



The Safety of Herbal Medicines (Phytovigilance) from Community Pharmacists' Perspective: A Cross-Sectional Study

✉ Merve MEMİŞOĞLU*, ✉ Gizem OTLATICI

Biruni University, Faculty of Pharmacy, Department of Pharmacy Management, Istanbul, Türkiye

ABSTRACT

Objectives: The “safe if natural” perception of herbal products may have several undesirable side effects. It is important to raise awareness in public order to change this perception and ensure safer use of herbal products. The role of pharmacists is to supply herbal medicines safely and to provide accurate information to the patients about herbal products. The aim of this study was to analyze the perspective, knowledge, attitude, and behavior of community pharmacists about phytovigilance.

Materials and Methods: A cross-sectional analysis was performed using community pharmacists (n= 879) using face-to-face surveys between April-June 2019 in Istanbul. For statistical analysis, student's *t*-test and one-way ANOVA were used to compare the mean values of the groups.

Results: It was determined that 58.1% of the pharmacists heard phytovigilance for the first time and 93.5% of them had not reported any safety-related herbal medicine reported so far. Among the reasons for not reporting, well-known adverse reactions were found to be 24.2% and the difficulty of reporting was found to be 21.8%. 84.6% of pharmacists have never received training related to phytovigilance. It was found that pharmacists with a working experience of more than 20 years primarily selected herbal products provided in their pharmacy based on the manufacturing company primarily, whereas others selected based on the efficacy of the products.

Conclusion: The results of this study have revealed the necessity to increase training on the safety of herbal medicines to cover all stakeholders and to give due importance to phytovigilance. The phytovigilance systems established in some countries for public health should be expanded to other countries. There is a need for a more user-friendly reporting system to increase adverse reaction reporting by pharmacists and other healthcare professionals. In the future, plan to perform studies to raise awareness in the public and promote reporting with digital technologies.

Key words: Adverse drug reactions, community pharmacists, herbal medicines, herbal products, phytovigilance, safety of herbal medicines

INTRODUCTION

The use of plants for therapeutic purposes is as ancient as human history. There is a public perception that plants and herbal products in widespread use are safe because of their natural origin and traditional use.¹ On the other hand, studies and regulatory guidelines have shown that this perception is inaccurate.²⁻⁷ Likewise, the lack of adverse reaction reports does not mean that these herbal products have no adverse effects. Some plants may also be poisonous. For example; the ancient Greek philosopher Socrates was sentenced to death with *Conium maculatum L.*, which is a highly toxic plant. Additionally, factors including improper use, high dose, drug interactions, drug addiction, ineffectiveness may also harm

the patient. The most important differences in herbal products compared to conventional drugs are their unknown active metabolites, complex structures, difficulties in standardization and stability, quality of raw material, quality in manufacturing, use of different plants or plant parts, errors in botanical identification, insufficient clinical and ethnopharmacovigilance studies, poor packaging and labeling, lack of regulations, uncontrolled distribution channels, and lack of knowledge.⁸⁻¹⁴ Herbal products contain complex structures. Their qualitative and quantitative composition varies depending on their geographical origin, genotype, which part of the plant is used, time of harvest, storage conditions, extraction and other related process.¹²⁻¹⁴

*Correspondence: mmerve.memisoglu@gmail.com, ORCID-ID: orcid.org/0000-0002-8068-6836

Received: 27.07.2021, Accepted: 25.08.2021

©Turk J Pharm Sci, Published by Galenos Publishing House.

Hepatotoxicity, nephrotoxicity, and carcinogenic effects are particularly remarkable in the toxicity of herbal medicines and herbal supplements.^{12,15-17} Herbal cosmetics can cause undesirable conditions on the skin, such as irritation, phototoxicity, immediate-type of allergy *etc.*¹⁵ However, it is difficult to access data regarding the incidence and causality assessment of adverse effects caused by the herbal products.⁷ One of the main reasons for this is that a phytovigilance system is not available in many countries.

