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Evaluation of Herbal Product Use and Preanaesthetic Questioning of Couples Undergoing *In Vitro* Fertilisation

Leyla İyilikçi[1], Sibel Büyükçoban[1], İçten Ezgi İnce[1], Müge Kovalı[2]
[1]Department of Anaesthesiology and Reanimation, Dokuz Eylül University School of Medicine, İzmir, Turkey
[2]IVF Unit, Dokuz Eylül University Hospital, İzmir, Turkey

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Abstract

Objective: This study aimed to determine the levels of herbal product use among couples *in vitro* fertilisation (IVF) treatment in Turkey and the status of questioning in terms of herbal product usage.

Methods: After ethics committee approval, the study included 257 people, which were the couples receiving treatment in Dokuz Eylül University IVF units from 1st August, 2018, to 28th February, 2019. The couples were given 16-questions survey form to determine their herbal product use. Vitamin and herbal product use in the past 3 months was separately questioned.

Results: Significant differences were identified between women and men only in terms of age group. The rate of answering yes to the question about herbal product use in the study group was 13.6%, whereas 40.8% participants marked at least 1 item on the list of herbal products. Most people stated that they used herbal products by increasing the amounts in daily consumption. The top 5 products included onion, garlic, thyme, cinnamon and carob. Of the female patients being treated with IVF, 62.5% used vitamin supplements and 48.6% used herbal products. Of the men undergoing the same treatment (partners of the female participants), 37.5% used vitamin supplements and 51.4% used herbal products.

Conclusion: Asking questions to patients receiving infertility treatment or anaesthesia is important in terms of medication interactions and treatment success. For a laborious and costly treatment, such as IVF, detailed history should be taken and herbal product used and cessation times must be searched in detail.

Keywords: *In vitro* fertilisation, preanaesthetic preparation, herbal products, vitamin supplements

Introduction

The current interest in complementary medicine and treatment with herbal medications is increasing. Plants are commonly used in many countries in the world as folk medications, food supplements and herbal medications. The mistaken belief among patients that these products are all natural and safe has caused an increase in their consumption. In addition, other factors for their popularity and widespread use are the marketing of herbal products through media and access through the Internet. In the United States of America (USA), it was stated that annually 3.5 million dollars are spent on herbal products (1). The American Society of Anesthesiologists reported that nearly 15 million people in the USA use herbal products (1).

The number of cases with organ transplants as a result of renal and liver failure linked to herbal products is increasing (2). A study in Nigeria has reported that 9% of patients using herbal products had different varieties of reaction from these products, and 2% of patients experienced complications owing to interaction of these products when used with prescription medications (3). The probability of morbidity and mortality related to the use of herbal products is greater in the perioperative period (2, 4). These medications are implicated in causing coagulopathy and organ dysfunction in the perioperative period (5).

Corresponding Author: İçten Ezgi İnce E-mail: icten_ezgi@hotmail.com

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In recent years, herbal treatment methods and centres related to these treatments have gained attention in our country. A study in Turkey has identified that 40% of patients attending family medical practitioners used herbal medications for treatment (6), whereas another study has identified that 58.5% of individuals with a chronic disease attended an internal medicine clinic (7). A study by İyilikci et al. (8) in 2006 has questioned herbal product use before elective surgery and reported 50.9% of 997 patients used herbal products before surgery. Another study of patients staying in surgical wards has identified that 25% of patients used herbal products (9).

Herbal products are very widely used for infertility treatment (10). In the USA, a study of couples attending infertility treatment has reported that 17% of the couples used herbal products (10). Another study in Australia has found that herbal product use in the field of infertility treatment was stated to be 29%, with the most commonly used products defined as green tea, mint, Echinacea, chamomile and ginseng (11). A study in Ireland has identified 38% herbal product use in the past 3 months among women undergoing *in vitro* fertilisation (IVF) with sedation administered before removing the oocytes or ovarian cyst aspiration and found that none of these women provided this information to their anaesthesiologist (12).

