The efficacy of dietary supplements and herbal extracts in treating female infertility

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Abstract

Aim: To determine types of dietary supplement and herbal extract which have been used in treatment of female infertility in Diyala governorate

Patients and methods: This is a cross sectional study. It was conducted in the period from July 2023 to January 2024. We collected 58 patients who have been suffering from infertility and took a dietary supplement as adjuvant therapy for the infertility and 42 patients who used herbal extracts only. We collected the sample from the patients who attended Al-Batool teaching hospital in Diyala governorate. we

collected information about age, supportive drugs, type of infertility, type of supplements and herbal extracts, etc.

Results: 100 patients were enrolled in our study. 58% used dietary supplements and 42% used herbal extracts. 55.2% of women in this study used folic and 44.8 % used folate and none of them used 5-MTHF. 72% of them suffered from primary infertility and 28% suffered from secondary infertility. Letrozole was the most common supportive drug with percentage of 19%. Myo-inositol was the most common used supplement with percentage of 65% and Shatavari was the most common herbal used (95.2%).

Conclusion: There is need to use certain supplement more beneficial than other in treatment of female infertility.

Introduction

infertility is a medical disorder that manifests as the inability to conceive following a year of unprotected sexual activity. Many gynecological and systemic disorders, such as endometriosis, premature ovarian failure, pelvic inflammatory disease, and polycystic ovarian syndrome (PCOS), can impact the female reproductive system and possibly result in infertility. A woman's physiological reproductive processes may be hampered by lifestyle choices including a poor diet and nutritional imbalance in addition to organic illnesses (1).

Ovulatory dysfunction is the most common cause of infertility in women. About 25% of cases of infertility are caused by ovulatory abnormalities; PCOS affects 70% of anovulating women. A combination of clinical (anovulation and hyperandrogenism), biochemical (excessive androgen and luteinizing hormone concentrations), and ovarian morphological (polycystic ovaries) aspects describe this multifactorial illness. The etiology of PCOS is multifaceted and contentious, involving genetic, environmental, and lifestyle variables; nonetheless, a crucial etiological aspect is insulin resistance. These tenets lead to the proposal of various nutrients as novel therapy approaches for PCOS infertile patients (2).

Many women request treatment or self-medicate with various adjuvant therapies, such as dietary supplements (DS) with varied contents, to increase their chances of becoming pregnant. Recent research at a UK fertility center with women slated for in vitro fertilization (IVF) found that 55% had used some form of dermal sealant (DS) including different substances. Furthermore, 16% of patients said they were solely taking folic acid (4).

Dietary supplements (DS) are employed either to address deficiencies in essential substances or to attain an optimal dosage (such as minerals, vitamins, carbohydrates, fatty acids, and proteins), potentially enhancing different fertility aspects, including hormonal equilibrium, ovulation, oocyte quality, embryo quality, and ultimately, the likelihood of conception. The utilization of DS for female infertility has surged in recent years, fostering a multi-million-euro industry that offers diverse DS formulations containing various substances at varying strengths. Unlike medications, DS formulations are not subject to government regulation or patent protection. (5).

Several compounds have been studied as fertility enhancers in recent years. The safest substance among them all that has shown promise in treating problems

with conception and pregnancy is myo-inositol, or myo-ins. As myo-ins are involved in a number of signaling pathways, such as those involving insulin and gonadotropins, fertility is probably positively impacted by them. Extant data indicates that myo-ins supplementation increases the likelihood of conception and delays the onset of negative effects on the mother and the outcomes of the newborn. More precisely, myo-ins have been shown to help infertile women—especially those with PCOS—induce ovulation and restore the normal menstrual cycle in an effort to conceive. Additionally, women receiving ART can benefit from myo-ins supplementation, which enhances the quality of their oocytes and embryos (6).