Phytovigilance system established in Italy has drawn attention. Research on the adverse effects of herbal food supplements used in weight control has revealed that safety-related risks are associated with product quality and self-medication. Spontaneous reporting is considered the only way to monitor these products.¹⁶ Similarly, another retrospective analysis on the Italian Phytovigilance System Data examined herbal products used in children and determined that herbal products containing more than two active substances and those that are used along with conventional drugs have potential safety risks in children.¹⁷

In many studies conducted on herbal slimming products sold on the internet, there is adulteration. In a study, in which content analyzes were conducted by nine different herbal slimming products sold over the internet, it was seen that three of them contained sibutramine, three caffeine, three caffeine + temazepam, and the amount of sibutramine in each capsule was over 10 mg. These chemical substances were in high doses. They also contained trace toxic metals.¹⁸

It is seen that the other distribution channels, except the pharmacies, misinform public about the products, especially those that are sold over the internet. The fact that herbal products are easily accessible and that patients are directed to these products with incomplete and incorrect information increases the need for monitoring.¹⁹

Due to the increased safety concerns, many researchers recommend integrating herbal products into the existing pharmacovigilance system and using a single reporting form.²⁰ Similarly, a guideline on the monitoring of herbal medicines in the pharmacovigilance system was published by the World Health Organization (WHO) in 2004.²¹ As emphasized by The International Pharmaceutical Federation, pharmacists need to play an active role in ensuring patient safety.²² Considering that pharmacists provide consultancy and supply herbal products to the patient, the approach of pharmacists to such herbal products needs to be examined. Therefore, this study aims to understand the perspective, knowledge, attitude, and behavior of pharmacists, who are easily accessible as primary healthcare providers, about herbal products.

MATERIALS AND METHODS

Study design and population

A survey was conducted among community pharmacists between April 2019 and June 2019 in Istanbul. Face-to-face surveys were determined based on the number of pharmacies in Istanbul districts randomly. If a pharmacist was not available,

the survey was conducted with the nearest pharmacy to make up a sufficient number in the same district. Each subgroup was weighted according to its representative share of the main population. In this context, the sample size of this study was calculated to be 879 community pharmacists at a 95% +/- 3 confidence level and cross-sectional analysis was performed.

Questionnaire design

The questionnaire was developed based on existing literatures.²³⁻³² The survey consisted of 30 questions and three sections: Pharmacists' socio-demographic and professional characteristics; pharmacists' knowledge and opinions about herbal medicines; pharmacists' behaviors and attitudes toward herbal medicines. The questions of third section consisted of a 5 point Likert-type scale ranging from "strongly disagree" to "strongly agree".

After obtaining ethical approval, a pilot study was conducted on 20 pharmacists, who were excluded from the main study. Thus, the final version of the questionnaire was comprised.

Statistical analysis

Parametric tests were used without the normality test according to the Central Limit Theorem.³³ In statistical analysis, student's *t*-test was used to compare the mean values of two groups. The one-way ANOVA test was used to compare the mean values of more than two groups. The significant difference found with ANOVA was confirmed with Tukey as the *post-hoc* test. Chi-square test statistics were used to evaluate the relationship between categorical variables. The mean and standard deviation, the minimum and maximum values of the variables were used when analyzing the continuous data in the scales; whereas, frequency and percentage values were used when analyzing categorical variables. E-picos New York software and the MedCalc statistics package program were used to evaluate the data. Statistical significance was defined as $p < 0.05$.

RESULTS

The demographic data of the participants are listed in Table 1.

Our findings showed that the distribution of male and female was almost similar to 46.8% and 53.2%, respectively. Many pharmacists obtained bachelor's degree (86.3%). Since the highest rates in the years of practice were more than 21 years (25.1%) and 6-10 years (23.9%), the sample comprised both old and young pharmacists. Their average age was 40.4 ± 11.9 . In terms of the location of pharmacy, most of the pharmacy were on a street (49.1%) and near a hospital (23.3%).

