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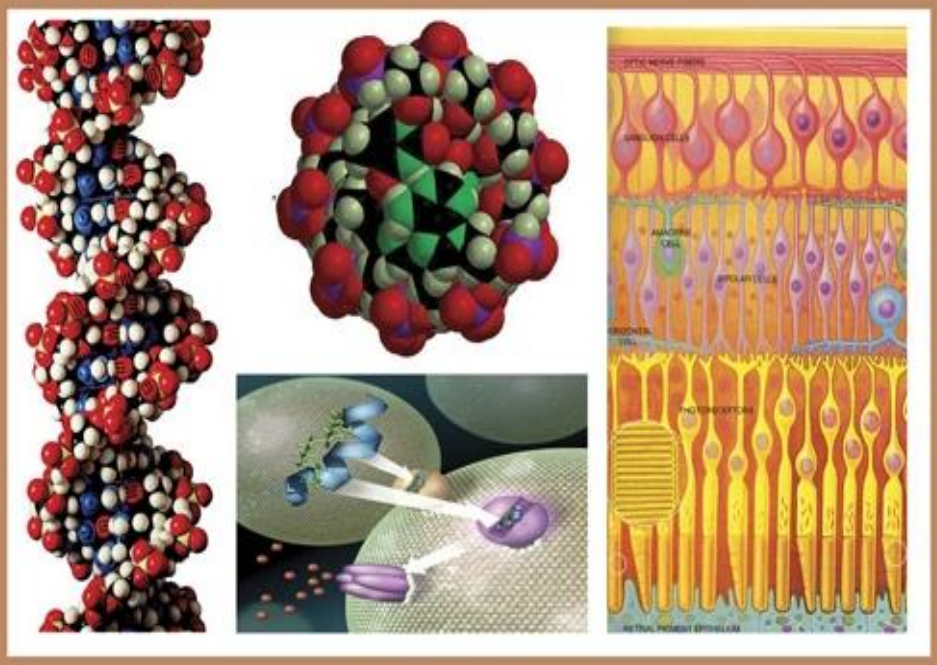

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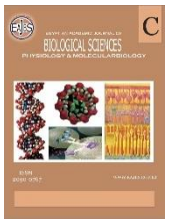

Herbal Medicine: Promising Treatment for Chemotherapy-Induced Ovarian Dysfunction

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ABSTRACT

Premature ovarian failure (POF) is a disorder that occurs before the age of 40 among women and characterized by amenorrhea. POF usually occurs due to autoimmune disorders, X-chromosome disorders, viral infections, or after chemotherapeutic treatment. POF can be discovered either by histopathology or by using molecular techniques such as real-time PCR to measure the expression of miRNAs that has a role in POF development. Cyclophosphamide (CP) is a well-known chemotherapy used in the treatment of leukemia, lymphoma, and breast cancer, but it has many harsh side effects on many body organs such as the heart, liver, and gonads, especially after high doses administration. Cyclophosphamide-induced POF usually ends with a loss of follicles and granulose cell damage. Herbal medicine is the promising therapeutic approach of POF especially because of its great safety, availability, and low cost. *Moringa oleifera (MO)* is a plant distributed all around the world; cultivated in tropical and subtropical areas. It has antioxidant and antimicrobial activity and high nutritional and medicinal values and it is also used in different industries as cosmetics and lubricants for machines. Different parts of its plant are used in the treatment of edema, skin infections, inflammations, rheumatism, fever, anemia, bronchitis, and digestive problems. Furthermore, *MO* has a great promising effect on treating the toxicity of ovaries caused by chemotherapy or heavy metals. On the other side, *Withania somnifera* (Ashwagandha) is also a herb with great medical importance that is cultivated in tropical and sub-tropical countries, and it has anti-cancer activities, anti-inflammatory and antimicrobial activities. It plays a role in regulating the hormonal balance and enhancing the gonads activity by increasing the ovaries' weight. It enhances immunity due to its high antioxidant activities. Ashwagandha can reduce stress, anxiety, and depression. Furthermore, it can reduce the symptoms of COVID-19. The leaves and roots are used in treating fever and joint inflammation, and roots have also been nominated among the drugs that neutralize the effect of snake venom.

