Clinical Outcome of Herbal Medicine-related Problems for Respiratory Viral Infections

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ABSTRACT

Background: The use of herbal medicine to treat dissimilar respiratory conditions has been assumed for many decades. This survey analysis explores the clinical outcomes of herbal medicine-related problems for respiratory viral infections in Saudi Arabia. **Design and Setting:** A self-administered, structured questionnaire was sent to the public online, counting questions on the responders' demographics and questions gaging different clinical outcomes of herbal medicine-related problems when treating respiratory viral infections in Saudi Arabia. Data analysis was performed through SPSS program version 26. **Results:** 486 participants responded to this questionnaire. 89.92% of the responders were from the west area in Saudi Arabia, 56.49% were in the age group between 18 and 30 years old. 18.32% were healthcare practitioners, while 53.85% of these practitioners were physicians. 18.74% of the responders applied herbal medications three times daily for respiratory viral infections. Only 4.31% of the responders established having side effects during the past year from herbal medications, while 3.58% visited a pharmacy for these side effects. Their healthcare professionals asked 20.04% about the use of herbal medications. Factors increasing the occurrence of adverse events were: that residents of the western region (p value=0.002), age group between 18 and 30 (p-value=0.046), females (p-value<0.001), low monthly income (p-value=0.013) and non-healthcare professionals (p-value=0.001). **Conclusion:** Although the occurrence of herbal medication-related problems is not common in Saudi Arabia, it can need medical assistance. Awareness of the public of the herbal medications adverse events is decisive.

Key words: Clinical, Outcome, Herbal Medicine, Problems, Viral Infections Saudi Arabia.

INTRODUCTION

Patient safety is flattering an essential part of medical practice.[1] Guaranteeing that medications are safe and operative and is vital for the current approval of any new medications.[2] This is also used for herbal medicines that are totally or partially of herbal origin.[3] Consequently, pharmaceutical companies are now mandatory to mention the incidence of every adverse event.[4] Although there is an inherited belief that herbal medications are safe, many herbal medicines have been conveyed for adverse events and withdrawn from the market during the past few years.[5]

The major drug-related problems are usually related to wrong doses, wrong route, wrong method of administration, incorrect indication, allergy, or occurrence of adverse effects.[6] However, recently a new pharmaceutical discipline has been familiarised, which is pharmacovigilance.[7] This new field permits better tracking for drug-related problems, not only of chemical origin but also of herbal origin, thus allowing better management for these problems.[8]

Despite all these strategies for classifying and solving drug-related problems, public and even healthcare professionals' awareness about reporting adverse events for medications, especially herbal ones, is mediocre.[9] Accordingly,

the clinical outcomes of these problems remain unidentified and undervalued.[10] Hence, evaluating clinical outcomes of common herbal medication-related problems should come first through patients themselves.[11]

The problem of herbal medication-related problems is even more convoluted. It is attributed to the more common use of herbal medications and their availability as over-the-counter medications, expressly in the gulf area.[12] Consequently, the reporting and identification of these problems is nearly absent and entails exploration. Accordingly, the existing study inspects the clinical outcomes of herbal medicine-related issues to treat viral respiratory infections in Saudi Arabia.

MATERIALS AND METHODS

Study Design

This quantitative cross-sectional survey study was carried out in Saudi Arabia through a self-administered electronic questionnaire for two months. All Saudi Arabia citizens were comprised. The survey was interview-based at shopping malls, parks, hospitals and mosques online.

Data Collection

An online interview-based questionnaire was dispersed to members of the public in different regions in Saudi Arabia. The first part of the survey encompassed the demographics of the included participants. While the second part comprised information about the duration of using herbal medications over the last 12 months and any side effects due to herbal medication use over the previous 12 months. Besides, suppose a physician or pharmacist asks you about your herbal medicines before starting the treatment and any side effects or problems using herbal medications. In that case, that leads to any visits to the pharmacy or clinic, hospital admission general wards, or critical care services. A 5-point Likert response scale system was applied. The survey had been disseminated to a convenient sample of public responders. It was through social media of WhatsApp and telegram, and personal contact. The prompt message is sent every 1-2 weeks. The completed survey and Saudi public will be encompassed in the final analysis.