As seen in Table 2, it was determined that most of the pharmacists heard the concept of phytovigilance for the first time (58.1%). Others mostly had familiarity with this concept in undergraduate education (20.8%). The knowledge of the concept of phytovigilance differed by pharmacists' age ($p < 0.001$). Similarly, there was a statistically significant difference between the working experience and the knowledge of the concept of phytovigilance ($p < 0.001$). It has been determined that those who were young and had less working experience

gained information about the safety of herbal medicines during undergraduate education, while others learned phytovigilance from vocational training with the increase in working experience and age. According to these results, we can make an assessment that the importance given to phytovigilance and safety of herbal medicines has been increased over time and the education curriculum has been revised accordingly. However, the higher rate of those unaware of phytovigilance reveals that there is a need for additional training in herbal medicines.

On the other hand, it has been observed that 84.6% of pharmacists have never received training related to phytovigilance (n= 744). It was determined that 54.8% of those, who received training have received it during his/her undergraduate education.

93.5% (n= 822) of the participants have not completed any safety reporting for herbal medicines so far. The answer to the question of "In which case do you report adverse reactions?" was that "if the effect is serious" at a rate of 41.4% (n= 345). This is followed by the answers of "if the effect is unusual"

(32.3%, n= 269), "if the effect is due to a new product" (25.9%, n= 216) and "if the adverse effect is certain" (25.2%, n= 210). However, it is impossible for a pharmacist to understand by himself/herself that the adverse reaction is certain. This can only be decided by the national pharmacovigilance center through the analysis and evaluation of the reports. Achieving the minimum reportability criteria would be sufficient for the pharmacist to make a report.

Regarding the question of "where they should report the adverse effects", the answer of the majority of the pharmacists was Turkish Pharmacovigilance Center (TÜFAM), established within Turkish Medicines and Medical Devices Agency (TİTCK) (47.7%, n= 387).

However, it was observed that more than half of the participants did not know exactly how to obtain the suspected adverse drug reaction (ADR) reporting form (52.4% no, 14.6% partially).

A significant difference was observed between the working experience of the pharmacist and the knowledge of how to obtain the reporting form ($p < 0.006$). According to the results, pharmacists with a working experience of 15 years or more did not know how to obtain the reporting form.

Regarding the barriers to reporting, pharmacists stated primarily as the well-known adverse reaction at a rate of 24.2% and the difficulty of reporting at a rate of 21.8%. This was followed by "Do not know reporting rules" (16.1%), "ADR forms not easily available" (12.7%), "Not enough information for reporting" (10.6%), "The patient's privacy" (5.1%), "Unsure if it is an ADR" (4.7%), "Time constraints" (2.7%), "The doctors' responsibility" (0.8%), "Fear of making mistakes" (0.7%), and "Not receiving feedback after reporting" (0.6%). These results again emphasize insufficient knowledge and the difficulty of the process (Figure 1).

When the pharmacists were asked to give an example of herbal medicine with potential adverse effects, 43.6% of them did not know any example, whereas 7.4% answered as digoxin and 6.6% answered as *Ginkgo biloba*.

A significant difference was determined between age and priorities in herbal product selection ($p < 0.05$). Patient/consumer preference and price promotions were the primary reasons for product selection for young pharmacists, while the manufacturing company and efficacy of herbal product became a priority in selection of herbal products as the age increases.

Table 1. Socio-demographic characteristics of the pharmacists

Socio-demographics	The mean \pm SD	Min - max
Age	40.4 \pm 11.9	23-82
	Frequency (n)	%
Gender		
Male	411	46.8
Female	468	53.2
Educational level		
Bachelor	753	86.3
Master	105	12
Doctorate	15	1.7
Working experience		
1-5 years	190	21.7
6-10 years	209	23.9
11-15 years	142	16.2
16-20 years	115	13.1
21+ years	220	25.1
Location of community pharmacy		
Neighborhood pharmacy	116	13.2
Pharmacy on a street	432	49.1
Pharmacy near the hospital	205	23.3
Pharmacy near a family health center	123	14
Pharmacy in a mall	3	0.3

SD: Standard deviation, Min: Minimum, max: Maximum

Table 2. Correlation between pharmacists' age and the familiarity with the concept of phytovigilance

	n	%	Mean \pm SD	p
Now, I learned in this survey	504	58.1	39.925 \pm 12.08	
During undergraduate education	180	20.8	37.139 \pm 9.48	
In continuous education programs	114	13.1	45.018 \pm 11.67	
At the congresses	10	1.2	42.1 \pm 15.358	< 0.001
In scientific articles	44	5.1	44.886 \pm 14.728	
From manufacturers	12	1.4	40.167 \pm 11.907	
Other	3	0.3	44.667 \pm 18.009	