The synthetic version of the vitamin, folic acid, is typically found in foods and supplements. Cell metabolism in the body is required to convert it into the bioactive folate derivative (6S)5-MTHF. A lack of folate raises the risk of cardiovascular disease and is linked to a number of other health problems, including neurological diseases. Pregnant women, women of reproductive age, and those with MTHFR polymorphism are the main groups at risk for folate insufficiency. Folate supplementation is a common strategy for improving fertility, preventing neural tube abnormalities (NTDs) in fetuses, and reducing homocysteine levels. Because (6S)5-MTHF can get around the block in folic acid metabolism caused by enzymatic polymorphism, it is recommended to take supplements of this compound instead of folic acid during pregnancy (7)

N-acetylcysteine (NAC) is a widely recognized antioxidant known as a precursor to reduced glutathione (GSH). Numerous studies have demonstrated NAC's antioxidant properties through various methods, substrates, and oxidants used to assess oxidative processes in vitro. Consequently, NAC has been employed as an antioxidant in numerous in vivo studies. In aged mice, NAC has shown potential in reducing free radicals and enhancing egg quality post-cryopreservation. However,

studies investigating the efficacy of NAC in elderly individuals are limited. Mitochondrial function significantly influences oocyte quality, and NAC has been shown to improve oocyte quality by enhancing antioxidant activity, leading to the development of high-quality blastocysts through increased GSH content. Additionally, pretreatment with NAC may enhance the ovary's responsiveness to exogenous gonadotropins in older women, potentially enhancing oocyte development capacity. (8).

Levocarnitine, also referred to as L-carnitine (LC), is a physiologically active stereoisomer of 3-carboxy-2-hydroxy-N, N, and N-trimethyl-1-propanaminium. This hydrophilic small molecule plays a crucial role in mitochondrial function and lipid metabolism, both of which support various physiological processes. There's evidence suggesting that L-carnitine and its derivatives, namely propionyl-L-carnitine (PLC) and acetyl-L-carnitine (ALC), may enhance reproductive functions. Furthermore, the fundamental principle underlying their effects has been elucidated. L-carnitine likely mediates the development of oocytes and embryos through several mechanisms. Firstly, it may promote lipid metabolism by facilitating the transportation of fatty acids to mitochondria for β-oxidation, thus maintaining energy production. Secondly, it might modulate glucose metabolism by stimulating pyruvate dehydrogenase (PDH) and enhancing the activities of respiratory chain enzymes. Additionally, L-carnitine can shield cells from oxidative stress by reducing the production of free radicals, augmenting the activities of antioxidant enzymes, or enhancing the turnover of phospholipid fatty acids in membranes. Furthermore, it has the potential to suppress the oxidative stress signal associated with apoptosis (9).

Among the five molecules that make up vitamin D, a steroid hormone, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are essential for reproductive health. Previous studies have demonstrated the expression of vitamin D receptors

and 1α-hydroxylase, or vitamin D enzymes, in human decidua and first trimester. 1,25(OH)2D3 and vitamin D receptors controlled the transcription of HOXA10, the main target gene linked to implantation. Growing data from prospective random and cohort observational studies suggested a connection between infertility and vitamin D deficiency or insufficiency. It has been suggested that the level of vitamin D may affect the first embryo to implant by controlling the immune cells (natural killer cells, dendritic cells, macrophages, and T cells) in the tissue of the uterus and decidua (10).

Coenzyme Q10 (CoQ10) plays a vital role in the inner mitochondrial membrane, facilitating electron transport in the mitochondrial respiratory chain to produce adenosine triphosphate (ATP), the energy substrate. Additionally, it functions as an antioxidant within the oocyte. Research, including observational studies and a randomized controlled trial (RCT), indicates that the concentration of CoQ10 in follicular fluid decreases with age. Furthermore, a low CoQ10 antioxidant level may be associated with diminished oocyte quality. Therefore, there is a justification for considering the use of CoQ10 supplementation during fertility treatment for women with perceived 'poor oocyte quality (11)

Melatonin is a low molecular weight indoleamine that is produced by several human systems and cells. Melatonin and its synthesis machinery are found in the placenta and the ovary in the reproductive system. Indoleamine is recognized as a multifunctional molecule with exceptional biological properties, such as immune response, reproduction, and biological rhythm modulation, in addition to its anticancer and metabolic impacts. More significantly, melatonin is a superb antioxidant that prevents oxidative stress by scavenging reactive oxygen species (ROS) and activating the body's own antioxidant enzymes (12).

