (52.7%) respectively. Least common herb used by patients was Artemisia species (2.8%). A majority of patients (53.4%) used

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traditional medicine at least once daily, and 83% used traditional medicine without their physician's prescription.

**Conclusion:** Concomitant use of herbal and conventional anti-diabetic medication was a common practice among patients in Saudi Arabia, therefore, pharmacists-led educational programs should target both prescribers and general public about the possible interactions/risks of herbal medicines.

*Keywords:* Herb-drug interactions; herbs; herbal medicines; diabetes; interaction; Saudi Arabia.

## 1. INTRODUCTION

Diabetes mellitus refers to a group of metabolic disorders with the main feature of chronic hyperglycemia, resulting from either impaired insulin secretion or impaired insulin efficacy or, in most cases, both [1]. Of the many types of diabetes mellitus that are encountered in clinical practice, type-2 diabetes accounts for 90-95 % of the cases, followed by type-1 diabetes which accounts for most of the remaining cases [2].

The chronic hyperglycemia associated with diabetes leads to acute and long-term complications [2]. It is estimated that adult patients with diabetes are 2-3 times more likely to have heart attacks and strokes [3]. Furthermore, diabetic retinopathy is thought to be responsible for 2.6% of blindness cases globally [4], and diabetic neuropathy coupled with impaired blood flow lead to increased risk of foot ulcers, infections and eventually leg amputations [5]. These complications have devastating effects on patients' quality of life and independence, and drive-up demand for services and healthcare costs. Diabetes prescription costs in primary care in the UK, for example, exceed £1 billion annually [6]. In the USA, \$1 in \$7 healthcare dollars is spent on diabetes diagnosis and complications management, pushing the annual bill to a staggering \$327 billion [7].

The rising costs of diabetes care are largely attributed to the high incidence of the condition. Around 537 million adults are currently living with diabetes. This number is predicted to rise to 643 million adults by 2030 [8]. The Middle East and North Africa (MENA) region has the highest age-adjusted prevalence of diabetes in adults worldwide, with a devastating 12.2% of the population living with the condition [9]. The prevalence rate is even higher in Saudi Arabia where 14.4% of the population are living with the condition, 34% are obese, 68% are overweight, and 59% lead sedentary lifestyles [10].

Diabetes is a unique long-term condition in that contact with healthcare professionals and

services is only done for a few hours a year. Outside of that, people have to manage their condition by themselves to ensure adequate control over blood glucose levels. In fact, Diabetes UK estimates that 95 per cent of diabetes management is self-management [11]. Diabetes self-management refers to the practices, choices and decisions of patients to manage their condition and minimize the risk of developing diabetes complications [11]. This includes managing and adhering to prescribed medication, healthy eating, maintaining regular physical activity, routine foot checks, frequent monitoring of blood glucose levels as recommended by clinicians, and managing symptoms of hypo- and hyper- glycaemia [12]. However, patients also use complementary and alternative therapies, including herbal remedies, to self-manage their condition [13,14]. Hundreds of herbal remedies are claimed to have anti-diabetic effects ranging from simply lowering blood glucose levels to curing diabetes altogether [15]. This is not surprising given that some of the glucose lowering medicines used for the management of diabetes come from plants including the most commonly prescribed antidiabetic drug; metformin [16].

The WHO defines herbal medicines as herbs, herbal materials and herbal preparations and products that contain as active ingredients parts of plants, or other plant materials, or combinations [17]. The organization has listed 21000 plants for medicinal purposes. However, only a few plants have undergone rigorous scientific assessments for their efficacy. It has been reported that phenolic analogs, flavonoids, terpenoids, and coumarins in medicinal plants play an essential role as anti-diabetic agents by reducing blood glucose levels [18]. The practice of using herbal remedies in the self-management of diabetes is common in Saudi Arabia and many other countries in the region [13,14,19].

Myrrh, black seed, helteet, fenugreek and aloes are commonly used herbal remedies for diabetes management [20,21]. Many patients also use herbal remedies such as green tea and ginger to

lose weight [22], given the overlap between diabetes and obesity management.

