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Potential Adverse Effects of Commonly Used Herbal Medicine and Phytopharmaceuticals in Patients Undergoing Surgery Under General Anaesthesia: A Cross-sectional Study in Jordan

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Abstract

Purpose: The usage of herbal medicine (HM) and phytopharmaceuticals (Phyph) has become increasingly popular among individuals in Jordan. This study aims to assess the current use of HM and Phyph among patients who are admitted into the hospital and are scheduled for surgery under general anaesthesia.

Methods: This cross-sectional study was conducted at Al-Hussein Hospital, Salt, Jordan using a data collection sheet. All patients who were admitted to surgical operation under general anaesthesia were included.

Results: About 98 patients were enrolled in this study with a mean age of 42.44 ± 16.83 years, of which 55.1% were women. Endocrine and cardiovascular diseases were the most common medical conditions. Most patients reported using HM (N= 61.2%), and Phyph (31.6%) on regular bases. The most used HM were sage, chamomile, mint, and rosemary. Longer recovery time, hypotension, and hypoglycemia were significantly higher post-surgery in patients who used HM, 40%, 28.3%, and 18.3%, respectively, $p<0.05$. Average INR test values for patients using Phyph were significantly higher than non-users (1.22 ± 0.75 and 1.03 ± 0.19, respectively, $p <0.05$).

Conclusion: Information concerning HM and Phyph use among patients undergoing general anaesthesia should be investigated. In addition, there is a need to raise healthcare providers' awareness of the potential risk associated with the use of these products.

Keywords

Adverse Effects, Cross-sectional Study, General Anesthesia, Herbal Medicine, Phytopharmaceuticals, Surgical Operations.

Introduction

Herbal medicines (HM) are edible or drinkable substances that may contain vitamins, minerals, herbs, or parts of these substances, used for their scent, flavour, or therapeutic properties (El-Dahiyat et al., 2020). The term phytopharmaceutical (Phyph) is known as herbal remedies which are prepared from single or multiple herbal substances traditionally known to cure undesired conditions or illnesses. These herbal preparations are extracts in optimized form with known extraction solvent, drug-extract ratios, and processing steps finalized as pharmacologically active dry extracts (Bhusnure et al., 2019).

While many plants that have been used historically for healing and culinary purposes are generally safe, it is also important to understand that few plants are extremely poisonous or harmful (Fuchs et al., 2011). However, it is becoming increasingly clear that phytochemicals can influence the healing outcomes of medications, by influencing their absorption properties via interactions with drug transporters and drug-metabolizing enzyme systems (Amadi & Mgbahurike, 2018). Some databases that allow physicians to search for these interactions are available, such as the NIH Office of Dietary Supplements (Office of Dietary Supplements (ODS), n.d.), and the Natural Medicines Comprehensive Database (NatMed Pro, n.d.).

A descriptive study conducted in Hungary has shown that 7.2% of patients have used herbs at least two weeks prior to their hospitalization, and only a quarter of them reported their use to their physicians (Soós et al., 2015). Another important issue to consider is the interaction with medicines and food that may lead to serious complications. Therefore, special consideration must be given to those undergoing or planning to undergo surgery as many of these herbs may interact with anaesthetics, increase perioperative bleeding or cause cardiovascular instability (deAzevedo Pribitkin, 2005). For example, Hawthorne (Crataegus monogyna) may interact with digoxin through an additive effect to increase vasodilatation (deAzevedo Pribitkin, 2005). Ginkgo (Ginkgo biloba), garlic (Allium sativum), and ginseng (Panax quinquefolius L.) have direct effects on platelet aggregation and coagulation activity, which might increase bleeding tendency during surgery, ephedra (Ephedra sinica) may cause cardiovascular instability, and ginseng may exacerbate hypoglycemia (Ang-Lee et al., 2001). On the other hand, St John's wort (Hypericum perforatum) may increase the metabolism of many drugs, while valerian (Valeriana officinalis) roots potentiate the sedative effects of anaesthetics (Ang-Lee et al., 2001).