Folate represents the naturally occurring form of vitamin B9, its name deriving from the Latin word "folium," meaning leaf. Leafy greens indeed stand out as excellent dietary sources of folate. This vitamin encompasses a group of related compounds with similar nutritional properties under its generic name. The active form of vitamin B9 is a specific type of folate called levomefolic acid or 5-methyltetrahydrofolate (5-MTHF). On the other hand, folic acid, also known as pteroylmonoglutamic acid, is a synthetic form of vitamin B9 utilized in supplements and incorporated into processed food items like flour and breakfast cereals. Unlike folate, not all folic acid gets converted into the active form of vitamin B9 in the digestive system; instead, this conversion typically occurs in the liver or other tissues (13).

Many people tend to use the terms "folic acid" and "folate" interchangeably since they both refer to vitamin B9. However, there exists a significant difference between the two. Folic acid is the synthetic form commonly added to processed foods and supplements, while folate naturally occurs in whole foods such as leafy vegetables, eggs, and citrus fruits. Both folic acid and methylated folate, known as 5-MTHF, are distinct forms of the same nutrient (folate) and contribute to maintaining adequate folate levels, crucial for supporting neural tube development. According to the U.S. Food and Drug Administration (FDA), diets rich in folate may help decrease the risk of neural tube defects in newborns. (14).

The FDA does not hold the view that folic acid is the sole form of folate beneficial for supporting neural tube development. According to the American Pregnancy Association, considering that the neural tube forms within the initial 28 days of pregnancy, it is advised that women of reproductive age incorporate folate into their diets (15).

The escalating concern over the adverse impacts of chemical drugs on reproductive health, coupled with the high costs associated with pharmaceuticals and modern fertility treatments, has led to a growing inclination among women towards herbal medicines. Herbal remedies are increasingly perceived as viable alternatives to chemical drugs, primarily due to their rich array of compounds with phytoestrogenic, antioxidant, and nutritional properties. Leveraging estrogen-mimetic phytoestrogens is recognized as a beneficial and healthful approach to alleviate menopausal symptoms in women resulting from estrogen deficiency (16).

One of the most renowned herbal remedies for addressing reproductive health issues in women is shatavari (Asparagus racemosus), derived from Sanskrit where 'ayur' signifies "life" and 'ved' means knowledge. Shatavari is widely employed to alleviate various female reproductive problems, including irregular menstrual cycles, dysmenorrhea, uterine bleeding, amenorrhea, sexual weakness, dysfunctional menopause, pelvic inflammatory diseases, sexual dysfunction, and endometriosis. In ancient times, it was utilized as a uterine tonic for PMS, as it is believed to fortify, nourish, cleanse, and potentially address issues like uterine prolapse (17).

Vitamin C is a crucial nutrient that humans, along with only a few other species like guinea pigs, obtain exclusively from their diet, owing to the absence of a functional gulonolactone oxidase enzyme. Around the time of ovulation, concentrations of vitamin C in the ovaries rise. This phenomenon has been observed in various species, including guinea pigs, rats, and cattle. Similarly, in women, a shift occurs in the balance between retaining vitamin C and excreting it in urine during the mid-phase of the menstrual cycle. When dietary intake is sufficient, urinary excretion of vitamin C decreases just before ovulation. This trend indicates an

escalated need for and absorption of vitamin C by the ovaries to support optimal ovulation and uterine function (18).

Dong Quai, or Angelica Sinensis, holds a longstanding position in traditional Chinese medicine for addressing infertility concerns. Rich in potent compounds, this herbal remedy aids in enhancing blood circulation and balancing hormone levels in both genders. Research indicates that Dong Quai has the potential to positively impact sperm count, egg quality, and sperm motility, consequently boosting the likelihood of conception. Additionally, it is suggested that Dong Quai may offer protective benefits against specific pregnancy-related complications, including miscarriage and pre-eclampsia (19).

Ginseng, a prominent traditional herb in Eastern Asia, is often employed as a tonic to mitigate the aging process. Its primary active component is ginseng saponin, comprising numerous ginsenosides. Presently, around 30 ginsenosides have been recognized. While several studies have explored its potential to enhance fertility, investigations into the effects of ginseng on fertility and the mechanisms involved are yet to be thoroughly examined in humans. This gap persists because most related studies have been conducted in vitro, warranting further research in human subjects (20).