Although humans have used herbal remedies for millions of years, and will likely continue using them to manage acute and long-term illnesses in the future, healthcare professionals often oppose their use alongside, or instead of, mainstream medicine [23,24]. Mainstream medicines are thoroughly tested for safety and efficacy, and are heavily regulated. All components of the medicine are known and quantified with a known pharmacokinetic profile [25]. Herbal medicines, however, many include a mixture of plants and many unknown ingredients. The strength of the preparation often varies from batch to batch, and may contain a different amount of the active ingredients, depending on which part of the plant is used, geographical location of origin, age of the plant, how it was processed and stored after picking. Furthermore, evaluating their safety and efficacy in large randomized controlled trials may not be possible [15]. In addition, pharmacodynamic and pharmacokinetic interactions between herbal remedies and medicines used in the management of diabetes are highly likely [24,26], which may affect the efficacy and safety of diabetes medicines, and induce avoidable adverse drug reactions. Metabolic interactions via induction or inhibition of the cytochrome P450 (CYP450) isoenzymes are particularly common. Pioglitazone and repaglinide affect CYP2C8, glibenclamide, glimepiride, glipizide, and nateglinide affect CYP2C9, and pioglitazone and repaginate affect CYP3A4 [27,28]. A large number of herbs have also been suggested to affect the CYP450 system, such as St John's wort's inhibition of CYP2C and CYP3A and ginkgo's inhibition of CYP3A4, CYP2C9 and CYP2C19 [29]. Since the CYP2C9 enzyme metabolizes sulfonyleureas, herbs such as ginkgo biloba induce sulfonyleureas metabolism via CYP2C9.

Despite the common practice of using herbal remedies for disease management, healthcare professionals in Saudi Arabia and other countries are not adequately trained to advise on or manage interactions and adverse drug reactions associated with the concomitant use of herbal remedies [30,31]. Furthermore, patients rarely question the potential of interaction between herbal and conventional remedies [32,33]. Given the high prevalence of diabetes in the country, and the pressing need to help patients achieve adequate diabetes control, it is imperative to investigate patients' herbal remedies' use. This will also highlight the training needs for

healthcare professionals and patients to promote the safe use of conventional medicines and herbal remedies. This study aims to explore the prevalence of herbal medicines' use among Saudi patients with diabetes, and highlight their potential interactions with anti-diabetic medicines.

## 2. METHODOLOGY

### 2.1 Subjects and Settings

Patients with diabetes attending diabetes clinics in all Ministry of Health (MOH) hospitals and primary healthcare centers (PHCs) in the 10 governorates in Al Baha region, Saudi Arabia, were potential targeted in this study.

### 2.2 Questionnaire Development, Validation, and Piloting

A cross-sectional self-administered survey was developed, based on a thorough review of the literature and previous research instruments [33,34]. The survey was reviewed by an internal medicine consultant and two diabetic specialist pharmacists for content validity. Thirty patients were randomly selected to respond to the pilot questionnaire. Their feedback was used to improve the research instrument and its reliability, as some changes were made to the instrument in terms of wording, order of questions, length of the survey, and clarity (meaning) of some questions. The questionnaire includes two main sections: demographic characteristics (4 items) and medical history (7 items). Invitation letters and a copy of the survey were distributed to the potential participants through pharmacists working in the targeted MOH hospitals and PHCs. Data was collected from October to December 2020.

### 2.3 Sampling, Setting and Sample Size

Participants were enlisted utilizing a purposive/convenience sampling method. The survey was distributed, in paper format, in the 7 MOH hospitals and some PHCs in Al Baha region, Saudi Arabia. All patients treated with diabetes medications were targeted. A total of 50 surveys were distributed in each of the 10 governorates (areas) in Al Baha (in hospitals and/or PHCs) targeting diabetic patients, in order to cover the whole area of Al Baha region, and in case the 50 surveys were used by patients, more surveys were provided to the site (Hospitals or

PHCs). Patients with mental illnesses and patients less than 18 years of age were excluded from the study.

## 2.4 Data Analysis

Data were retrieved and manually entered into Microsoft Excel 2016. Frequencies and percentages were utilized to perform descriptive analysis.

## 3. RESULTS

A total of 347 responses were recorded from the distributed 500 surveys (69.4% response rate)

with the exclusion of thirty-four incomplete surveys. From the total of 313 responses, most participants were male (N = 169, 54%), between the age of 41 and 64 years (N= 165, 53%), and had no formal education (N = 111, 35.5%). Most patients were from Al Baha area (N= 44, 14%). Most commonly occurring comorbidity was cardiovascular disorders (N = 144, 46%). Most patients were on oral hypoglycemic medications (N= 219, 70%) and had suffered from diabetes for 5 – 10 years (N= 167, 53.3%). Further details are presented in Table 1.