INTRODUCTION

Premature ovarian insufficiency, premature menopause, and premature ovarian failure (POF) are terms used to describe ovarian dysfunction. The ovary is not only important for the fertility of a woman but also it regulates the endocrinology balance before the age of menopause (De Vos *et al.,* 2010; Hao et al., 2019). Usually, the age of menopause in healthy women ranges from 50-60 years, before this age or before the age of 40 is described as a non-physiological disorder that indicates the presence of ovarian dysfunction (Jewelewicz *et al.,* 1986; De Vos *et al.,* 2010).

The number of ovarian follicles is decreased gradually with age leading to menopause. The prevalence of POF before the age of 40 is 1 in 100 women, and it is described as a critical disease as it may cause other complications such as cardiovascular diseases (Jewelewicz *et al.,* 1986; Maclaran *et al.,* 2011; Sheikhansari *et al.,* 2018).

Symptoms of POF:

The absence of menstruation or amenorrhea is the main symptom of ovarian dysfunction. Amenorrhea can be divided into 2 types; primary amenorrhea in which the woman never had menstruation before and it can be related to genetic disorders and appears as an abnormality in karyotype, while secondary amenorrhea occurs after taking contraceptive pills or after viral infections and does not appear in the karyotype. Other symptoms may occur such as hot flashes, depression, vaginal dryness, and fatigue (Beck *et al.,* 2006; De Vos *et al.,* 2010; Jankowska, 2017).

Etiology of POF:

There are many reasons that increase the risk of POF, and it is important to know the reason for ovarian dysfunction for the treatment

1.Autoimmunity:

Addison's disease is a disorder that is characterized by insufficiency of adrenocortical hormones; previous studies proved that POF can be developed before Addison's disease by 8 to 14 years. Other autoimmune diseases that may cause POF are rheumatoid, diabetes and systemic lupus erythematosus (Maclaran *et al.,* 2011; Jankowska, 2017; Sheikhansari *et al.,* 2018).

2.Genetic Disorders:

The X-chromosome-related disorders can cause POF as in Turner syndrome, in which the X chromosome is missed or a part of it is missed, or the fragile X syndrome (FXS) can be also called Martin-bell syndrome which occurs due to an increase in the repeats number of CGG in the untranslated region of 5' of the FMR1 gene that leads to secondary amenorrhea and POF. Pseudohypoparathyroidism disorder which is known for its inadequate response to parathyroid hormone (PTH) also can cause POF (Sherman, 2000; Beck *et al.,* 2006; Jankowska, 2017; Sheikhansari *et al.,* 2018).

3.Viral Infections:

Cytomegalovirus (CMV), varicella zoster virus (virus of chickenpox), mumps virus (MuV), malaria and tuberculosis can lead to POF (Maclaran *et al.,* 2011; Jankowska, 2017; Sheikhansari *et al.,* 2018).

4.Enzymatic Defects:

The 17 α-hydroxylase deficiency that affects the gonads and adrenal glands, aromatase deficiency (CYP191A gene mutation) which causes a reduction in female sex hormones that cause POF (De Vos *et al.,* 2010; Jankowska, 2017; Sheikhansari *et al.,* 2018).

5.Chemotherapy and Radiotherapy:

Chemotherapy and radiotherapy side effects after cancer treatment can cause POF such as, cyclophosphamide, doxorubicin, busulfan and methotrexate (Jankowska, 2017; Sheikhansari *et al.,* 2018).