Tribulus terrestris L., belonging to the *Zygophyllaceae* family, is commonly referred to as *Tribulus,* Hard thorns, and goat head in China. This perennial plant is found extensively across the Mediterranean region, subtropical zones, and deserts worldwide. Renowned for its potential to enhance sexual activity, it is widely utilized in traditional herbal medicine. Research into its pharmacological properties suggests that *T. terrestris* can positively influence the reproductive systems of both males and females. It has been observed to elevate hormone levels, including estradiol and

testosterone to a lesser extent, while also boosting libido, sperm production, spermatogenesis, and ovulation. (21).

Aim of study

To determine types of dietary supplement and herbal extract which have been used in treatment of female infertility in Diyala governorate

Materials and methods

This is a cross sectional study. It was conducted in the period from July 2023 to January 2024. We collected 58 patients who have been suffering from infertility and took a dietary supplement as adjuvant therapy for the infertility and 42 patients who used herbal extracts only. We collected the sample from the patients who attended Al-Batool teaching hospital in Diyala governorate. we collected information about age, supportive drugs, type of infertility, type of supplements and herbal extracts, etc. we collected the information using prepared written

questionnaire and by direct interview with the patients. We preserved the privacy and we coded the patients for the reasons of confidentiality and risk of bias.

Statistical analysis

Statistical analysis was done by using SPSS Version 25 for the description of the data. We expressed the quantitative data by arithmetic mean, standard deviation and mode and the qualitative data by frequencies.

Results

58 patients who took dietary supplements were enrolled in our study. Their age groups are demonstrated in table 1.

Table 1. age groups of the women who took dietary supplements

Age groups	Frequency	Percent

20-25 years	20	34.5
26-30 years	10	17.2
31-35 years	10	17.2
36-40 years	3	5.2
> 40 years	15	25.9
Total	58	100.0

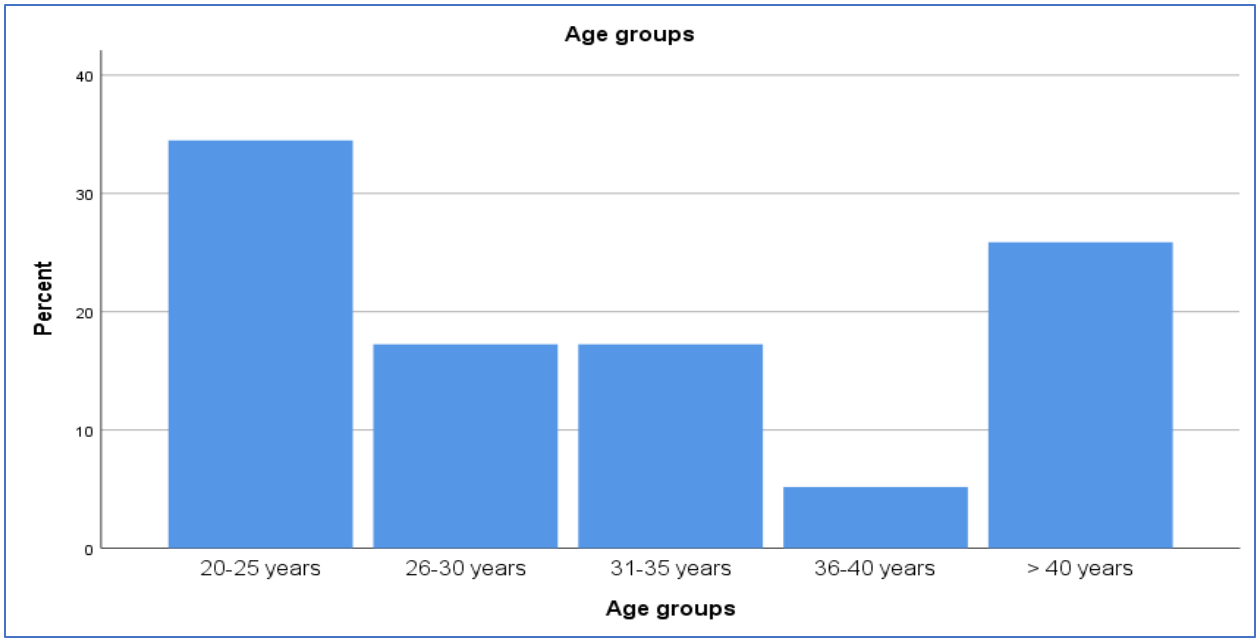

Figure 1. age groups of the women who took dietary supplements

The age groups of the women who took herbal extracts are demonstrated in table 2.