Black tea was used by the majority of patients (N= 253, 80%) while peppermint and ginger were

**Table 1. Demographic characteristic of respondents (N=313)**

<b>Variables</b>	<b>Frequency</b>	<b>Percentage</b>
<b>Gender</b>		
Male	169	54%
Female	144	46%
<b>Age</b>		
18-40	40	12.8%
41-64	165	52.7%
> 64	108	34.5%
<b>Educational level</b>		
Unable to read or write	29	9.3%
Non-formal education	111	35.5%
High school	74	23.6%
University education	99	31.6%
<b>Governorate (Area)</b>		
Al Baha	44	14.1%
Baljurashi	41	13.1%
Almikwah	37	11.8%
Alaqiq	34	10.9%
Almandaq	31	9.9%
Qilwah	29	9.3%
Alqara	27	8.6%
Alhajrah	25	8%
Bani Hassan	23	7.3%
GhamidAlzanad	22	7%
<b>Comorbidities</b>		
Cardiovascular disorders	144	46%
Hyperlipidemia	110	35%
Arthritis	26	8.3%
Asthma	10	3.2%
Hypothyroidism	5	1.6%
Stroke	2	0.6%
<b>Type of anti-diabetic medications</b>		
Insulin	54	17.2%
Oral hypoglycemic	219	70%
Both	40	12.8%
<b>Years with diabetes mellitus</b>		
<5	44	14.1%
5-10	167	53.3%
>10	102	32.6%

**Table 2. The Frequency and percentage of most commonly used medicinal plants/herbal medicines in diabetic patients and their interaction interpretation based on literature (N = 313)**

Name of medicinal plants	Frequency	(%)	Type of herb-drug interaction
Black tea	253	80%	Black tea may decrease drugs metabolism by cytochrome P450 3A4, 2C9, 2C19, 2D6 [35], therefore, increase the side effects of many drugs [36], digoxin, beta blockers, diuretics, statins [37].
Peppermint	177	56.5%	Felodipine ( <b>Potentialiation</b> ) [37], Peppermint oil may decrease drugs metabolism by cytochrome P450 3A4 substrates cyclosporine, amitriptyline, propranolol, diazepam diclofenac, warfarin ( <b>potentialiation</b> ), Antibiotics, Calcium Channel blockers, (potentialiation) [38,39].
Ginger	165	52.7%	<b>Warfarin, NSAIDs (to cause bleeding), antidiabetics (potentialiation), Calcium channel blockers (potentialiation), Metronidazole Benzodiazepines (potentialiation), Anti-arrhythmic drugs (Increase of Ca2t ATPase), SSRIs (potentialiation)</b> [37,40].
Green tea	149	47.6%	Bortezomib [37], Anti-androgens, Antilipaemics, anticoagulants, antiplatelet ( <b>potentialiation</b> ), Analgesics ( <b>potentialiation</b> ), Antiseizures ( <b>potentialiation</b> ), antivirals ( <b>potentialiation</b> ), MAOIs, beta-adrenoceptor blockers ( <b>potentialiation</b> ) Theophylline, Hepatotoxic agents ( <b>potentialiation</b> ), Cytochrome P450-metabolized agents, Hormonal agents and sedative agents, ( <b>activity reduction</b> ), iron ( <b>absorption decreased</b> ) [38,40].
Olive oil	144	46%	antidiabetics, Antihypertensive <b>drugs (potentialiation)</b> [41,42].
Black seeds	98	31%	amoxicillin ( <b>potentialiation</b> ) [43], losartan, (( <b>potentialiation</b> ) [44].
Garlic	94	30%	Antidiabetics, anticoagulants ( <b>potentialiation</b> ), INH (decreased the absorption), ), anti-HIV- drugs (decreased activity (Efavirenz), Contraceptives (decreased effectiveness) cyclosporine (decreased activity) [39].
Fenugreek	82	26%	fenugreek may reduce absorptionof all medications used concurrently. antidiabetics ( <b>potentialiation</b> ), estrogen like effect [37], Antilipaemics ( <b>potentialiation</b> ), Laxatives ( <b>potentialiation</b> ), Anticoagulants and antiplatelets ( <b>inhibition</b> ) MAOIs: [38,39], losartan, ( <b>potentialiation</b> ) [44].
Anise	79	25.2%	Contraceptive drugs, tamoxifen ( <b>decrease effectiveness</b> ), anticoagulants, iron absorption ( <b>potentialiation</b> ) [39].
Arabic coffee	78	25%	Ephedrine, selective serotonin reuptake inhibitors,(SSRIs) antiarrhythmics, MAOIs, lithium, bronchodilators(theophylline) and quinolones, ( <b>potentialiation</b> ) , alendronate, Dipyridamole, Antacids, H2-blockers, proton pump inhibitors, Benzodiazepines ( <b>decrease effectiveness</b> ) [39].
Rosemary	42	13%	immunosuppressant ( <b>potentialiation</b> ), ACEIs ( <b>potentialiation</b> ), anticoagulants ( <b>potentialiation</b> ), antidiabetics ( <b>potentialiation</b> ) Antibiotics ( <b>potentialiation</b> ) Anxiolytics ( <b>potentialiation</b> ) [38].
Sage	40	12.8%	Antidiabetics, sedatives ( <b>potentialiation</b> ), Anticonvulsants, iron absorption ( <b>Effect reduction</b> ) [39].
Thyme	14	4.5%	Antineoplastic agents5-fluorouracil, Anti-Leishmanial and Entamoeba drugs, Increased estrogen and progesterone effects, Immunosuppressive agents ( <b>potentialiation</b> ), Fluoroquinolones, Amphotericin B, Caffeine ( <b>activity reduction</b> ) Anti-thyroid drugs ( <b>Decrease of TSH</b> ) [39,40].
Artemisia spec	9	2.8%	Black, tarry stool (Anticoagulants) warfarin [39,45].