SD: Standard deviation

Table 3. Correlation between pharmacists' years of practice and the priority of pharmacists in herbal product selection

Working experience (years)	1-5 n (%)	6-10 n (%)	11-15 n (%)	16-20 n (%)	20< n (%)	p
Product quality	49 (26.9)	70 (34)	47 (33.8)	30 (26.8)	47 (22.5)	
Manufacturing company	53 (29.1)	50 (24.3)	38 (27.3)	37 (33)	80 (38.3)	
Efficacy of the product	54 (29.7)	72 (35)	48 (34.5)	42 (37.5)	73 (34.9)	<0.002
Prices and promotions	15 (8.2)	9 (4.4)	6 (4.3)	2 (1.8)	6 (2.9)	
Patient/consumer preferences	11 (6)	4 (1.9)	-	1 (0.9)	3 (1.4)	

Similarly, a significant difference was also determined by working experience ($p < 0.002$). It was found that pharmacists with a working experience of more than 20 years primarily selected herbal products provided in their pharmacy based on the manufacturing company primarily, whereas others selected herbal products based on efficacy of herbal product (Table 3).

To the question of "Why the safety of herbal medicines is important", 23% of the pharmacists responded as unknown adverse reactions ($n = 202$), 17% as the complex structure of plants ($n = 149$), 10.5% as poor knowledge ($n = 92$) and 10.1% as insufficient clinical trials ($n = 89$) (Table 4).

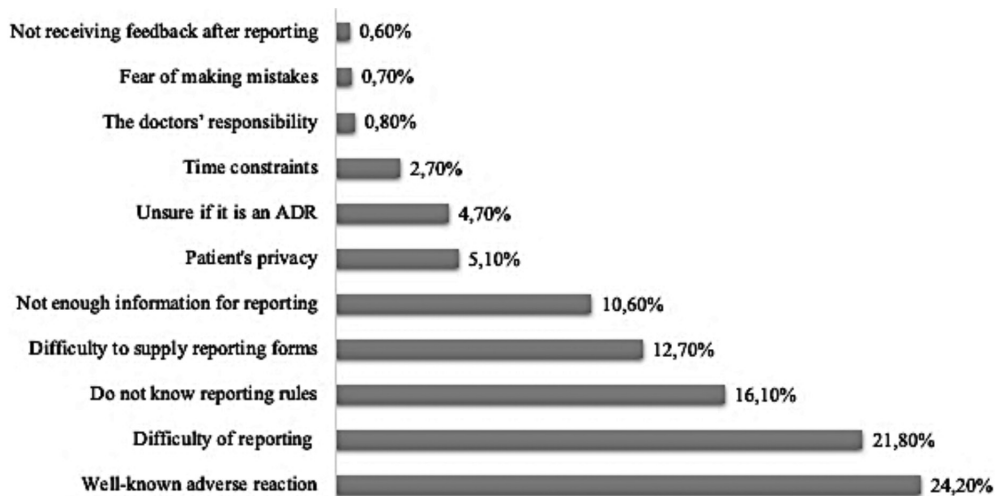
Table 4. Importance of the safety of herbal medicines

	n	%
The complex structure of the plants	149	17
Difficult standardization	74	8.4
Poor impurity	67	7.6
Unknown adverse reactions	202	23
Insufficient clinical trials	89	10.1
Low production quality	55	6.3
Adulteration/counterfeiting	81	9.2
Different distribution channels	70	8
Poor knowledge	92	10.5

A significant difference was determined between the importance of the safety of herbal medicines and the working experience of pharmacists ($p < 0.05$). It has been observed that pharmacists with more than 25 years of working experience considered the unknown adverse reactions, whereas pharmacists who have less than 5 years of working experience remarkably considered difficult standardization of herbal products as important. This result could be related to the revised education curriculum over time (Table 5).