Table 2. The age groups of the women who took herbal extracts

Age groups	Frequency	Percent
20-25 years	16	38.1

26-30 years	16	38.1
31-35 years	6	14.3
36-40 years	4	9.5
Total	42	100.0

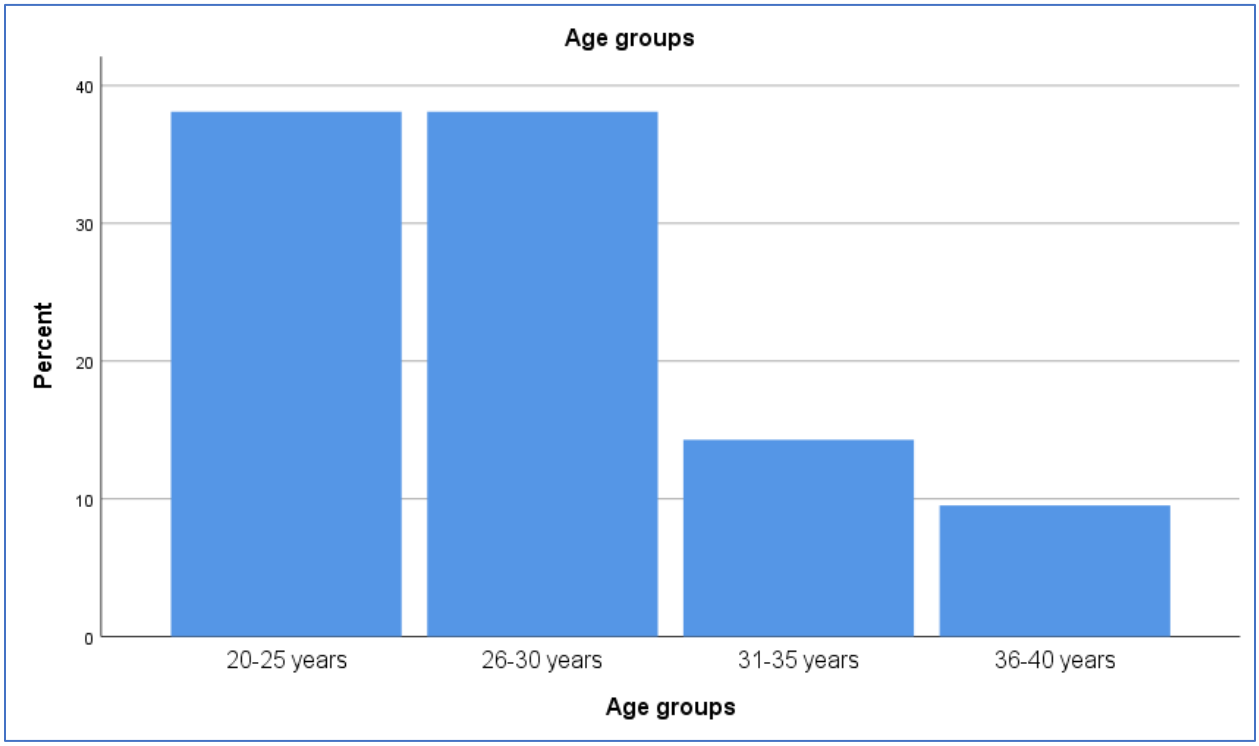

Figure 2. The age groups of the women who took herbal extracts

all of the patients were diagnosed with infertility, the type of infertility is demonstrated in table 3.