**Table 3. Use of medicinal plants/herbal medicines and their source**

<b>Duration</b>	<b>Frequency</b>	<b>Percentage</b>
Used once	20	6.4%
Once-daily	167	53.4%
More than once daily	46	14.7%
Once weekly	33	10.5%
More than once weekly	47	15%
<b>Have you told your doctor that you are using herbal plants?</b>		
Yes	53	17%
No	260	83%
<b>Source of the herbal medicine</b>		
Pharmacy	9	3%
Herbal store	67	21%
Personal	239	76%
Friends	23	7%

used by more than half of patients, i.e., (N= 177, 56.5%) and (N= 165, 52.7%) respectively. The least commonly used herb was *Artemisia* species (N= 9, 2.8%). These details are presented in Table 2.

Most patients used herbal medicines once daily (N=167, 53.4%) and never informed their doctor about their use (N=260, 83%). The most common source of herbal medicines was personal source (N=239, 76%). The details are presented in Table 3.

#### 4. DISCUSSION

This study explored diabetes patients' concomitant use of herbal remedies in Saudi Arabia, and the potential interactions they might have with antidiabetic and other medicines. Herbs and herbal products are frequently used concomitantly with anti-diabetic drugs as patients think they are safe, but many reports have suggested that they are not safe. Some combinations might have synergistic effects, while few may also be harmful [46].

The study estimated that, from total patients with diabetes mellitus, many patients had comorbidities. Most of these patients were already taking oral hypoglycemic medications, and had diabetes for 5 – 19 years. Some patients also used insulin. It was observed that black tea was used by most diabetic patients. It is reported that black tea may decrease drug metabolism by cytochrome P450 3A4, 2C9, 2C19, 2D6 [35]. Therefore, it may increase the side effects of many drugs [36]. More than half of the diabetic patients surveyed used peppermint oil, that may decrease drug metabolism by cytochrome P450 3A4 substrates cyclosporine, amitriptyline,

propranolol, diazepam, diclofenac, warfarin (potentiation), antibiotics, calcium channel blockers, (potentiation) [38,39].

Ginger is the third most commonly used herbal medicine used by diabetic patients. Additionally, green tea and olive oil were used by a similar proportion of diabetic patients. It has been reported that black seeds demonstrated significant reduction in glucose concentration [47]. A third of diabetic patients in our study used black seed and garlic. Fenugreek may reduce the absorption of all medications used concurrently, and slightly more than a quarter of patients used it.

In our study, Fenugreek was used by a quarter of diabetic patients while in the study involving Ethiopian patients, its use was documented in very few patients (7.3%) [34]. Besides, our study reported a third of patients who used black seeds and garlic while a study by [34] reported 6.6% and 5.6% of patients who used black seeds and garlic, respectively. On the other hand, 17.4% of Ethiopian patients used thyme while in our study only 4.5% patients used it. Despite the difference in proportion of patients, it could be said that our findings are in line with the results of [34]. Our study report that almost half of patients (47.6%) consumed green tea while in a Nigerian study, the figure was 0.9% [33].

The present study also revealed that most diabetic patients used these herbal medicines once daily, while a small percentage used these herbal medicines more than once. Interestingly, most of the patients used herbal medicines without informing their physician. This occurrence was similar to an Ethiopian study where it was reported that slightly more than a

third of patients informed their physicians about using such products [34]. This occurrence in our study may be a result of participant's demographics but it cannot be determined unless it is further investigated. One more interesting finding is that most patients (76%) used herbal medicine regularly, while 21 were buying from herbal stores.

## 5. CONCLUSION

The study further confirms the common practice of using herbal medicines concomitantly with conventional anti-diabetic medicines. Combining herbal remedies and conventional anti-diabetic medication may lead to severe toxic effects owing to herb-drug interactions. Black tea, Peppermint, ginger, green tea, and black seed were the most commonly used herbs by patients with diabetes. Therefore, pharmacists-led educational programs should target both prescribers and general public about the possible interactions/risks of herbal medicines' interactions.

## CONSENT

The author declares that "written informed consent was obtained from the patient for publication of the finding of this study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

## ETHICAL APPROVAL

The study was approved by the Scientific and Research Committee of the main hospital taking part in the study (King Fahad Hospital in Al Baha, Saudi Arabia), Ethics approval number (43110955, Date: 16/06/2020).

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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