5.1.Effects of Chemotherapy:

Amenorrhea resulting from chemotherapy varies according to different factors such as the dose and type of chemotherapy used, the type of patient's disease and the age of the patient. Chemotherapeutic agents cause different consequences as 38% of women after

treatment are less likely to get pregnant (Spears *et al.,* 2019; Shin *et al.,* 2021; Xiong *et al.,* 2021).

5.2.Uses of Cyclophosphamide:

Cyclophosphamide (CP) is one of the most famous chemotherapeutic agents used in the treatment of various types of malignancies alone or in combination with other chemotherapies as breast cancer, sarcoma, lymphoma (Hodgkin and non-Hodgkin lymphoma) and leukemia (Acute lymphoblastic leukemia and chronic lymphoblastic leukemia). It is also used before bone marrow transplantation for different types of malignancies, aplastic anemia, and leukemia, and in immunosuppressive protocols in systemic lupus erythematosus and rheumatoid arthritis (Zhang *et al.,* 2005; Emadi *et al.,* 2009; Ahlmann *et al.,* 2016).

5.3.Toxic Side Effects of CP:

Cyclophosphamide develops many side effects as cardiac toxicity, nephrotoxicity, and hepato-toxicity, but the major complication after using high doses of cyclophosphamide is gonadal toxicity. Usually, CP decreases the glutathione (GSH) in ovaries leading to granulose cell apoptosis and it can destroy follicles. More than 50% of women treated with high doses of CP are more likely to have amenorrhea after the age of 30 years as CP causes oocyte, granulose cells damage and damage the ovarian medulla blood vessels by increasing immune inflammation response (Emadi *et al.,* 2009; Gürgen *et al.,* 2013; Avci *et al.,* 2017; Xiong *et al.,* 2021). CP not only affects women but also affects men and can cause azoospermia and oligospermia (Hassanpour *et al.,* 2017).

5.4.Chemotherapeutic Agents' Modes Of Action:

There are several types of chemotherapeutic agents classified according to the mode of action of each agent. They are divided into alkylating agents which produce alkyl group that is unstable and leads to disruption of DNA replication (examples: cyclophosphamide, temozolomide and busulfan), antimetabolites which inhibit DNA replication (examples: methotrexate, azacitidine and cladribine), antibiotics that inhibit the synthesis of DNA and RNA (examples: daunomycin, actinomycin D and bleomycin) and antimicrotubular agents that inhibit the synthesis of DNA and RNA (examples: Doxorubicin, paclitaxel and topotecan) (Abotaleb *et al.,* 2018; Amjad *et al.,* 2022; El shinety *et al.,* 2022).

5.6.Mode of Action of CP:

Cyclophosphamide has toxic side effects on both reproductive cells and cancer cells. These cytotoxic effects of CP are due to the chemically reactive metabolites, acrolein and phosphoramide mustard, that cause DNA alkylation through binding to guanine of DNA and disrupt its synthesis and producing crosslink leading to cell death (Emadi *et al.,* 2009; Ahlmann *et al.,* 2016; Avci *et al.,* 2017; Abogresha *et al.,* 2021; Kim *et al.,* 2021). Exposure to CP leads to an increase in the reactive oxygen species (ROS) in oocytes that leads to disturbance in mitochondria and thus disrupts the meiotic spindle (Kim *et al.,* 2021).

Diagnosis of POF:

1.Histopathology

Premature ovarian failure has 2 types depending on the ovarian follicles status, the 1st type (follicular) occurs when the follicles are preserved or trapped inside ovaries, and it is reversible and can be treated. It can be found as very few follicles present or ovarian follicles inflammation (oophoritis) or follicles are present in huge numbers in ovaries and that syndrome is called resistant ovary syndrome (ROS). The 2nd type (afollicular) occurs due to the complete depletion of follicles and that has occurred when germ cells are not found or cannot develop (De Vos *et al.,* 2010; Jankowska, 2017; Sheikhansari *et al.,* 2018).