Table 3. type of infertility

Type	Frequency	Percent
Primary	72	72.0

Secondary	28	28.0
Total	100	100.0

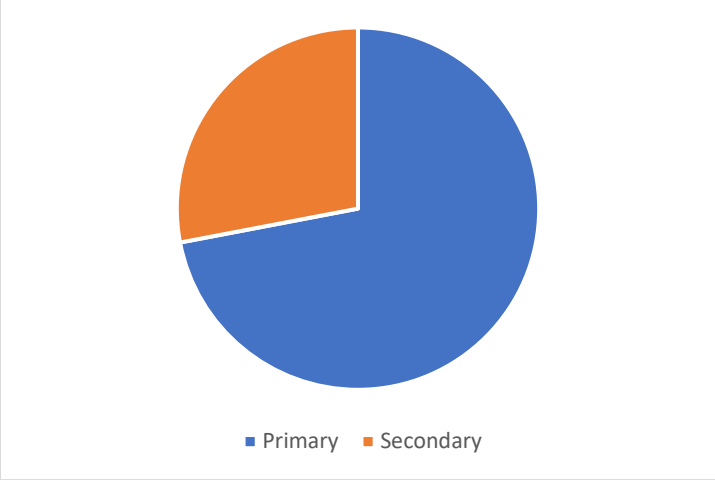

Figure 3. type of infertility

High percentages of the patients took supportive drugs, the drugs and their frequencies are enlisted in table 4 below.

Table 4. distribution of the supportive drugs in our study.

Drugs	Frequency	Percent
None	38	38.0
Choriogonadotropin alfa injection	16	16.0

HCG injection	17	17.0
Letrozole tab	19	19.0
Clomiphene	8	8.0
Total	100	100.0

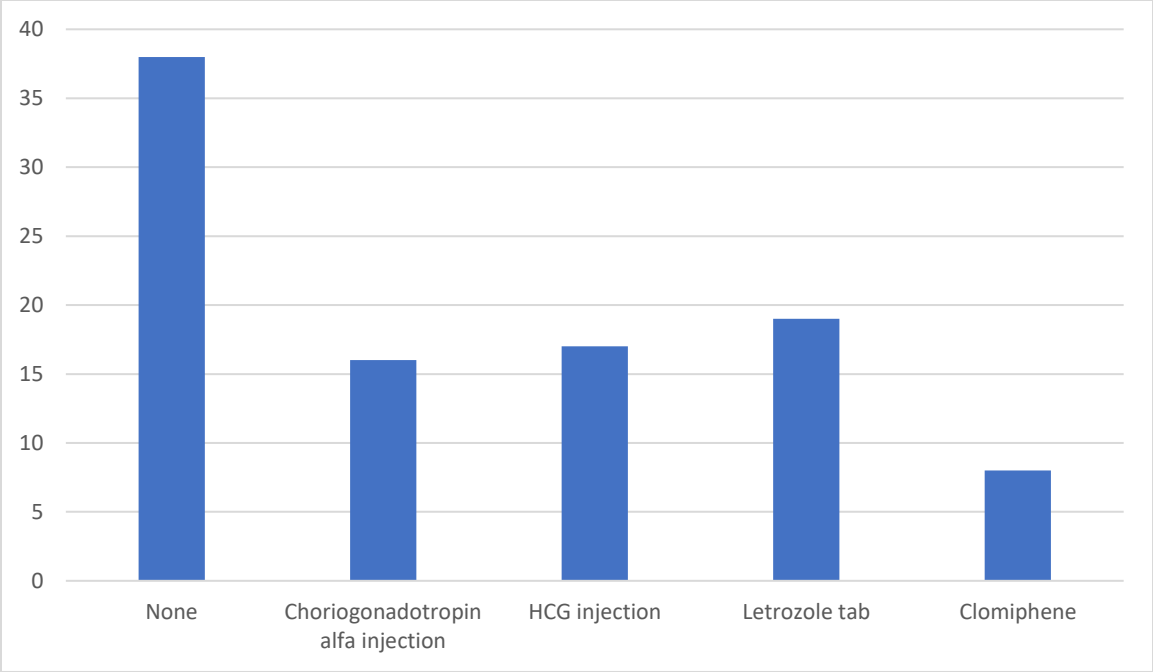

Figure 4. supportive drugs

58% of them took dietary supplements which are enlisted in table 5.