Statistical Analyses

According to the earlier literature with unlimited population size, the sample was calculated, the population percentage of 50%, the confidence level 95%, with a z score of 1.96 and margin of error 5%, and drop-out rate 10%. As a result, the sample size calculated as a minimum sample of 418 with the power of study of 80%.[13-15] The response rate mandatory of calculated sample size at least 60-70 % and above.[15,16] The survey was authenticated through the revision of expert reviewers and pilot testing. Moreover, the reliability tests McDonald's ω, Cronbach's α, Guttmann's 2, and Guttmann's. The data analysis was finalized through the survey monkey system. In addition, the statistical package of social sciences (SPSS), Jeffery's Amazing Statistics Program (JASP), and Microsoft excel sheet version 16 with description and frequency analysis, good fitness analysis, correlation analysis, inferential analysis between independent variables responders. The STROBE (Strengthening the reporting of observational studies in epidemiology statement: guidelines for reporting observational studies) directed the existing study's reporting.[17,18]

RESULTS

Four hundred and eighty-six responders contributed in this online questionnaire. Only participants who finished all the sections in the questionnaire were comprised. Therefore, the reliability test of Mac, Cronbach, Guttmann 2, and Guttmann 6 cannot be used because all data and variables were nominal data. Socio-demographics of responders and analysis of the questionnaire are shown below.

General Characters of Responders

Out of 486 participants, 89.92% of the responders were from the west area with statistically significant differences with other regions ($p<0.001$), and 94.62% had a Saudi nationality. Also, 80.45% were females with statistically momentous differences from males ($p<0.001$), where 59.17% were single. As for the age of the responders, it was considered into seven sub-categories. The most prevalent age group was between 18 and 30 years old, with 56.49% of the responses with statistically significant differences between age groups ($p<0.001$). All socio-demographic data is exposed in detail in Table 1.

Social and Professional Information of the Responders

Regarding the responders' education level, 66.1% had a bachelor's degree, while 46.27% were still students, and only 23.44% were employees, with statistically significant differences among them ($p<0.001$). Monthly income was also assessed; it has been shown that 53.69% had an income <3000 SR with statistically significant differences with other responder's incomes ($p<0.001$). Participants

Table 1: Shows the socio-demographic data of responders to the questionnaire.

Nationality	Response Count	Response Percent	*p*-value
Central area	11	2.26%	<0.001
North area	6	1.23%	
South area	20	4.12%	
East area	12	2.47%	
West area	437	89.92%	
Answered question	486		
Skipped question	0		
Nationality	**Response Count**	**Response Percent**	
Saudi	457	94.62%	<0.001
Non-Saudi	26	5.38%	
Answered question	483		
Skipped question	3		
Gender	**Response Count**	**Response Percent**	
Female	391	80.45%	<0.001
Male	95	19.55%	
Answered question	486		
Skipped question	0		
Material Status	**Response Count**	**Response Percent**	
Single	284	59.17%	<0.001
Married	187	38.96%	
Divorced	9	1.88%	
Answered question	480		
Skipped question	6		
Age	**Response Count**	**Response Percent**	
<18	32	6.60%	<0.001
18 - 30	274	56.49%	
31 - 40	81	16.70%	
41 - 50	58	11.96%	
51 - 60	22	4.54%	
61 - 70	15	3.09%	
> 70	3	0.62%	
Answered question	485		
Skipped question	1		

were also requested if they were working in the medical field. Only 18.32% were healthcare practitioners, while 53.85% of these practitioners were physicians with statistically substantial differences with other specialties (*p*<0.001), as shown in Table 2.