2.Molecular Diagnostic Marker:

Micro-RNAs (miRNAs) are the best molecular marker for POF diagnosis. miRNAs are non-coding RNA ranging from 18-22 nucleotides, found across the chromosome and can regulate one gene or more even hundreds or thousands at the same time. They have a role in the post-transition silencing of the genes, so it

negatively regulates the genes. Also, they have a role in many processes as apoptosis, differentiation, and proliferation of cells. Furthermore, they are involved in the development of ovarian follicles, the growth of follicles and ovulation (Li *et al.,* 2015; Guo *et al.,* 2017; Tu *et al.,* 2019; Rapani *et al.,* 2021).

2.1.Biogenesis of miRNA:

The miRNAs biogenesis is done through two-step cleavage started in the nucleus. First, primary-miRNA (pri-miRNA) is obtained from the transcription of miRNA genes using RNA polymerase II, then by using Drosha; which is RNAse III endonuclease enzyme; pri-miRNA is changed to precursor miRNA (pre-miRNA) which has hairpin shape, and this pre-miRNA is transported from nucleus to cytoplasm by exportin-5 (EXP 5). The final step is the modification of pre-miRNA to miRNA using Dicer which unfolds the hairpin and gives duplex miRNA. Then by binding to the argonaut protein (AGO), RNA-induced silencing protein complex (RISC) forms the active miRNA form and miRNA starts regulating or inhibiting actions through targeting mRNA transcripts 3'UTR (McGinnis *et al.,* 2015; Tu *et al.,* 2019; Aziz *et al.,*2020; Kumar *et al.,* 2020; Zhao *et al.,*2022).

2.2.Role of miR-146a:

The miR-146a plays a role in regulating the immune mechanisms, it is also participating in cytokines production as tumor necrosis factor alpha (TNF-α). In toll-like-receptor signaling (TLR), miR-146a regulates innate immunity through a negative feedback mechanism (Shahriar *et al.,* 2020). Nuclear factor Kβ (NF-Kβ) is a protein involved in many processes as apoptosis and inflammation, it is regulated by interleukin receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6). The miR-146a controls cell apoptosis through JAK-STAT signaling pathway by targeting TRAF6 and IRAK1 and alters their expressions through negative feedback of NF-Kβ. It interferes with the caspase cascade and activates caspase 8 and caspase 9 which in turn initiates cell apoptosis and activate caspase 3, leading to granulose cell apoptosis. So, it was found that miR-146a is upregulated in the serum or granulose cells in the case of POF, so it can be used as a diagnostic marker for POF (Chen *et al.,* 2015; Cho *et al.,* 2017; Guo *et al.,* 2017; Tu *et al.,* 2019; Rapani *et al.,* 2021).

2.3.Role of miR-23a:

X-linked inhibitor of apoptosis protein (XIAP) has an antiapoptotic function by inhibiting caspase 3 and modulation the pathway of mitochondrial death. XIAP enhances the development of ovarian follicles and granulose cells through its antiapoptotic function. The miR-23a regulates the function of XIAP. In the case of POF patients, miR-23a is found to be upregulated, hence causing down-regulation of XIAP, so increase the cleavage of caspase 3 leading to apoptosis of granulose cells (Yang *et al.,* 2012; Li *et al.,* 2015; Guo *et al.,* 2017; Rapani *et al.,* 2021).

2.4.Role of miR-196a:

It was found in the previous studies that miR-196a is upregulated in the case of POF, it inhibits newborn ovary homeobox (NOBOX) gene expression. mRNA and protein of NOBOX gene that is found in the oocytes during folliculogenesis, so any mutation found in NOBOX gene will be associated with POF (Tripurani *et al.,* 2011; Guo *et al.,* 2017).