Because of the adverse effects occurring especially in the perioperative period owing to herbal medications, several guidelines emphasise the need to question these medications for premedication and to stop taking them for at least 2 weeks before the operation (13). Preanaesthetic assessment records which medications the patient uses but does not question the use of herbal products and may put anaesthesiologists and surgeons in difficult situations because of unexpected complications occurring during anaesthesia administration or surgical procedures (4). We did not encounter any study in the literature in Turkey about the use of herbal medications in patients undergoing IVF treatment. There is an international research published about the use of herbal products by infertile couples and pregnant patients (14, 15).

This study aimed to determine the level of herbal product use in couples undergoing preanaesthetic assessment before IVF treatment in Turkey and to determine the status of questioning of herbal medication use in the preoperative period.

Main Points:

- Asking questions to patients receiving infertility treatment or anaesthesia is important in terms of medication interactions and treatment success.
- Most people stated that they used herbal products by increasing the amounts in daily consumption. The top 5 products included onion, garlic, thyme, cinnamon and carob.
- For IVF detailed anamnesis should be taken and herbal product used and cessation times must be researched in detail.

Methods

This cross-sectional study received ethics committee approval from Dokuz Eylül University Non-interventional studies ethics committee dated 27th July, 2016, and numbered 2016-20-08.

The study sample included couples receiving treatment in Dokuz Eylül University IVF units from 1st August, 2018, to 28th February, 2019, including a total of 257 people. The inclusion criteria for the study were receiving treatment for at least 1 week in the IVF unit, being at least a primary school graduate, and voluntary participation; however, those who answered less than half the questions in the survey form were excluded from the study.

A 16-question survey form was used to determine the herbal product use in the study group. The survey form included 5 questions to determine the sociodemographic variables, such as age, sex, educational level, income perception and presence of health insurance, and 11 questions about the use and questioning in relation to herbal products. The relevant literature was screened, and the survey form was created by the researchers (12, 16). The survey form administered to the research group is shown in Table 1.

To determine the use of herbal products, vitamin and herbal product use in the past 3 months was separately questioned. In the literature, as directly asked questions do not receive full and reliable responses and even those responding 'I do not use it' were determined to mark high rates when a list of herbal products was given (16), the participants were also given a list of herbal products and requested to mark the herbs or herbal products they used. Those who marked items on this list were assessed as 'using herbal products'.

If the patients receiving IVF treatment had an anaesthesia plan, they were evaluated at least 1 week before by the anaesthesia clinic. The survey forms were given to volunteers on the day when anaesthesia administration was planned during the preoperative preparation stage. The aim of the study was explained and after receiving consent, the couples, or only the partner who agreed to participate, were given the survey form. After completing the survey form, they were requested to leave the form in a box with the unit secretary.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences statistical programme (IBM SPSS statistics version 22, USA), and correlations between indepen-

Table 1. Survey form applied to the research group

Dear patient,

We wish to perform a survey evaluation about the use of herbal products by patients receiving treatment in our IVF unit. If you wish to participate, we ask that you fill in the following form. We wish to state that any information and responses to survey questions will remain confidential.

Thank you in advance for your participation.

Get well soon

1. Your age:…….

2. Your gender ❑ Female ❑ Male

3. Your educational level: ❑ primary school ❑ middle school ❑ high school ❑ university

4. Your health insurance: ❑ have insurance ❑ don't have insurance

5. How do you assess your income level? ❑ very good ❑ good ❑ moderate ❑ poor ❑ very poor

6. Have you regularly used vitamin or food supplements in the last three months?

❑ Yes (please write the names ……..) ❑ No

7. Have you regularly used any herbal products for treatment of any health problem in the last three months?

❑ Yes ❑ No

8. If the answer to the previous question was yes, did you use this product in order to have a baby?

❑ Yes ❑ No (Which problem did you treat?