It is a remarkable result that 37.1% of the participants agreed to the statement that "I do not sell herbal products in my pharmacy". There was a significant difference between this statement and the location of the pharmacy ($p < 0.001$). While neighborhood pharmacies strongly disagreed, hospital pharmacies agreed with this statement. We can assume that hospital pharmacies do not supply herbal medicines because they mostly provide prescription drugs and their patient profiles are different as compared to neighborhood pharmacies. Similarly, there was a statistically significant difference between this statement and the knowledge of the concept of phytovigilance ($p < 0.001$).

Another remarkable result was that 47.4% of pharmacists agreed to the statement that "Herbal medicines have fewer side effects than synthetic drugs because they are natural", which is also a common understanding by public. Similarly, there was a significant difference between pharmacy location and this statement ($p < 0.009$). It is observed that neighborhood pharmacies strongly agreed with this statement and were

**Figure 1. Barriers to the reporting of adverse reactions**

more confident in herbal medicines compared with synthetic drugs.

Many pharmacists (74.8%) agreed that herbal medicines should only be sold in pharmacies. These results show that there may be pharmacists who supply herbal medicines only if they are sold only in pharmacies. Similarly, a significant difference was found with gender ($p < 0.006$). It was determined that women were undecided, while male participants agreed with this statement. These data could be related to women's need for more detailed information.

Whereas 78.7% of pharmacists agreed to the statement that "Herbal medicines are used to maintain health and prevent diseases", more than two-thirds of pharmacists agreed to the statement that "Herbal medicines are used to treat diseases". There was a significant difference between gender and the statement that "Herbal medicines are used to treat diseases" ($p < 0.004$). Accordingly, it was observed that male participants disagreed with this statement, while the female participants agreed.

71.4% of participants agreed that the therapeutic ineffectiveness of herbal medicines should be reported. 41.2% of pharmacists agreed to the statement that "Herbal medicines have adverse effects limited to hepatotoxicity and nephrotoxicity". In Türkiye, pharmacists can report only hepatotoxicity and nephrotoxicity-related adverse reactions to herbal medicines.

"The stability and expiration date should be questioned for herbal medicines" (75.5%) and "I inform my patients about the points that should be considered in the use of herbal medicines" (73.4%) statements were largely confirmed by community pharmacists.

A significant difference was found between gender and the statement that "I inform my patients about the points to be considered in the use of herbal medicines" ($p < 0.03$). Male participants disagreed with this statement, while the female ones agreed. According to these results, it can be concluded that male participants give more importance to synthetic drugs than herbal medicines.

The pharmacists also stated that they can participate in awareness-raising campaigns for the safe use of herbal medicines as resolution advisory (58.1%). This result shows that pharmacists are eager to participate in such studies.

To encourage adverse reaction reporting, establishing phytovigilance contact points in hospitals was suggested at a rate of 20.9%, increasing informative campaigns at a rate of 18.6% and organizing more training for pharmacists at a rate of 17.9%. This was followed by increasing the priority of phytovigilance by the Ministry of Health (TİTCK, TÜFAM) (17.7%), increasing the role of pharmacists in improved phytovigilance system (16.1%), and the development of mobile applications that facilitate reporting (8.8%) (Figure 2).

DISCUSSION

Interest in herbal products has increased worldwide. The availability of herbal products from various sources raises safety problems.^{8-14,18-19} At this point, there is a greater need for pharmacies and pharmacist counseling. In our study, it is found that pharmacists are eager to participate in informative activities, although they have a lack of knowledge and education.