2.5.Role of miR-22-3p:

The miR-22-3p was found to be downregulated in the POF case. It is negatively regulating the secretion of FSH; suppresses its secretion and promotes the apoptosis of granulose cells and targets phosphatase and tensin homolog (PTEN) along with estrogen receptor gene (ESR1) and PTEN which are genes candidates for POF. The miR-22-3p leads to down-regulation of mRNA of PTEN, PTEN/AKT pathway enhances the expression of miR-22-3p and it can regulate the pathway by forming a loop in the pathway (Dang *et al.,* 2015; Li *et al.,* 2015; Guo *et al.,* 2017).

2.6.Role of miR-29a:

In the case of POF, miR-29a expression is found to be downregulated. Previous studies showed that miR-29a expression leads to the suppression of PLA2G4A transcription (Kuang *et al.,* 2014; Li *et al.,* 2015; Zhu *et al.,* 2015). PLA2G4A is a gene involved in the development of POF by increasing the concentration of prostaglandin, as it is responsible for prostaglandin biosynthesis. PLA2G4A plays a role as a catalytic enzyme in arachidonic acid (AA) release, which in turn leads to the biosynthesis of prostaglandin. Prostaglandin-endoperoxide synthase 2 (PTGS2) which can be called cyclooxygenase-2 (COX-2), is found in prostaglandin biosynthesis and it is regulated by PLA2G4A. The high concentration of LH can increase the expression of PTGS2 resulting in an increase in PGE_2; which is a prostaglandins' subtype leading to POF (Kuang *et al.,* 2014; Li *et al.,* 2015; Zhu *et al.,* 2015).

Conventional treatments for POF:

There are several treatments for POF such as hormone replacement therapy, *in-vitro* activation, and stem cell therapy. These treatments have problems as hormone replacement therapy is not sufficient to restore ovarian function and increase the risk for coronary heart disease, while the *in-vitro* activation depends on the oocyte age and quality, so it is not beneficial all the time. Stem cell therapy is expensive and takes many steps for isolation, so a new approach should be discovered and used like herbal medicine treatment (Yan *et al.,* 2018; Ghahremani *et al.,* 2020).

The Promising Treatment for POF:

Herbal Treatment:

India and China are the most countries that use herbal medicine in the treatment of diseases, it is considered the best method of treatment used among other methods of treatments in Chinese medicine (*Lin et al.,* 2021).

***1.Moringa oleifera*:**

Origin of *Moringa oleifera*:

Moringa oleifera (MO), a native plant found in northern India, Asia, and Africa, is used as a medicinal herb due to its high medicinal and nutritional value (Abdull *et al.,* 2014; Brilhante *et al.,* 2017). It is also called drumstick tree related to the appearance of its seeds pods before maturation, or horseradish tree because the taste of *Moringa* roots is like the horseradish, or miracle tree due to its high healing properties for different diseases, or ben oil tree or Nebedaye which is in African languages means never die (Abdull *et al.,* 2014; Stohs *et al.,* 2015; Vergara *et al.,* 2017; Zeng *et al.,* 2018; Matic *et al.,* 2018; George *et al.,* 2021).

Properties of *Moringa*:

Moringa belongs to the family Moringaceae which is cultivated in subtropical and tropical countries, it can adapt to different cultivation circumstances as a change in climate ranges from 18^{o}C to 35^{o}C, changes in PH of soil ranges from 5.0 to 9.0, dryness and poor different species, each species cultivated in a specific country. The extract's metabolites can vary depending on different circumstances such as the geographical area for cultivation, soil component, exposure to sun and climate variation (Leone *et al.,* 2015; Gopalakrishnan *et al.,* 2016; Brilhante *et al.,* 2017; Abo-Rhyem, 2018; Mohamed *et al.,* 2021; Farooq *et al.,* 2022). *Moringa* is considered the most famous plant that has multiple uses in different applications and industries such as fertilizers, the food industry, the fuel industry, food for animals and natural products in medicine (Liu *et al.,* 2018).