Please explain ……)

9. Which herbal products do you use? (you may mark more than one, add any others beside the empty boxes)

❑ Garlic	❑ Thyme	❑ Nettle
❑ Green tea	❑ Gingko biloba	❑ Licorice
❑ St. John's Wort	❑ Aloe	❑ Mistletoe
❑ Echinacea	❑ Cinnamon	❑ Cumin
❑ Ginger	❑ Swedish bitters	❑ Onion
❑ Soya granules	❑ Buckthorn	❑ Carob

If you don't use herbal products, there is no need to continue the survey. The following questions should be answered by those using herbal products.

9. Have you continued taking these products in the last two weeks?

❑ Yes ❑ No

10. How did you begin using the herbal products stated?

❑ Doctor recommendation	❑ Pharmacist recommendation
❑ Herbal product sellers	❑ Friend recommendation
❑ Relative recommendation	❑ Newspaper, internet or other media organ

❑ Other (please write…….)

11. Have you continued to use herbal products during treatment in our unit?

❑ Yes ❑ No

12. Did you tell your doctor in the IVF centre that you use herbal products?

❑ Yes ❑ No

13. Did you tell your anaesthesiologist you use herbal products before anaesthesia?

❑ Yes ❑ No

14. Did your anaesthesiologist ask you about herbal product use before anaesthesia?

❑ Yes ❑ No

15. Do you have information about the side effects of herbal products?

❑ Yes ❑ No

16. Have you experienced any side effects from linked to use of herbal products?

❑ Yes (please write……) ❑ No

THANK YOU FOR PARTICIPATING IN OUR SURVEY

Table 2. Distribution of the study group by sociodemographic characteristics

Sociodemographic features	Number of women, n (%)*	Number of men, n (%)*	p	Total number, n (%)**
Age (years)				
<35	85 (62.5)	51 (37.5)	0.000	136 (52.9)
35 and above	47 (38.8)	74 (61.2)		121 (47.1)
Education				
Primary/middle school	37 (48.1)	40 (51.9)	0.487	77 (30.0)
High school and university	95 (52.8)	85 (47.2)		123 (70.0)
Health Insurance				
Have	127 (51.4)	120 (48.5)		247 (96.1)
Do not have	5 (50.0)	5 (50.0)	0.930	10 (3.9)
Income perception				
Very good and good	44 (53.0)	39 (47.0)	0.715	83 (32.3)
Medium and low	88 (50.6)	86 (49.4)		174 (67.7)
Total	132 (51.4)	125 (48.6)		257

*Percentage of Rows, **Percentage of Columns

Table 3. Vitamin and food supplement and herbal product use in the past 3 months according to gender

Products used	Women, n (%)*	Men, n (%)*	Total	p
Vitamin supplement	35 (62.5)	21 (37.5)	56	0.06
Herbal product	17 (48.6)	12 (51.4)	35	0.72
Those who marked at least 1 herbal product from the list	85 (55.6)	68 (44.4)	105	0.10

Table 4. Herbal products used in the past 3 months

Herbal Product	Number of people (%)
Onion	104 (40.5)
Garlic	97 (37.7)
Thyme	69 (26.8)
Cinnamon	59 (23.0)
Carob	38 (14.8)
Green tea	37 (14.4)
Ginger	33 (12.8)
Cumin	29 (11.3)
Nettle	8 (3.1)
Fig-date-apricot	4 (1.6)
Licorice	3 (1.2)
Aloe vera	3 (1.2)
Ginkgo biloba	2 (0.8)
Echinacea	2 (0.8)
St. John's Wort	2 (0.8)
Swedish bitters	1 (0.4)
Turmeric	1 (0.4)
Blackberry root	1 (0.4)
Mistletoe	1 (0.4)

dent variables and herbal plant use were tested with the chi-squared analysis.

Results

A total of 257 people in 125 pairs participated in the study. The mean age of the participants was 34.1±5.8 years. Of those receiving IVF and participating in the study, 48.6% were men, with the distribution of sociodemographic properties according to gender given in Table 2. There was a significant difference between men and women only in terms of age groups.