A cross-sectional study by Issa and Basheti (2017), aimed to assess the current use of herbal products among chronically ill patients in Jordan and to review the impact of the used herbal products on the safety and efficacy of their treatments. Results revealed that about (57.4%) of the interviewed patients were using 43 different herbal products. The most common chronic diseases were hypertension, diabetes and hyperlipidemia. Additionally, males and older patients were more likely to experience unsafe or inefficient use of herbal products. Only 54.2% of patients informed their pharmacists of their use of herbal products. On the other hand, a minority of pharmacists (8.2%) reported very good knowledge about the usage of herbal products and herbal-drug interactions. While only (11.3%) of these pharmacists always ask their patients about their use of herbal products (Issa & Basheti, 2017).

To our knowledge, no previous study was performed investigating the effect of the regular use of HM and Phyph prior to the use of anaesthetic agents among Jordanian patients. This area of research should gain more interest, to investigate patients who regularly use these products and undergo anaesthesia before any surgical procedure; an aim is to report any potential interactions that could occur due to this combination. This information may be used to improve the clinical outcomes of patients, and to reduce complications in this group of patients.

Methods

Study design

A cross-sectional study was conducted at the Department of Surgery, Al-Hussein Hospital, Salt, Jordan. A total of 98 patients admitted for surgical operation under general anaesthesia were included. Data collections were performed during the period February 20 to August 9, 2022.

A structured data collection sheet was utilized to collect the data. Candidates were interviewed face-to-face to record their consumption of HM, and Phyph. In addition, their demographic data, and medical history were also collected. Prior to admission to the operating room, the patient's vital signs, consciousness level, and medical conditions were all recorded.

The data collection sheet was developed after extensive literature review of similar studies and revised by two field experts to insure the inclusion of relevant data. A pilot study of 10 patients was conducted to identify any problems in the data collection sheet, clarity of questions, and the time needed to complete the interview and modifications were made accordingly. The data collection sheet was standardized for all patients, and they were asked the questions in the same manner. The researcher was instructed to explain the questions if they were not clear to the participant, but not to guide the response in any way.

During surgery, the anesthetic agent used was reported. Patients´ post-operational vital signs and relevant clinical laboratory data were collected and compared with the normal parameters of the institution. The laboratory data that were monitored during this study, post-surgery, including haemoglobin (Hb), prothrombin Time (PT), international normalized ratio (INR), random blood glucose and blood pressure. Recovery time (min) was also recorded based on the clinic's reports.

Hakeem program was used to assist in collecting relevant data (https://emed.hakeem.jo/index-en.html). This database is constantly updated with all patient data, who already received medical care from any of the automated health facilities under the Jordanian Royal Medical Services, or the Ministry of Health in the Hashemite Kingdom of Jordan.

Ethical approval

After acquiring the Institutional Review Board (IRB) approval from the Ministry of Health (MOH) in February 2022, only patients that meet the inclusion criteria were approached for consent. A consent form was provided and signed by the patients and archived by the research group. IRB approval number MBA/Ethical Committee/1363.

Inclusion and exclusion criteria

All patients undergoing general anesthesia and 18 years or older were approached for enrollment in the study. Patients under the age of 18 and those who were unable to provide informed consent were excluded from this study. All patients who fulfilled the inclusion criteria consented to participate (response rate 100%). All patients who were approached agreed to participate since those who were distressed or with cognitive issues were excluded. Interviews were conducted while waiting for the operation and patients were eager to exchange information with the researcher.

Patients reported that the duration of use for HM or Phyph was at least for the last 2 weeks prior to the surgery. The amount used was based on the dietary intake allowance for Phyph, or the normal food amount intake for HM.

Study population and sampling

The sample size was calculated according to the equation (Pourhoseingholi et al., 2013):

$$n = \frac{Z^2 P(1-P)}{d^2}$$

n: the sample size. Z: the statistic corresponding to the level of confidence (Z for a 95% confidence interval is 1.96). P: the expected prevalence (results from similar studies). d: precision (corresponding to effect size) .

The calculated sample size

This study sample size was calculated to be 98 patients.

Z= 1.96, Z2= 3.8

P= 0.44 (Levy et al., 2017), 1-p=0.56

3.8*0.44*0.56=0.94

d=0.1, d2=0.01, 0.94/0.01= 94 patients (Levy et al., 2017).

d=0.1, d2=0.01, 0.94/0.01= 94 patients(Levy et al., 2017).

Statistical Analysis

The statistical analysis was performed using a Statistical Package for the Social Sciences (SPSS), version 27.0 for Windows (Chicago, IL, USA). Descriptive analysis was carried out to determine the frequencies calculated for the categorical variables. Chi-square test (X^2) or Fisher's Exact Test were used to assess association between categorical variables, and independent samples t-test for association between continuous variables. P value ≤ 0.05 was considered statistically significant.