Table 5. dietary supplements

Supplements		**Frequency**	**Percentage**
Folic acid	Yes	32	55.2%

	No	26	44.8%
Folate	Yes	26	44.8%
	No	32	55.2%
CoQ 10	Yes	38	65.5%
	No	20	34.5%
Myo-inositol	Yes	38	65.5%
	No	20	34.5%
L- Arginine	Yes	18	31.0%
	No	40	69.0%
Vitamin D	Yes	36	62.1%
	No	22	37.9%
Melatonin	Yes	18	31.0%
	No	40	69.0%
Choline	Yes	12	20.7%
	No	46	79.3%

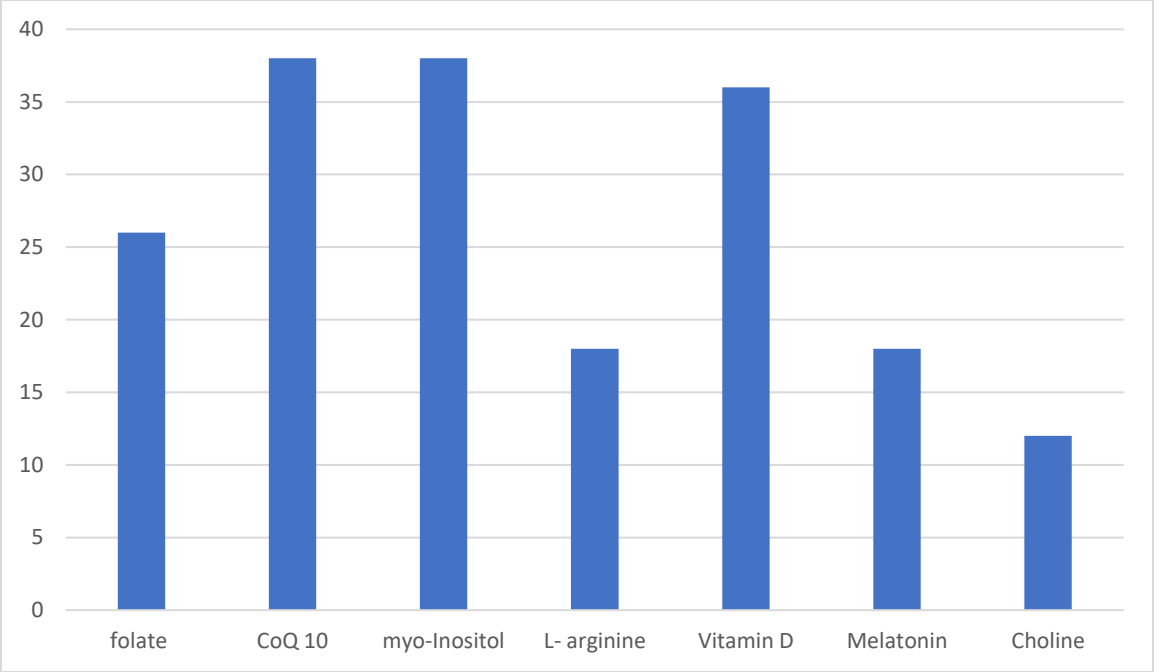

Figure 5. dietary supplements

The frequency of PCOS in our study is demonstrated in table 6.

Table 6. frequency of PCOS

PCOS	Frequency	Percent
Yes	36	36.0
NO	64	64.0
Total	100	100.0

42% of them took only herbal extracts as shown by table 7.

Table 7. herbal extract

Supplements		Frequency	Percentage
Asparagus recemosus (Shatavari)	Yes	40	95.2%
	No	2	4.8%
Angellca sinensis	Yes	23	54.7%
	No	19	45.3%
Rice flour	Yes	38	90.4%
	No	4	9.6%
Vitamin C	Yes	37	88%
	No	5	12%
Ginseng Extract	Yes	19	45.3%
	No	23	54.7%
Tribulus Terrestris	Yes	7	16.7%
	No	35	83.3%