Medical Uses:

Moringa tree is classified as the most important tree currently because every part of the tree is used in different industries. *Moringa* extract is used to treat anemia as it increases hemoglobin, treating anxiety, and blood impurities. Also, it increases milk production in women and animals and increases the production of meat. The leaves of *Moringa* are used in feeding animals to increase their weight (Anwar *et al.,* 2007; Abo-Rhyem, 2018; Matic *et al.,* 2018; Shousha *et al.,* 2019). Roots are used to decrease the pain of a toothache, edema

treatment, rheumatism treatment and cleaning of wounds. The bark is used for skin infection treatment and treatment of upper respiratory infections. Seeds are used to treat problems of the bladder and prostate and in fever treatment. Flowers are used in diseases of muscles, inflammation treatments, and in hypercholesteremia. *Moringa* gum is used to relieve headache pain (Anwar *et al.,* 2007; Leone *et al.,* 2015; Matic *et al.,* 2018; Mohamed *et al.,* 2021). Besides, previous studies discovered that *Moringa* and usually its ethanolic extracts have anticancer properties against liver cancer and colorectal cancer, this anticancer property is related to the bioactive components hexadecanoicacidethyl ester, isopropyl isothiocyanate and D-allose that are found in the extract (Brilhante *et al.,* 2017; Tiloke *et al.,* 2018). It also has a role in inhibiting pancreatic cancer by targeting the cell cycle leading to the accumulation of cells in the G1 phase, also it regulates the NF-Kβ pathway by its downregulation (Tiloke *et al.,* 2018).

Phytochemistry of *Moringa* leaves:

Moringa leaves are rich in minerals such as magnesium, calcium, iron and zinc, amino acids such as lysine, tryptophan, cysteine and methionine, vitamins such as vitamin C, vitamin E and vitamin A and antioxidant compounds such as carotenoids, flavonoids, phenols and ascorbic acid (Anwar *et al.,* 2007; Leone *et al.,* 2015; Stohs *et al.,* 2015; Vergara *et al.,* 2017; Abo-Rhyem, 2018; Shousha *et al.,* 2019). Leaves of *Moringa* have a high protein percentage in comparison to other leaves of other plants used in nutrition (Oyeyinka et al., 2016; Matic *et al.,* 2018). The highest moisture content is found in the fresh leaves of *Moringa* as they preserve the water content, on the other hand, the dried leaves lost their water content, and they have the highest content of other ingredients (Abo-Rhyem, 2018).

Uses of *Moringa* Leaves:

It can be cooked or eaten as fresh leaves; also, it can be preserved for a long time as a powder without losing its nutritional value. Boiled leaves contain bioavailable iron three times greater than raw leaves. Leaves are used as a food source to compensate for malnutrition in infants and children. Also, it is used to regulate the imbalance of thyroid hormone and used to treat typhoid, hypertension, cardiovascular diseases, and diabetes, used as an anti-inflammatory and anti-microbial agent against gram-positive and gram-negative bacteria (Abdull *et al.,* 2014; Torondel *et al.,* 2014; Leone *et al.,* 2015; Oyeyinka *et al.,* 2016; Brilhante *et al.,* 2017; Abo-Rhyem, 2018; Mohamed *et al.,* 2021). Also, it was found that *Moringa* leaves can protect or decrease the damage to the liver and kidney occurred after using different drugs such as acetaminophen, rifampicin, or gentamicin. It can be used in iron deficiency anemia rather than supplements as it is a rich source of iron (Oyeyinka *et al.,* 2016; Brilhante et al., 2017). One of the flavonoids present in *Moringa* leaves is quercetin which is a strong bioactive element used to decrease the activation of 17 α-hydroxylase, protecting ovaries from dysfunction. Also, *Moringa* leaves to increase the mature oocytes (Amelia *et al.,* 2018; Zeng *et al.,* 2019).