The distribution of the use of vitamin supplements and herbal products in different forms in the past 3 months among those receiving IVF according to gender is given in Table 3. Of the study group, 13.6% answered yes to the question about herbal product use, whereas 40.8% marked at least 1 item on the herbal product list. Most of these people stated that they used herbal products by increasing daily consumption amounts. The most commonly used herbal product was onion, with garlic, thyme, cinnamon and carob among the 5 most commonly used products (Table 4).

Of people participating in the study, 33.1% (85 people) continued to use these products in the past 2 weeks and 24.1% (62 people) said that they continued to use these supplementary products during treatment. However, 8.6% (22 people) of these people stated that they had informed the doctor in the IVF centre, and 7.4% (19 people) stated that they informed their anaesthesiologist. Only 9.3% (24 people) of participants stated that they were asked about the use of these types of products by their anaesthesiologist.

Table 5. Information/advice resources on the herbal product used

Information/advice resource	Number (%)
Newspaper, magazine, books	30 (36.5)
Friend, relative	28 (34.1)
Doctor	16 (19.5)
Pharmacist	5 (6.1)
Herbal product supplier	3 (3.6)
Total	82 (100)

Of those using herbal products, 19.5% (50 people) stated that they knew the side effects of the products used, whereas only 1.56% (4 people) themselves stated that they developed side effects because of these products.

Of those using herbal products in the past 3 months, 82 people responded to the question about where they received information or advice about the herbal product. According to these responses, they received information or advice about herbal products mainly from newspapers, magazines, relatives or friends (Table 5).

Discussion

Herbal products are commonly used for infertility treatment just as they are used for chronic diseases, such as cancer, hypertension, hyperlipidaemia, diabetes and immune system failure; for psychological disorders, such as anxiety and depression; for upper respiratory tract infections and stomach-intestinal disorders; and with the aim of increasing physical or cognitive performance. In recent years, delay in becoming a mother till a late age has increased the frequency of infertility treatment (17).

Herbal product use has become an important topic requiring great care in surgery or non-operating room anaesthesia administration because of the increase in herbal product use in Turkey and worldwide. The use of herbal products with medications may cause severe herbal-product-medication interactions (18). As many effect mechanisms of plants are not fully defined, the definite mechanism for herbal product and medication interactions has not been fully explained. On the basis of *in vitro* and *in vivo* research and published clinical research and case reports about this topic, it appears that pharmacokinetic and pharmacodynamic interactions play a role in the mechanism of herbal product and medication interaction, as with medication-medication interactions (19).

In the literature, 22%–43% of patients undergoing surgical interventions reported using herbal products (2). Kaye et al. (2) have questioned 1,017 adult patients with planned operations in a survey study about premedication herbal product use and identified that 32% of the patients used herbal products. In this study, 43% of these patients used garlic, 32% used *Ginkgo biloba*, 30% St. John's Wort, 18% Ma Hung, 12% Echinacea, 10% aloe vera, 8% cascara and 3% licorice.

Herbal products are commonly used for infertility treatment (10). In the USA, a study of couples receiving infertility treatment showed that 17% of couples used herbal products (10). Another study in Australia has stated there was 29% herbal product use among those receiving infertility treatment, with the most commonly used products as green tea, mint, Echinacea, chamomile and ginseng (11). In our study, we observed 62.5% of female patients receiving treatment for IVF used vitamin supplements, whereas 48.6% used herbal products. This rate is very high compared with that of other studies. For men undergoing the same treatment (partners of the female participants), 37.5% used vitamin supplements and 51.4% used herbal products. Of these participants attending the IVF centre for interventions, 33.1% continued to use these products in the past 2 weeks. A study in Ireland has identified that the rate of herbal product use in the past 3 months among women receiving IVF with sedation for oocyte removal or ovarian cyst aspiration was 38% and that none of them informed their anaesthesiologists (12). In our research, a very low rate of 7.4% participants informed the doctor performing the intervention about this risky situation for patients in terms of medication interactions with herbal products. The results of our study are consistent with the literature in terms of the need to persistently question the patients about whether they use these products during premedication because of the adverse effects that may occur in the perioperative period linked to herbal medications (20, 21).