Table 5. Distribution of the participants according to the Likert scale scores

	Strongly disagree, n (%)	Disagree n (%)	Neither agree nor disagree n (%)	Agree n (%)	Strongly agree n (%)
It is almost impossible to determine whether herbal medicine is responsible for a particular adverse reaction	34 (3.9)	158 (18)	320 (36.4)	290 (33)	77 (8.8)
I do not sell herbal products in my pharmacy	185 (21)	187 (21.3)	181 (20.6)	276 (31.4)	50 (5.7)
Herbal medicines are used to maintain health and prevent diseases	11 (1.3)	46 (5.2)	130 (14.8)	458 (52.1)	234 (26.6)
Herbal medicines are used to treat diseases	21 (2.4)	69 (7.9)	185 (21.1)	457 (52.2)	144 (16.4)
If the herbal medicine is ineffective, I report	12 (1.4)	44 (5)	195 (22.2)	461 (52.4)	167 (19)
Herbal medicines have fewer side effects than synthetic drugs because they are natural	100 (11.4)	174 (19.8)	188 (21.4)	320 (36.4)	97 (11)
The stability and expiration date should be questioned for herbal medicines	14 (1.6)	49 (5.6)	152 (17.3)	401 (45.6)	263 (29.9)
Herbal medicines have adverse effects limited to hepatotoxicity and nephrotoxicity	102 (11.6)	166 (18.9)	249 (28.3)	260 (29.6)	102 (11.6)
Herbal products should be sold only in pharmacies	12 (1.4)	40 (4.6)	169 (19.2)	352 (40)	306 (34.8)
I want to participate in awareness-raising campaigns for the safe use of herbal medicines	29 (3.3)	75 (8.5)	264 (30)	403 (45.8)	108 (12.3)
I inform my patients about the points that should be considered in the use of herbal medicines	13 (1.5)	59 (6.7)	162 (18.4)	428 (48.7)	217 (24.7)

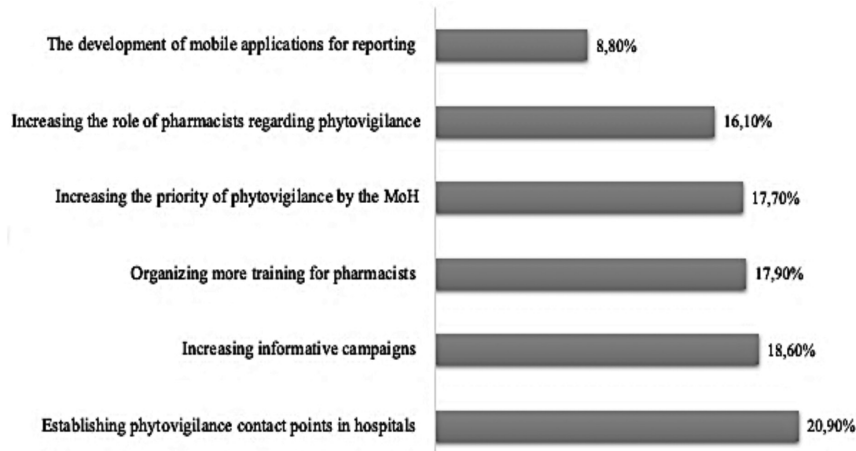


Figure 2. Suggestions for encouraging adverse reaction reporting

It was found that 58.1% pharmacists never heard of phytovigilance in our study. In contrary, in a study by Pellegrino et al.³⁴, it was found that 90% family pediatricians, who are other healthcare professionals, were able to answer correctly on the definition of phytovigilance in Italy.

Whereas in our study 13.1% of pharmacists stated that they learned the term of phytovigilance during continuous education programs and 42.3% of pharmacists sold herbal medicines, Chang et al.³⁵ showed that 45.1% of the participants had previous continuing education on herbal medications, and 73.6% sold herbal medicines.

In this study, it was found that more than half of the participants did not know exactly how to obtain the suspected ADR reporting form for herbal drugs (52.4% no, 14.6% partially). Similarly, Toklu and Uysal³⁶ showed that 87.6% of pharmacists admitted that they do not know how and where to obtain ADR reporting forms for medications in Türkiye.

When comparing the literature covering plants with adverse reactions, the most reported plants in VigiSearch are *Hypericum perforatum*, *Citrus x paradisi*, *Ginkgo biloba*, *Cannabis sativa*, and *Digitalis purpurea*.²⁰ The use of these herbal products without professional advice from a pharmacist or a physician increases the risk.²⁰ Similarly, *Ginkgo biloba* with its potential adverse effects was also stated by pharmacists, who participated in our study.

On the other hand, it has been determined that some pharmacists (37.1%) have negative perceptions of herbal products. It is thought that those perceptions will be changed in time by using improving the quality, efficacy and safety of herbal products and increasing related training of pharmacists.