Use of Herbal Medications over the Last 12 Months

Responders were requested about their use of herbal medicines during the preceding 12 months for respiratory viral infections. 18.74% of the responders used them three times daily, while 41.89% have never applied herbal medications for this purpose, and 2.53% of the responders used them for one month. Additionally, 36.82% used herbal medicines solely, while 29.22% used them with other regularly approved medications with statistically significant differences between them (*p*<0.001).

Participants were also enquired about the incidence of side effects because of herbal medications. Only 4.31% of the responders established having side effects during the past year from herbal medicines, while only 3.58% visited a pharmacy for these side effects. In addition, just below half of the responders (42.57%) educated their healthcare professionals about the use of herbal medications. In comparison, only 20.04% of the responders were asked by their healthcare professionals about herbal medicines, as shown in Table 3.

Furthermore, the responders were inquired about their use of herbal medications for dental management with other medicines. 55.18% of the responders did not apply herbal medication with any other medical conditions. In comparison, 18.77% of the patients used herbal medications concurrently with asthma and respiratory disease medications, as shown in Table 4.

Independent Variable Analysis
Age

There is no statistically noteworthy difference between males and females in different regions, ages, material status, nationality, healthcare provider or public, and healthcare professionals spheres (*p*>0.05). In contrast, the male 12 (63%) is higher than female 3 (0.74%) in age 61 years old and above with statistically significant alteration (*p*<0.05). The male has higher academic qualifications than females master degree 12 (12.77%) vs. 17 (4.24%) or diploma 9 (9.57% vs. 14 (3.49%), while females more had of bachelor's degree 271 (67.58%) vs. 53 (56.38%) with statistically significant difference (*p*<0.05). The males more engaged than female 32 (34.04%) vs. 84 (20.9%), and

Table 2: Social and professional information of responders.			
Responder Qualifications	**Response Count**	**Response Percent**	***p*-value**
Doctorate	10	2.08%	<0.001
Master's degree	28	5.82%	
Bachelor's degree	318	66.11%	
Diploma	21	4.37%	
High school	99	20.58%	
Intermediate School	3	0.62%	
Primary School	1	0.21%	
Not educated	1	0.21%	
Answered question	481		
Skipped question	7		
Occupational status	**Response Count**	**Response Percent**	
Employee	113	23.44%	<0.001
Non-employee	109	22.61%	
Retried	37	7.68%	
Student	223	46.27%	
Answered question	482		
Skipped question	4		
Monthly income	**Response Count**	**Response Percent**	
< 3000 SR	233	53.69%	<0.001
3001-6000 SR	37	8.53%	
6001-9000 SR	38	8.76%	
9001-12000 SR	44	10.14%	
> 12000 SR	82	18.89%	
Answered question	434		
Skipped question	52		
Are you a health care practitioner (Medical Doctor-Dentist- Pharmacist- Nurse-Others?	**Response Count**	**Response Percent**	
Yes	87	18.32%	<0.001
No	388	81.68%	
Answered question	475		
Skipped question	11		
If you are a health care practitioner, you are a	**Response Count**	**Response Percent**	
Physician	49	53.85%	<0.001
Dentist	6	6.59%	
Pharmacist	8	8.79%	
Nurse	28	30.77%	
Other (please specify)	66		
Answered question	91		
Skipped question	395		

more retried 19 (2021%) vs. 18 (4.48%), while more females of non-employed 111 (27.61%) vs. 8 (8.51%) with statistically significant difference (*p*<0.05). The males had a higher monthly income (>12,000 SR) than females, 27 (30%) vs. 56 (15.77%). In contrast, the female had inferior monthly income than males, 200 (56.34%) vs. 37 (41.11%), with a statistically substantial difference (*p*<0.05).