Different uses of *Moringa* seeds:

Moringa seeds are used in cosmetics and hair care products such as conditioners and in skin care as ointments. Also, it is used as a lubricant for machines and in biodiesel. Oil can be extracted from seeds and used in cooking instead of olive oil. After extraction of oil, the remaining seed or the seed cake is used in water purification as it removes heavy metals such as copper, cadmium, lead and chromium from water because seeds act as a coagulating substance for the suspended matters found in water, also it is used as a natural fertilizer to enhance the production of agricultural crops (Anwar *et al.,* 2007; Abdull *et al.,* 2014; Brilhante *et al.,* 2017; Abo-Rhyem, 2018; Matic *et al.,* 2018; George *et al.,* 2021).

Other Benefits of *Moringa*:

Moringa oleifera does not only have medicinal value but is also used in different

industries. It can be used as a spice to enhance food taste and used as flavored tea. *Moringa* leaves contain a growth hormone called zeatin which is a great foliar and is used to enhance the yield of the crops. The gum is used in calico printing (Abo-Rhyem, 2018; Matic *et al.*, 2018).

1.Withania somnifera:

Origin of *Withania somnifera*:

Withania somnifera; is a plant that belongs to the family Solanaceae and is also known as winter cherry, Ashwagandha, *or Indian ginseng.* It is found in tropical and subtropical countries, especially in hot and dry areas. *It grows in South Africa, China, Sri Lanka, Pakistan, and India (*Singh *et al.*, 2011; Mandlik *et al.*, 2020).

Properties of *Withania somnifera*:

*Withania belongs to somnifera species which is a Latin word that means sleep-induce, referring to its anti-stress properties. It is called Indian ginseng because it has pharmacological effects and is used in ginseng tea. The term ashwagandha means horse smell, referring to the characteristic of the root that has the smell of a wet horse (*Singh *et al.*, 2011; Namdeo *et al.*, 2020; Joshi *et al.*, 2021; Paul *et al.*, 2021). *Withania* height ranges from 0.5 - 2 m. It has 23 different species; it grows in a temperature range from 20-38^{o}C. It is widely used in Ayurvedic medicine; which is the Indian traditional system of medicine (Mishra *et al.*, 2000; Singh *et al.*, 2011; Manivannan *et al.*, 2012; Mukherjee *et al.*, 2021; Paul *et al.*, 2021). The effect of its active metabolites can vary according to the extract type, it can be either aqueous extract or alcoholic extract (methanol or ethanol extract) and usually extracted from the stem, leaves, and roots (Dutta *et al.*, 2019).

Phytochemistry of *Withania*:

Active metabolites of *Withania* are saponins with an extra acyl group, alkaloids such as isopelletierine and tropine, steroidal lactones such as withanolides, salts and withanolides glycosides that have glucose on carbon number 27. Also, it is a rich source of iron (Mishra et al., 2000; Dutta et al., 2019). Roots contain amino acids, starch, volatile oils, reducing sugars and steroids (Paul et al., 2021).

Medicinal uses of *Withania*:

Every part of the plant can be used in treating different diseases. Roots can reduce joint inflammations, and ulcers and can be used with other drugs to neutralize the effect of snake venom. Leaves are used in cases of fever and swellings, while flowers are used as a diuretic and astringent (Singh *et al.*, 2011; Paul *et al.*, 2021). Besides, *Withania* has anticancer, antimicrobial, and anti-inflammatory activities, influences gonads as it increases the weight of ovaries by increasing the size of growing follicles and also it increases the count of sperms, also it regulates the hormonal balance of FSH, LH and testosterone hormones. Also, it has an effect on the brain and the nervous system and some of their diseases like anxiety, depression, Parkinson's disease, and Alzheimer's disease (Al-Qarawi *et al.*, 2000; Singh *et al.*, 2011; Nasimi *et al.*, 2018; Mukherjee *et al.*, 2021; Paul *et al.*, 2021). *Withania* can be also used to reduce stress and lower the level of cortisol rather than using medications that have side effects. Stress and anxiety usually occur due to the production of nitric oxide, and *Withania* reduces the production of nitric oxide so decreasing the stress level (Akhgarjand *et al.*, 2022). *Withania* has antioxidant activities and enhances immunity and the defense system against diseases, also it can decrease stress levels (Mukherjee *et al.*, 2021)**.** Recent studies have reported the role of *Withania* in managing the symptoms of COVID-19 as it disrupts the protein's spike electrostatic interaction (Prajapati *et al.*, 2022; Thorat *et al.*, 2022).