Similar to the pharmacovigilance system, harmonization of the phytovigilance system is critical among countries. Manufacturers, healthcare professionals, and patients should be informed by providing the necessary training. At this point, pharmacists may provide guidance to the public. As recommended by WHO, it will be crucial to integrate phytovigilance into the pharmacy education curriculum and

Good Pharmacy Practices (GPP).³ The results of our study support this recommendation.

CONCLUSION

The phytovigilance systems established in some countries should be expanded to others. There is a need for a more user-friendly reporting system to increase adverse reaction reporting by pharmacists and other healthcare professionals.

It should be taken into account that pharmacy is a health center and a business center and pharmacists should have sufficient knowledge about the product (P), which is the main component of the marketing mix required for the sustainability of the business. This not only ensures the sustainability of the business but also contributes to public health through the safe use of herbal products. The pharmacist needs to guide the community at this point, however, it will be critical for the pharmacist to update knowledge about the herbal products first and focus on patient health with a holistic approach.

Not to ignore the patient's safety, authorities should establish a phytovigilance system that identifies the possible risks and monitors adverse reactions of herbal products.

Ethics

Ethics Committee Approval: Ethical approval was provided by Biruni University Ethical Committee (CSS ref: 2019-27-43).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.M., G.O., Design: M.M., G.O., Data Collection or Processing: M.M., G.O., Analysis or Interpretation: M.M., G.O., Literature Search: M.M., G.O., Writing: M.M., G.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