Healthcare Provider's vs. Public

There is no statistically weighty difference between responders healthcare providers and public residents in living regions, gender, nationality and monthly income ($p>0.05$). However, the age of healthcare providers is advanced than the public with (18-30 years) 72 (80.9%) vs. 196 (49.25%). In contrast, the people higher than professionals in ages (41-50 years) with percent 58 (14.57%) vs. 1 (1.12%), and age (51-60) with percent 22 (5.53%) vs. 0 (0%) with statistically noteworthy difference ($p<0.05$). Most healthcare professionals were single 70 (80.46%) vs. public 208 (52.66%), while the majority of public responders were married 180 (45.57%) vs. healthcare professionals 16 (18.39%) with statistically significant difference ($p<0.05$). The healthcare providers had more bachelor's degree 70 (79.55%) than public 248 (62.78%), while the public had a more high school degree 90 (22.78%) than healthcare providers 10 (11.36%) with statistically significant difference ($p<0.05$). The public responders had more non-employment 106 (26.77%) and retired 37 (9.34%) than healthcare providers 12 (13.64%) and 0 (0%) respectively. In contrast, the healthcare providers had more student qualifications 56 (63.64%) than public responders 160 (40.4%), with a statistically momentous difference ($p<0.05$).

Nationality

There is no statistically important difference between Saudi and non-Saudi in the different regions came from, ages group, gender, material status, educational levels, occupational status, monthly income, healthcare provider or public, and healthcare professionals subjects ($p>0.05$)

Independent Variable Correlation

There is a positive suggestion between age and material status and monthly income with spearman outcomes (0.738) and (0.566) respectively, while the Kendal taw was (0.678), (0.499) with statistically significant ($p<0.001$). In contrast, there was a negative overtone between age and occupational status with spearman results (-0.582) and Kendal taw (-0.83) with statistically significant ($p<0.001$). There was a positive association between material status and monthly income of spearman results was 0.518 and Kendal taw (0.476) with statistically significant ($p<0.001$). While there was a negative correlation between material status and occupational level, spearman's results were -0.627 and Kendal taw (-0.580) with statistically noteworthy ($p<0.001$). There is a negative correlation between occupational levels and monthly income with spearman results (-0.578) and Kendal taw (-0.501) with statistically momentous ($p<0.001$).

Table 3: Herbal medicine-related problems.			
How many days have you used herbal medications over the last 12 months for respiratory viral management?	**Response Count**	**Response Percent**	
one day	66	13.89%	<0.001
three-time	89	18.74%	
one week	49	10.32%	
Two weeks	31	6.53%	
one month	12	2.53%	
more than one month	29	6.11%	
never	199	41.89%	
Answered question	**475**		
Skipped question	**11**		
How did use herbal medications for respiratory viral management	**Response Count**	**Response Percent**	
I used alone	155	36.82%	<0.001
I used it with regular medications	123	29.22%	
I used medicine from a physician	111	26.37%	
Other (please specify)	32	7.60%	
Answered question	**421**		
Skipped question	**65**		
Have you suffered from any side effects due to herbal medications use over the last 12 months?			
Have you suffered from any side effects due to herbal medications use over the last 12 months?	**Responses**		
Yes	19	4.31%	<0.001
No	330	74.83%	
uncertain	92	20.86%	
Answered	**441**		
Skipped			
Have you informed your physician about using herbal medications??			
Have you informed your physician about using herbal medications??	**Responses**		
Yes	189	42.57%	<0.001
No	193	43.47%	
uncertain	62	13.96%	
Answered	**444**		
Skipped	**42**		
Have you ever the physician or pharmacist asked you about your herbal medication use before starting the treatment?			
Have you ever the physician or pharmacist asked you about your herbal medication use before starting the treatment?	**Responses**		
Yes	90	20.04%	<0.001
No	262	58.35%	
uncertain	97	21.60%	
Answered	**449**		
Skipped	**37**		
Have you ever had any side effects or problems from using herbal medications that lead to any of the following..?			
Have you ever had any side effects or problems from using herbal medications that lead to any of the following..?	**Responses**		
visit the pharmacy	15	3.58%	
visit the physician office	2	0.48%	
visit the emergency department	8	1.91%	
hospital admission	6	1.43%	

admission to critical care	2	0.48%	
Nothing happened at all	375	89.50%	
Other (please specify)	21	5.01%	
Answered	**419**	3.58%	
Skipped	**67**	0.48%	