Results

Demographic data

A total of 98 patients were enrolled in the study, with a response rate of 94.23%. The mean age of participants was 42.44 ± 16.83 years (minimum=19, maximum=88). The majority of participants were educated and held a bachelor's degree, with a low income of <400 JD/ month. The general characteristics of the participants are shown in Table 1.

Table 1. Demographic data for patients

	Demographic data	Frequency (%)
	Gender	
Male		44 (44.9%)
Female		54 (55.1%)
	Marital status	
Married		85 (86.7%)
Single		13 (13.3%)
	Education level	
Basic education		21 (21.4%)
High school		28 (28.6%)
Bachelor's degree		49 (50.0%)
	Monthly income (Jordanian Dinars)	
	250-400	52 (53.1%)
	400-800	44 (44.9%)
	>800	2 (2.0%)
	Drug allergy	
	Yes	1 (1.0%)
	No	96 (98.0%)
Not available		1 (1.0%)
	Food allergy	
	Yes	0 (0%)
No		98 (100%)
	Chronic medical conditions	
	Yes	53 (54.1%)
	No	45 (45.9%)

Participants' medical conditions

The average number of chronic medical conditions that the patients were diagnosed with was 1.46 (± 0.74), (minimum = 0, maximum = 3). Endocrine and cardiovascular diseases were the most common medical conditions (41.5% and 43.3%, respectively).

Participants surgical conditions

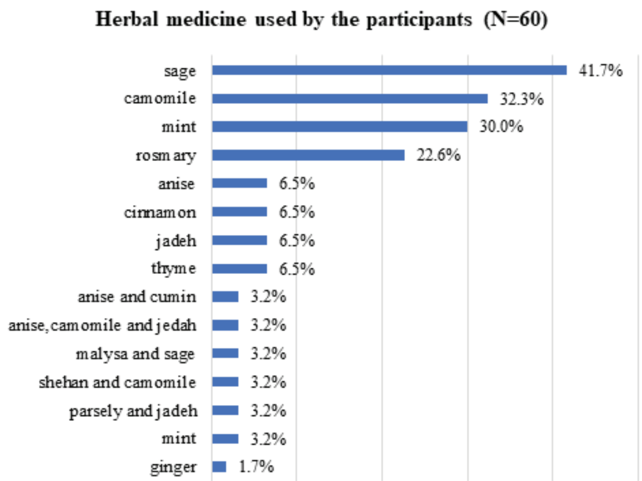
The most common surgery performed for the participants was abdominal surgeries (n= 26, 26.5%) followed by orthopaedic (n= 16, 16.3%), cardiac-thoracic (n=7, 7.1%), breast (n= 2, 2.0%), head (n= 1, 1.0%), and miscellaneous (n= 46, 46.9%). More than half of the patients received propofol as an anaesthetic agent (65.3%).

Prevalence of participants' use of HM

More than half of the patients reported using HM (n=60, 61.2%). There was no significant difference in the use of herbs between males and females, (n=26, 59.1%; n=34, 63.0%, respectively) (p-value= 0.696).

The number of participants reporting daily use of HM was higher than those using it weekly (n=42, 70.0%) vs (n= 18, 30.0%), respectively. The most common HM used by the participants is shown in Figure 1. Sage was the most frequently used herb, followed by chamomile, mint, and rosemary. Other herbs were occasionally used such as anise, cinnamon, ginger and thyme.

Figure 1. Herbs reported to be used by the participants prior to hospital admission



Effect of HM on clinical laboratory tests and observations

Haemoglobin, International Normalized Ratio (INR) and Prothrombin time (PT) test results.

The mean value of Hb tests was 12.08 ± 2.49 among patients who used herbs, compared to 12.39 ± 1.86 among those who did not use herbs (p-value = 0.501). The average PT test value was 15.04 ± 6.86 among patients who used HM, compared to 13.89 ± 2.04, among those who did not use herbs (p-value = 0.23). The average INR test values of 1.13 ± 0.56, for HM users, compared to an average of 1.01 ± 0.17 for non-users. (p-value = 0.199). No correlation was found between the Hb, INR, or PT status after surgery and the use of HM (Table 2).