- Verma A, Sharma A, Garg K. Herbal medicine and pharmacovigilance: a future prospective. *Int J Pharm Life Sci.* 2014;5:3413-3417.
- Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Braz J Med Biol Res.* 2000;33:179-189.
- World Health Organization. Pharmacovigilance for traditional medicine products: why and how?. 2018; (<https://apps.who.int/iris/handle/10665/259854>).
- Toklu HZ. Pharmacovigilance of herbal medicine: herbavigilance. *Adv Pharmacoepidemiol Drug Saf.* 2016;5:1000208.
- Shaw D. Toxicological risks of Chinese herbs. *Planta Med.* 2010;76:2012-2018.
- Shaw D, Graeme L, Pierre D, Elizabeth W, Kelvin C. Pharmacovigilance of herbal medicine. *J Ethnopharmacol.* 2012;140:513-518.
- Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther.* 2013;37:3-17.
- Moreira DDL, Teixeira SS, Monteiro MHD, De-Oliveira ACA, Paumgarten FJ. Traditional use and safety of herbal medicines. *Rev Bras Farmacogn.* 2014;24:248-257.
- Rodrigues E, Barnes J. Pharmacovigilance of herbal medicines: the potential contributions of ethnobotanical and ethnopharmacological studies. *Drug Saf.* 2013;36:1-12.
- De Smet PA. Health risks of herbal remedies. *Drug Saf.* 1995;13:81-93.
- Nortier JL, Vanherweghem JL. For patients taking herbal therapy-lessons from aristolochic acid nephropathy. *Nephrol Dial Transplant.* 2007;22:1512-1517.
- Perharic L, Shaw D, Leon C, De Smet PA, Murray VS. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. *Vet Hum Toxicol.* 1995;37:562-566.
- Dhami N, Mishra AD. Phytochemical variation: how to resolve the quality controversies of herbal medicinal products? *J Herb Med.* 2015;5:118-127.
- Singh R, Kotecha M. A review on the standardization of herbal medicines. *Int J Pharm Sci Res.* 2016;7:97-106.
- Antignac E, Nohynek GJ, Re T, Clouzeau J, Toutain H. Safety of botanical ingredients in personal care products/cosmetics. *Food Chem Toxicol.* 2011;49:324-341.
- Mazzanti G, Vitalone A, Da Cas R, Menniti-Ippolito F. Suspected adverse reactions associated with herbal products used for weight loss: spontaneous reports from the Italian Phytovigilance system. *Eur J Clin Pharmacol.* 2019;75:1599-1615.
- Lombardi N, Crescioli G, Bettiol A, Menniti-Ippolito F, Maggini V, Gallo E, Mugelli A, Vannacci A, Firenzuoli F. Safety of complementary and alternative medicine in children: a 16-years retrospective analysis of the Italian Phytovigilance system database. *Phytomedicine.* 2019;61:152856.
- Ozdemir B, Sahin I, Kapucu H, Celbis O, Karakoc Y, Erdogan S, Onal Y. How safe is the use of herbal weight-loss products sold over the internet? *Hum Exp Toxicol.* 2013;32:101-106.
- Maggini V, Gallo E, Vannacci A, Gori L, Mugelli A, Firenzuoli F. e-Phytovigilance for misleading herbal information. *Trends Pharmacol Sci.* 2013;34:594-595.
- Skalli S, Soulaymani Bencheikh R. Safety monitoring of herb-drug interactions: a component of pharmacovigilance. *Drug Saf.* 2012;35:785-791.
- World Health Organization. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems, 2004; (<https://apps.who.int/iris/handle/10665/43034>).
- Bader L, Kusynová Z, Duggan C. FIP perspectives: realising global patient safety goals requires an integrated approach with pharmacy at the core. *Res Social Adm Pharm.* 2019;15:815-817.
- Hajj A, Hallit S, Ramia E, Salameh P; Order of Pharmacists Scientific Committee - Medication Safety Subcommittee. Medication safety knowledge, attitudes and practices among community pharmacists in Lebanon. *Curr Med Res Opin.* 2018;34:149-156.
- Al-Worafi YM, Kassab YW, Alseragi WM, Almutairi MS, Ahmed A, Ming LC, Alkhoshaiban AS, Hadi MA. Pharmacovigilance and adverse drug reaction reporting: a perspective of community pharmacists and pharmacy technicians in Sana'a, Yemen. *Ther Clin Risk Manag.* 2017;13:1175-1181.
- Alraie NA, Saad AA, Sabry NA, Farid SF. Adverse drug reactions reporting: a questionnaire-based study on Egyptian pharmacists' attitudes following an awareness workshop. *J Eval Clin Pract.* 2016;22:349-355.
- Green CF, Mottram DR, Rowe PH, Pirmohamed M. Attitudes and knowledge of hospital pharmacists to adverse drug reaction reporting. *Br J Clin Pharmacol.* 2001;51:81-86.
- Belton KJ. Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union. The European Pharmacovigilance Research Group. *Eur J Clin Pharmacol.* 1997;52:423-427.
- Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BH. Attitudinal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharmacol.* 1999;48:623-627.
- Vessal G, Mardani Z, Mollai M. Knowledge, attitudes, and perceptions of pharmacists to adverse drug reaction reporting in Iran. *Pharm World Sci.* 2009;31:183-187.
- Granas AG, Buajordet M, Stenberg-Nilsen H, Harg P, Horn AM. Pharmacists' attitudes towards the reporting of suspected adverse drug reactions in Norway. *Pharmacoepidemiol Drug Saf.* 2007;16:429-434.
- Herdeiro MT, Figueiras A, Polónia J, Gestal-Otero JJ. Influence of pharmacists' attitudes on adverse drug reaction reporting : a case-control study in Portugal. *Drug Saf.* 2006;29:331-340.
- Rogers AS, Israel E, Smith CR, Levine D, McBean AM, Valente C, Faich G. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Arch Intern Med.* 1988;148:1596-1600.
- Norman G. Likert scales, levels of measurement and the "laws" of statistics. *Adv Health Sci Educ Theory Pract.* 2010;15:625-632.
- Pellegrino P, Carnovale C, Cattaneo D, Perrone V, Antoniazzi S, Pozzi M, Napoleone E, Filograna MR, Clementi E, Radice S. Pharmacovigilance knowledge in family paediatricians. A survey study in Italy. *Health Policy.* 2013;113:216-220.
- Chang ZG, Kennedy DT, Holdford DA, Small RE. Pharmacists' knowledge and attitudes toward herbal medicine. 2000. *Ann Pharmacother.* 2007;41:1272-1276.
- Toklu HZ, Uysal MK. The knowledge and attitude of the Turkish community pharmacists toward pharmacovigilance in the Kadikoy district of Istanbul. *Pharm World Sci.* 2008;30:556-562.