Table 4: The herbal medications usage for dental management with other medications.		
Do you use herbal medications for dental management with any of the following medical conditions?		
Answer Choices	**Responses**	
epilepsy and nerve diseases medications	9	2.52%
Asthma and respiratory diseases medications	67	18.77%
cardiac diseases medications	6	1.68%
blood diseases medications	8	2.24%
Anti-diabetes medications	32	8.96%
high/ low blood pressure medications	23	6.44%
digestive tract disease medications	54	15.13%
Antineoplastic medications	4	1.12%
I don't use herbal medications in the presence of any medical conditions	197	55.18%
Other (please specify)	39	10.92%
Answered	**357**	
Skipped	**129**	

DISCUSSION

Drug-related problems are one of the chief worries of using medications. It occupied a very high economic burden on the healthcare system in Saudi Arabia and else wide world. During of use for the treatment of viral infection with importance on COVID-19 is without a problem. However, each medication had a tricky that included adverse events. There is a general insight among the public's known members, counting healthcare professionals, that the use of herbal medications is generally safe.[19] However, it should be illustrious that some herbal medicines can have serious adverse events that may reach death (such as with digitalis) if not used properly or if they interacted with other medications.[20] Accordingly, guessing the Figures of drug-related problems arising from the use of herbal medicines are decisive.

The present search intended to assess the clinical outcomes of herbal medicine-related problems for respiratory viral infections among the Saudi population. The study reconnoitred the majority of responders from the west area, young age with student occupational status, and single with low monthly income because some authors worked as data collectors. They were students at the college of medicine at Um Alora University, located in the west region, and collected sufficiently from their society. The demographic information of the sample study has contained of two parts included public and healthcare professionals. The majority type was public residents, with one-fifth of healthcare providers. Most of the public is older, married, non-employments with low salaries and low academic qualifications.

In contrast, the healthcare providers were young, single, with employments, high academic qualifications. The demographic information was imitated in the entire society. There are no statistically significant differences between public and non-public responders in gender or nationality, monthly income. The responder's demographic data was decent that replicated the actual characters of Saudi populations. Those properly echoed the actual behaviour of usage of herbal medications during viral infection, highlighting coronavirus. There was a medium positive correlation between age, marital status, and high financial income. On the other hand, a negative correlation between occupational status, younger age, and student's positions, while old age linked with higher academic qualifications, counting mater science degree, had a negative connotation. Moreover, there was a negative correlation between income and occupational status, reproducing reliable social practice.

In the contemporary study to examine drug-related might ensued during viral illness management. The study displayed that one-fifth of them used herbal medicine to treat viral infection daily with high frequency, while low perception was applied for a long time. During those periods, the patients will agonise from adverse effects from high dose or long term used.

Herbal medication-related problems have been deliberated in different settings in the medical literature. For example, Lüde *et al*.[21] inspected the adverse events testified from a poisons center from herbal supplements and other herbal agents used as food. Lüde *et al*.[21] comprised 75 patients admitted to ten European and Brazilian poison centres. 76% of the patients had adverse events from using herbal supplements with liquorice and mint on the top 10 list of herbal agents. Although most of the cases conveyed by Lüde *et al*.[21] were mild, five patients were in severe condition.

In compliance with the findings of Lüde *et al*.[21] the current study exposed that the occurrence of adverse drug problems from herbal agents for respiratory viral infections is generally stumpy (not more than 5%), with mild concerns. However, it should be distinguished that some serious adverse events or mortalities might be under-reported. Also, only one-fifth of the encompassed responders were asked by their clinicians about herbal agents' use, underlining a negative attitude from healthcare professionals.