Table 2. Correlation between Hb, PT, and INR status post-surgery and the use of HMs

Laboratory test	Regular herb user (n=60)	Non-Regular herb user (n=38)	P value Ω
Haemoglobin (Hb)			0.465
No change in Hb	3 (5%)	2 (5.2%)	
Increased Hb	12 (20.0%)	4 (10.5%)	
Decreased Hb	45 (75.0%)	32 (84.2%)	
Prothrombin time (PT)			0.299
No change in PT after surgery	3 (5.0%)	3 (7.9%)	
Increased PT after surgery	27 (45.0%)	22 (57.9%)	
Decreased PT after surgery	30 (50.0%)	13 (34.2%)	
International normalized ratio (INR)			0.983
No change in INR after surgery	5 (8.3%)	3 (7.9%)	
Increased INR after surgery	32 (53.3%)	21 (55.3%)	
Decreased INR after surgery	23 (38.3%)	14 (36.8%)	

Ω: Chi-square test (X^2) or Fisher's Exact Test

Blood pressure effect

Hypotension during surgery was more frequent in patients who used HM (n=17/60, 28.3%), compared to those who didn't (n=4/38, 10.5%) (p-value = 0.036). The most frequently used HM among these patients were sage (41.1%), followed by mint (35.2%) and rosemary (23.5%).

Of the HM users who experienced hypotension post-surgery, 8 patients were also on hypotensive agents prior to hospital admission, including candesartan, metoprolol, enalapril, and bisoprolol. The rest of the patients (n=9/17, 52.9%) have not been exposed to any hypotensive medications prior to their admission to the hospital.

Blood glucose levels

Patients who were using HM had an increased incidence of hypoglycemia after surgery (n=11/60, 18.3%), compared to those who did not use herbs (n=0/38, 0%) (p-value = 0.005). The most commonly used herbs among these patients were mint (36.3%) and sage (45.4%) followed by rosemary (27.2%) and anise (18.2%). Only one patient was using an oral diabetic agent (metformin) before admission, and three others were on insulin.

Central nervous system effect

As shown in Table 3, no association was found between the use of HM and central nervous system depression. However, there was a significant correlation with the post-surgical recovery time. Patients using HM had longer than usual recovery time (40%) compared to those who did not use it (7.9%) (p-value = 0.002). The most frequently used HM among these patients were sage (45.8%), followed by mint (25%).

Table 3. Correlation between post-surgical recovery time and the use of HM

Time for recovery after surgery	Regular herb user (n=60)	Non-Regular herb user (n=38)	P value Ω
			0.002
Normal min range (5-10 min after anaesthetic ends)	31 (51.7%)	30 (78.9%)	
Sage	12 (38.7%)		
Mint	11 (35.5%)		
Other	8 (25.8%)		
Shorter than usual (<5min)	5 (8.3%)	5 (13.2%)	
Sage	2 (40.0%)		
Mint	1 (20.0%)		
Other	2 (40.0%)		
Longer than usual (>10min)	24 (40.0%)	3 (7.9%)	
Sage	11 (45.8%)		
Mint	6 (25.0%)		
Ginger	1 (4.2%)		
Other	6 (25.0%)		

Ω: Chi-square test (X^2) or Fisher's Exact Test

Prevalence of participants' use of Phyph

Thirty-one patients reported using Phyph such as fish oil (n= 19, 63.3%), green tea (n=10, 33.3%), glucosamine (n= 1, 3.3%), and garlic (n= 1, 3.3%). Most participants used these products daily (n=24/31, 80.0%), and less commonly on a weekly (n=6/31, 20%), or monthly (n=1/31, 3.3%) bases. Patients were either using Phyph like fish oil for promoting healthy heart status, which is the most common reason (46.7% of patients), or to burn fat for weight loss (green tea), or to decrease blood pressure (garlic) and lipids (fish oil), or to treat gastrointestinal disorders (green tea).

Effect of Phyph products on clinical laboratory tests and observations

Hb, INR and PT test results

The average INR test values for patients using Phyph were significantly higher than those who did not use these supplements (1.22 ± 0.75 and 1.03 ± 0.19, respectively (p-value = 0.047)). However, the sample size was too small to detect differences among the different Phyph products used. On the other hand, no association was found between the Hb and PT test values post-surgery (Table 4).