Without in-depth questioning, couples do not volunteer to disclose their herbal medication use. Only 9.3% of participants stated that they were questioned about the use of these types of products by their anaesthesiologist. Our study shows that although a full and reliable response is not given to the question of 'do you use herbal products?', high rates were observed for participants who marked items when given the herbal product list even among those stating that they do not use herbal products. It was observed that there were high rates of use of onion and garlic among responders to the survey. In addition, those responding to our survey were observed to use products, such as aloe vera, garlic, *Ginkgo biloba*, St. John's Wort and Echinacea, and also herbal products, such as nettles, ginger, St. John's Wort and Swedish bitters, different from the literature. The study by Vaabengaard et al. (22) has reported that adult patients frequently used fish oil, ginkgo and Echinacea along with different herbal products, such as garlic and Co-Q10. A survey study of adult patients by İyilikçi et al. (8) has identified that 50.9% of patients used herbal products. This rate is again higher than that of other countries.

The elevated use of herbal products in Turkey led us to focus on plants reported to interact with medications. The plants reported to interact with medications are St. John's Wort (*Hypericum perforatum*), ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*), ginger (*Zingiber officinale*), garlic (*Allium sativum*), Echinacea and valerian. The medications interacting with herbal products have a broad range, including anticoagulants, antithrombotics, cardiovascular medications, immunosuppressant medications, sedatives, antidepressants, statins, anticancer drugs and anti-human immunodeficiency virus medications (23).

Of the herbal products known to interact with medications, *Ginkgo biloba* increases cognitive function and peripheral perfusion (impotence and macular degeneration) and inhibits platelet activating factor (24, 25). *Ginkgo biloba*, cava and Echinacea have sedative effects and lengthen the effects of barbiturates (24-26). Without examining whether either partner has a pathological condition in couples receiving infertility treatment, they continue to take herbal supplements. Of our participants, 0.8% stated that they used *Ginkgo biloba*.

Echinacea stimulates the immune system. It may cause allergic reactions and hepatotoxicity and interact with immunosuppressive treatments (for example, organ transplantation) (2, 21, 27). Of the patients responding to our survey, 0.8% stated that they used Echinacea.

Cinnamon lowers the blood glucose levels. There is no information about when to stop the cinnamon use before a surgery (28). Of our participants attending the IVF centre for infertility treatment, 23% used cinnamon and they stated they did not even consider its use to be a herbal product use.

Green tea is considered being rejuvenating owing to renewing cells, preventing cancer because of its antioxidant properties and being a source of strength owing to the high content of vitamins, enzymes and coenzymes. It improves cholesterol and lipid levels and regulates the blood pressure and blood glucose levels. Thus, it protects against atherosclerosis. It causes vasoconstriction of the capillary veins and prevents formation of oedema. Because of its diuretic properties, it aids in slimming regimens (23). In our study, 14.4% of participants used green tea. Owing to the diuretic effect and effects of lowering blood pressure and blood glucose levels, we believe that care should be taken in the perioperative period.

Nettles are commonly consumed in Turkey as seeds, roots or leaf tea. It increases urination, resolves oedema and iron deficiency, prevents anaemia and is commonly used against prostate hypertrophy. Because of its diuretic effect, it may cause electrolyte changes in severe heart and kidney diseases (23). In our study, 3.1% of the participants used nettles.