The one-third percentage applied herbal medications alone or with regular medicines. The drug-related problems might happen during viral infection treatment; it was an herbal drug interaction problem. Most of our responders used herbal medicines for asthma or respiratory infection or GIT problem, or anti-diabetic medications that the herbal might interrelate with their regular medication. A systematic review by Posadzki *et al*.[22] appraised the drug interactions by herbal agents. Posadzki *et al*.[22] disclosed that serious interactions or consequences do not attend most herbal agents. However, the strength of the comprised studies was low. Although these findings obey with the present study, further inquiries are still mandatory.

Another systematic review by Lzzo *et al*.[23] scrutinised the adverse events and drug-related problems ascending from herbal medications. Lzzo *et al*.[23] involved different herbal agents to treat the common cold, premenstrual complaints, hypertension, and nausea during pregnancy, menopause, and hyperglycaemia. Lzzo *et al*.[23] established that despite a better tolerance for herbal medications compared to medications of chemical origin, the frequency of serious adverse events or drug interactions should be measured. These recommendations by Lzzo *et al*.[23] upkeep the present examination. Although less than

5% of the comprised participants had adverse events from herbal medications, it is unknown if any encompassed subjects were from a sole population with a higher risk of adverse events, such as cancer or pregnant patients.

The responders specified that some herbal-related problems ensued to them and progress of numerous percentages of emergency visits or hospital admissions or critical care admission according to the severity of ADR. Those drug-related problems that followed might be related to herbal medications history were not recognized because almost half of the responders did not notify the treating physicians about their usage of herbal medications. Sometimes, the healthcare provider enquired the patients about their history of herbal medication usage. All drugs applied for viral infection with importance on COVID-19 had drug-related problems, counting herbal medications. All drug-related problems of herbal medicines need to close monitoring and treat consequently. A medication reconciliation system should be executed to prevent any herbal medication-related problems during viral illness management in future.

Additionally, the existing study had some confines; the participants' responses depend largely on the responders' subjective opinion towards the adverse events that happened to them after using herbal medications, which could disturb the reliability of the outcomes. Nevertheless, it is measured the first study in Saudi Arabia to assess herbal medications' clinical outcomes related to respiratory viral infections.

CONCLUSION

Herbal drug-related problems are usually significant in Saudi Arabia, with frequently lead pharmacy visits or emergency and hospital admission. However, the public's awareness and healthcare professionals towards the adverse effects of herbal medications should be upgraded. It can be accomplished through national campaigns by pharmaceutical companies and healthcare organizations. Additionally, further research is obligatory to discover the incidence of adverse events from herbal medications for other indications, which could be more serious than those offered in the contemporary study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Consent for Publications

Informed consent was obtained from all the participants

Ethical Approval

This research is exempted from research and ethical committee or an institutional review board (IRB) approval.

https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts-2018/index.html

ABBREVIATIONS

MOH: Ministry of Health; **KSA:** Kingdom of Saudi Arabia; **Covid-19:** Coronavirus; **SPSS:** Statistical Package of Social Sciences; **JASP:** Jeffery's Amazing Statistics Program; **Strobe:** Strengthening the reporting of observational studies in epidemiology statement: guidelines for reporting observational studies.

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REFERENCES

1. Di Lorenzo C, Ceschi A, Kupferschmidt H, Lüde S, De Souza Nascimento E, Dos Santos A, *et al*. Adverse effects of plant food supplements and botanical preparations: A systematic review with critical evaluation of causality. Br J Clin Pharmacol. 2015;79(4):578-92. doi: 10.1111/bcp.12519, PMID 25251944.

2. Di Minno A, Frigerio B, Spadarella G, Ravani A, Sansaro D, Amato M, *et al*. Old and new oral anticoagulants: food, herbal medicines and drug interactions. Blood Rev. 2017;31(4):193-203. doi: 10.1016/j.blre.2017.02.001, PMID 28196633.

3. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: A systematic review of the world literature. BMC Med. 2016;14(1):10. doi: 10.1186/s12916-016-0553-2, PMID 26843061.

4. Karimi A, Majlesi M, Rafieian-Kopaei M. Herbal versus synthetic drugs; beliefs and facts. J Nephropharmacol. 2015;4(1):27-30. PMID 28197471.