Table 4. Correlation between Hb, PT, and INR status post-surgery and the use of Phyph

Clinical tests post-surgery (mean± SD) *	phytopharmaceuticals products users (n=31)	Non-phytopharmaceuticals products users (n=67)	P value[α]
INR	1.22 ± 0.75	1.03 ± 0.19	0.047
PT	16.04 ± 9.52	13.96 ± 1.93	0.244
Hb	12.25 ± 2.25	12.18 ± 2.29	0.883

[α]: Independent samples t-test

Other clinical effects

No association was found between the use of Phyph and hypotension, hypoglycemia, or post-surgical recovery time.

Discussion

In this cross-sectional study, participants hospitalized for surgery completed a questionnaire to report their use of HM and Phyph to explore the risk of these supplements in the perioperative setting. To our knowledge, this is the first study of its kind in Jordan that explores the potential adverse effects of commonly used HM and Phyph on patients undergoing general anaesthesia.

According to the WHO, 80% of people use HM for colds, stress relief, diabetes, urinary disorders, and many other diseases (Bhusnure et al., 2019), and up to 70% of users do not report their use of HM to their physicians or pharmacists (Fuchs et al., 2011). On the contrary, in the current study more than half of the patients reported using HM. Sage was the most frequently used herb, followed by chamomile, mint, and rosemary. These aromatic herbs users experienced longer than usual time for recovery post-surgery. It was reported that the intravenous anaesthetic agent commonly used in the current study was propofol. This agent acts as a positive allosteric modulator and direct activator of GABA A receptors (Jayakar et al., 2014). The GABAergic system is also linked to the effects of volatile odorants found in essential oils, as well as phytochemicals such as terpenoids, flavonoids, and alkaloids (Tsuchiya, 2017). This may explain the longer- than usual -recovery time some patients experienced post-surgery, who were using HM. No association was found between the use of Phyph and post-surgical recovery time, as fish oil, green tea, glucosamine and garlic don’t contain such components, which are available with relatively high content in the reported HM.

Although there’s no clear data on the adverse interactions between HM and anaesthetics, the American Society of Anaesthesiology recommends that all HM should be stopped at least 2 weeks before elective surgery (Wong & Townley, 2011). Moreover, Sage (Salvia species) is well known to possess a sedative and hypnotic effect, due to its content of carnosol and carnosic acid, apigenin, hispidulin and cirsimaritin (Imanshahidi & Hosseinzadeh, 2006). While mint contains menthol, one of the most abundant volatile oils, found with known anaesthetic activity (Tsuchiya, 2017). Several studies have found hypnotic-sedative properties, as well as allergic reactions caused by chamomile. Central Benzodiazepine receptors may be involved in the mechanism of interaction, causing hypnotic-sedative properties and reports of allergic reactions (Batra & Rajeev, 2007). In this study, one patient was using garlic and reported to have longer- than usual recovery time post-surgery. This finding was previously reported in a study by (Skalli et al., 2007) who showed that herbal medicines such as Allium sativum (garlic), when consumed during the preoperative period, could interact with allopathic anesthetic drugs, and cause many complications such as prolonged or inadequate anesthesia.

A review article highlighted that peppermint essential oil, which has been shown to lower blood glucose levels, increase insulin and C-peptide levels, and improve pancreatic beta cell structure, implying that peppermint essential oil may be used as a hypoglycemic agent. These data agree with the findings of this study, where 54.5% of patients exposed to hypoglycemia post-surgery were using mint on regular bases (Zhao et al., 2022). In addition, 36.3% and 27.2% of the patients exposed to hypoglycemia were using sage and rosemary, respectively. These data can be explained as rosmarinic acid is an important constituent in both herbs, and it was shown in previous studies that it significantly increases pancreatic catalase activity, and improves insulin sensitivity (Sharma et al., 2019).

Some patients experienced hypotension post-surgery and were using HM. The majority were using sage (41.1%), and mint (35.2%), followed by rosemary (23.5%). These finding agree with a recent study that showed that the use of sage in the Valencia region of Spain as a hypotensive agent was previously recorded in their folk medicine (Sharma et al., 2019). It was also found that ursolic acid (bioactive compound of rosemary) which is a pentacyclic triterpenoid carboxylic acid has an antioxidant, anti-inflammatory, anti-tumour, anti-atherosclerotic, and anti-hypertensive activities (Hassani et al., 2016). Similarly, an in vivo study conducted on Wistar rats (under anaesthesia), revealed that these animals suffered from hypotension and bradycardia after consuming hairy mint (Mentha X Villosa) (Silva, 2020).