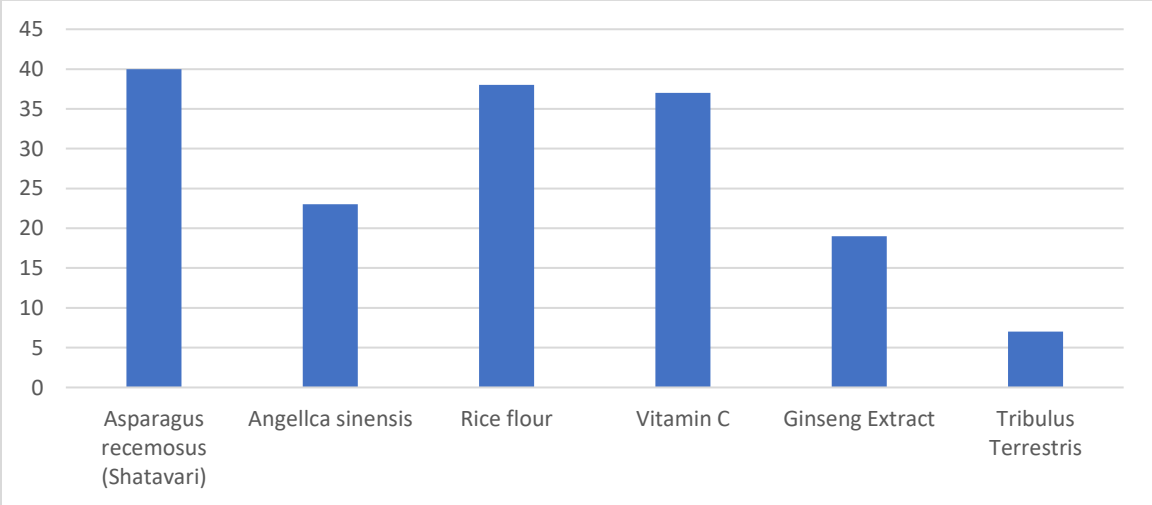

Figure 6. herbal extracts

Discussion

In our study, the most frequently used ingredients among the dietary supplements evaluated were myo-inositol and CoQ10 (both 65.5%). Inositols encompass a group of sugar alcohols consisting of nine stereoisomers, with myo-inositol and D-chiro inositol being the predominant isoforms in eukaryotic cells. These compounds play various roles in functions and signaling pathways such as reproduction, cell growth, and survival. Regarding female fertility, research has shown that inositols facilitate ovulatory processes through their insulin-sensitizing action (22), consistent with findings by Lagana et al. (23).

CoQ10 serves as a free radical scavenger, acting as an antioxidant within the mitochondrial respiratory chain and playing a pivotal role in regulating energy metabolism. Supplementation with CoQ10 has been linked to enhanced oocyte quality in studies conducted on both animals and humans. (24).

Folic acid emerged as the second most prevalent ingredient, present in 55.2% of the evaluated dietary supplements. Notably, in four supplements, the dosage fell short of the minimum effective dose (mED) of 400 mg. This observation is significant because the World Health Organization (WHO) strongly advocates for all women of reproductive age to consume 400 mg of folic acid daily, in conjunction with folate-rich foods from a diverse diet, to mitigate the risk of neural tube defects (NTDs) (25). Our findings align with those reported by Vitagliano et al. (26).

In our study, folate was utilized by 44.8% of the patients. Our discovery of a positive impact of folate intake on ovarian reserve is consistent with previous research, which has shown that women with higher folate intake experience a higher rate of conception, reduced risk of ovulatory infertility, shorter time to pregnancy, and increased success in infertility treatment. (27).

Reproductive health issues in women are often addressed using one of Ayurveda's most renowned herbal remedies, known as shatavari (Asparagus racemosus). Ayurveda, stemming from Sanskrit, combines "ayur," meaning "life," with "ved," signifying "knowledge," emphasizing a holistic approach to correcting health disorders using herbal medicines. Shatavari, a member of the Liliaceae family, is typically cultivated in tropical and subtropical regions of India, including the Himalayas. In our study, shatavari emerged as the most commonly utilized herbal extract, accounting for 95.2% of cases, a finding consistent with those reported by Pandey et al (28).

Conclusion

There is need to use certain supplement more beneficial than other in treatment of female infertility.

Recommendations

Herbs and dietary supplements should be evaluated for proof of efficacy in randomized clinical trials prior to use in clinical setting, and better to use 5 MTHF or folate more than using folic acid which is a synthetic form.