Herbal-product-medication interactions may be observed at cytochrome P450 enzymes (CYP450) and P-glycoprotein (P-gp) levels. Herbal products inhibit or induce CYP450 enzymes and P-gp and may change the absorption, distribution, metabolism and excretion of medications with these substrates. Changing the plasma levels of these medications may decrease or increase in the pharmacological effects or increase the risk of side effects and toxic effects. Herbal products have been shown to affect enzyme systems, especially CYP3A4 and CPY2C9 and the CYP2D6, CYP1A2, CYP2E1 and CYP2C19 enzyme activities (22, 29, 30). Herbal products affect P-gp responsible for excretion of medication through the lumen in the intestine, liver and kidneys and may affect the absorption, distribution and excretion of medications. As medications may have both CYP enzymes and P-gp substrates, they may also have separate substrates. Herbal products may inhibit or induce both CYP enzymes and P-gp and change the pharmacokinetics of a medication. For example, St. John's Wort (*Hypericum perforatum*) induces both CYP3A4 enzyme and P-gp and is reported to interact with many medications (22, 29).

The geographical region of the Aegean region, where our study was performed, is very rich in terms of St. John's Wort, with 2 people participating in our study stating that they used this herb. It is notable that 16 (6.2%) participants stated that the herbal products were recommended by a doctor and 5 (1.9%) participants stated they were recommended by a pharmacist. Of the people participating in the study, 33.1% (85 people) continued to use these products in the past 2 weeks, whereas 24.1% (62 people) stated that they continued to use these supplementary products during treatments.

In the perioperative period, being aware of the interactions between the herbal products and other medications used by these patients is of great importance. Owing to the possible side effects of herbal products and their interactions with medications used for anaesthesia, the American Society of Anesthesiologists recommend stopping the use of herbal products at least 2 weeks before surgical procedures. In the literature, cava and ephedra should be stopped 24 hours, ginkgo for more than 36 hours, St. John's Wort for 5 days, garlic for longer than 1 week, Echinacea for as long as possible before surgery and valerian should be slowly reduced in the weeks before surgery (20, 29).

Limitations of our study include some herbal items found on our survey being used in food and so not perceived as herbal products by patients and the amounts used not being known. Another limitation is that while answering the survey, those with a high educational level may not have reported the true amounts or types of herbal products owing to being aware that their use was wrong but still using the items or they feared

that the treatment centre's awareness of the use of herbal products would affect treatment.

In our anaesthesia clinic, patients preparing for elective operations meet the anaesthesiologists a short time (1 week or 1 day) before the surgery. If patients with previously planned operation dates are identified to have herbal medication use during premedication, the risks that may occur in the perioperative period should be explained in detail to patient and surgeon. The need to organise seminars about this topic for surgical departments outside of anaesthesia, discuss the effects of herbal products on mortality and morbidity in anaesthesia and surgery and to prepare guidelines (13) is evident. As there is a large variety of herbal product types known and defined according to regions in Turkey, we believe that our study will contribute to directing the literature and studies about this topic and emphasise the need for more advanced studies.

Herbal product use should definitely be questioned, and patients should be provided with information about herbal-product-medication interactions. Herbal products with unproven efficacy and reliability in clinical controlled research should definitely not be recommended.

In addition to the nutritional habits of the geographical region (Aegean region) of the study being rich in herbal products, participants in the study benefited more from sources, such as newspapers, books and the Internet, along with their educational level. In this period when the desire to try new and alternative treatments and increased Internet use, it appears that herbal medication access and use will increase. It is clearly observed that one of the areas which will leave the clinicians in difficult situations with questioning of some complications experienced perioperatively, especially in terms of malpractice, is herbal product use.

Conclusion

All patients undergoing anaesthesia administration should be questioned in detail about herbal product use; however, questioning the patients receiving infertility treatment or anaesthesia for infertility treatments carries separate importance in terms of medication interactions and treatment success. The laborious and costly treatment of IVF requires care at every stage, and detailed anamnesis about this topic should be taken with the herbal product use researched. The need to perform an in-depth investigation about herbal product use as the first and most valuable step of taking anamnesis is clear in approaches to patients by both the surgical and anaesthesia teams.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University (27th July, 2016, and numbered 2016-20-08).

Informed Consent: The aim of the study was explained and after receiving consent, the couples, or only the partner who agreed to participate, were given the survey form.

Peer-review: Externally peer-reviewed.

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