As expected, in this study, the average INR test values for patients using Phyph were significantly higher than those who did not use these products. These data were previously explained in a study which revealed that green tea possessed an antiplatelet effect by inhibiting arachidonic acid metabolism and TXA2 formation to reduce blood clots (Abebe, 2019). Although controversial, fish oil, which was used by some of the patients, may rarely increase the risk of bleeding when combined with warfarin as it was shown to affect platelet aggregation and vitamin-K dependant coagulation factors according to a case report (Buckley et al., 2004). Another case report has revealed that taking warfarin with an omega-3 fatty acid combination following a brain injury can be life-threatening (Gross et al., 2017). Evidence suggests that taking glucosamine with coumarin anticoagulants may increase the INR and bleeding risk (Statement on the Safety of Glucosamine for Patients Receiving Coumarin Anticoagulants | EFSA, 2011). As for garlic, a case study has shown a correlation between the consumption of raw garlic and an increased risk of bleeding (Persaud, 2022). On the other hand, aged garlic extract was shown to be relatively safe for patients who are on warfarin, but close monitoring is necessary (Macan et al., 2006).

Findings also revealed that 9 patients on herbal medicines suffered from bleeding post-surgery. Of these (33%) were using sage and mint, (25%) rosemary and anise, (12.5%) chamomile and ginger, in addition to 1 patient using green tea. These data were explained in a study by (Levy et al., 2017) that revealed that sage may increase the warfarin plasma level by potentially inhibiting CYP2C9, while chamomile contains coumarins which are known for their anticoagulant effect. In a study by (Abebe, 2019) green tea possessed antiplatelet effect by inhibiting arachidonic acid metabolism and thromboxane 2 (TXA2) formation to reduce blood clots. Additionally, ginger constituents were able to inhibit platelet aggregation by inhibition of TXA2 synthesis. Rosemary, on the other hand, has high severity of interaction leading to post-surgical bleeding via an additive antiplatelet effect, which was previously explained in a study by (Levy et al., 2017). Moreover, a study by (Tan & Lee, 2021) has revealed the severity of interaction between herbal/dietary supplement and warfarin, and has shown 3 case reports which indicate that menthol decreases anticoagulant effect by inhibition of CYP2C9. Furthermore, pimpinella anisum has been shown to enhance blood flow effect due to increased smooth muscle relaxation (Hashemnia et al., 2019).

It is evident that increasing community awareness of dietary supplements and herbs-drugs interactions is critical. HM can interact with a variety of allopathic drugs, causing enhanced or decreased pharmacological effects, as well as adverse drug reactions (Maideen & Balasubramaniam, 2018).

Limitations

This study was conducted during the period from February until August, that is in spring and summer seasons. Therefore, herbal beverages that are commonly consumed specifically during winter season were not included. Also, the exact amount of HM use is not reported, and this might have affected the significance of the results. Future research that focuses on adjusting for HM and Phyph effects on the outcome variable should be considered.

There were no baseline measurements available between the study groups. The time lag between measurements prior and post-surgery varied among patients, as these measurements were largely dependent on the clinician request and the hospital protocol. Therefore, adjustment for the study protocol for future research are required to minimize these variables.

In addition, larger population size that would represent different geographic areas of the country, as well as different social and economic levels, are also essential in aim to improve the representativeness and generalizability of findings, if new strategies would be implemented in the country.

In order to upgrade the levels of healthcare services provided for patients, who believe in the advantages of herbal and natural products and supplements, further investigations with specific interventions are needed.

Conclusion

Patients who used HM and were admitted into the hospital for surgical operation under general anaesthesia were found to experience significant abnormal test values for specific clinical observations and laboratory tests, compared to those who didn't use any supplements.

Despite the safety of the most frequently used herbs, which are considered common beverages or food materials, it seems that these may hold a high risk of adverse effects. Therefore, healthcare providers should be aware of the common natural product uses, especially for treating common conditions, and be able to evaluate and discuss its efficiency and safety with their patients using science-based evidence.

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Conflict of Interest

No conflict of interest is associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication.

Reem Issa and Lobna Gharaibeh: conceived and designed the study

Nour Arabiat and Omar AlHalleeq: collected and analysed the data.

Lilian Alnsour: wrote the manuscript

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