5. Hong M, Li S, Tan HY, Cheung F, Wang N, Huang J, Feng Y. A network-based pharmacology study of the herb-induced liver injury potential of traditional hepatoprotective Chinese herbal medicines. Molecules. 2017;22(4). doi: 10.3390/molecules22040632, PMID 28420096.

6. Sarker A, Gonzalez G. Portable automatic text classification for adverse drug reaction detection via multi-corpus training. J Biomed Inform. 2015;53:196-207. doi: 10.1016/j.jbi.2014.11.002, PMID 25451103.

7. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. Br J Clin Pharmacol. 2015;80(4):796-807. doi: 10.1111/bcp.12596, PMID 25619317.

8. Hong M, Li S, Tan HY, Wang N, Tsao SW, Feng Y. Current status of herbal medicines in chronic liver disease therapy: the biological effects, molecular targets and future prospects. Int J Mol Sci. 2015;16(12):28705-45. doi: 10.3390/ijms161226126, PMID 26633388.

9. Liu Y, Ai N, Keys A, Fan X, Chen M. Network pharmacology for traditional Chinese medicine research: methodologies and applications. Chin Herb Med. 2015;7(1):18-26. doi: 10.1016/S1674-6384(15)60015-6.

10. Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, Timbo BB, *et al*. Emergency department visits for adverse events related to dietary. J Med. 2015;16(373):1531-40 Supplement s N Engl.

11. Nair NP, Chalmers L, Connolly M, Bereznicki BJ, Peterson GM, Curtain C, *et al*. Prediction of hospitalization due to adverse drug reactions in elderly community-dwelling patients (The PADR-EC score). PLOS ONE. 2016;11(10):1-17.

12. Sen S, Chakraborty R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: importance, challenges and future. J Tradit Complement Med. 2017;7(2):234-44. doi: 10.1016/j.jtcme.2016.05.006, PMID 28417092.

13. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121-6. doi: 10.4103/0253-7176.116232, PMID 24049221.

14. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. Gastroenterol Hepatol Bed Bench. 2013;6(1):14-7. PMID 24834239.

15. Ezhumalai DG. How Big A Sample Do I Require?. Annals of SBV. 2017;6(1):39-41. doi: 10.5005/jp-journals-10085-6113.

16. Johnson TP, Wislar JS. Response rates and nonresponse errors in surveys [internet]. JAMA. 2012;307(17):1805-6. doi: 10.1001/jama.2012.3532, PMID 22550194.

17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLOS Med. 2007;4(10):1623-7. doi: 10.1371/journal.pmed.0040296.

18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [internet]. Vol. 370; 2007. Available from: http://www.thelancet.com. Available from: http://www.plosmedicine.org [cited 19/8/2021].

19. Colalto C. What phytotherapy needs: evidence-based guidelines for better clinical practice [internet]. Phytother Res. 2018;32(3):413-25. doi: 10.1002/ptr.5977, PMID 29193357.

20. Andrew R, Izzo AA. Principles of pharmacological research of nutraceuticals. Br J Pharmacol. 2017;174(11):1177-94. doi: 10.1111/bph.13779, PMID 28500635.

21. Lüde S, Vecchio S, Sinno-Tellier S, Dopter A, Mustonen H, Vucinic S, *et al*. Adverse effects of plant food supplements and plants consumed as food: results from the poisons centres-based PlantLIBRA study. Phytother Res. 2016 Jun 1;30(6):988-96. doi: 10.1002/ptr.5604, PMID 26948409.

22. Posadzki P, Watson L, Ernst E. Herb-drug interactions: an overview of systematic reviews. Br J Clin Pharmacol. 2013;75(3):603-18. doi: 10.1111/j.1365-2125.2012.04350.x, PMID 22670731.

23. Izzo AA, Hoon-Kim S, Radhakrishnan R, Williamson EM. A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies [internet]. Phytother Res. 2016;30(5):691-700. doi: 10.1002/ptr.5591, PMID 26887532.