2.Curcuma longa:

Origin of *Curcuma longa*:

Turmeric or *Curcuma longa* was first cultivated in India, Asia, China, and America. It belongs to the family *Zingiberaceae (*Nelson *et al.*, 2017; Kotha *et al.*, 2019).

Properties of *Curcuma longa*:

Curcuma longa has hydrophobic characteristics, has a yellowish color so it

can be used as coloring agent in different industries such as textile and food. Also, it is used in food spices and curry preparation (Nelson *et al.,* 2017; Kotha *et al.,* 2019). Its growth and quality can be affected according to geographical and cultivation conditions. It has light sensitivity properties due to the presence of curcumin (Gupta *et al.,* 2013; Kocaadam *et al.,* 2017). Turmeric preservation can be achieved after dehydration by different techniques and by removing moisture from it (Chumroenphat *et al.,* 2020). Its height ranges from 60-90 cm and grows in temperatures ranging from 20-30^{o}C (Singh *et al.,* 2010; Raza *et al.,* 2018).

Phytochemistry of *Curcuma longa*:

Demethoxycurcumin and dis-demethoxycurcumin together with curcumin are the bioactive components of turmeric. These three components together are called curcuminoids. Curcumin is supposed to be the most active component among them as it occupies the biggest volume of turmeric approximately 70%. It also contains proteins, carbohydrates, fats, and minerals (Gupta *et al.,* 2013; Lestari *et al.,* 2014; Kocaadam *et al.,* 2017; Nelson *et al.,*

Medical uses of *Curcuma longa*:

Turmeric has antiviral, antifungal, antibacterial, anti-inflammatory and antioxidant activities, it inhibits NF-κB pro-inflammatory expression and reduces the expression of interleukin-1β cytokine. It has anticancer activity as it can affect apoptosis and metastasis of the cells and it decreases the proliferation of cancer cells (Gupta *et al.,* 2013; Kocaadam *et al.,* 2017; Melekoglu *et al.,* 2018). It has an effect on inhibiting the growth of different types of bacteria such as *H.pylori* and E.coli. It can inhibit the replication of the hepatitis B virus (Gupta *et al.,* 2013). It enhances the status of ovaries as it promotes the proliferation of ovarian cells and reduces the apoptosis of cells; so, it increases the number of follicles. It also regulates the hormonal balance; it decreases FSH levels and elevates E2 levels so have an adverse effect on treating POF. It has a role in uterus purification (Gupta et al., 2013; Yan *et al.,* 2018). It has a good treatment effect in cases of diseases of the liver, heart diseases and respiratory diseases. It is used in case of skin infections or disorders and used to treat acne, used to decrease the level of glucose in the blood. It affects hematuria and reduces it (Kocaadam *et al.,* 2017; Soleimani *et al.,* 2018). The curcumin present in turmeric has an effect on lowering the LDL and the cholesterol level as well as neurological disorders like Alzheimer's disease and can be used in the treatment of depression and stress (Kocaadam *et al.,* 2017; Soleimani *et al.,* 2018). Furthermore, turmeric can be used in case of dental problems and relieve the pain of toothache (Gupta *et al.,* 2013).

Conclusion:

Depending on the aforementioned literature survey it is found that *Moringa oleifera* is the best herbal treatment to use as it has too many uses. It has a promising effect on treating ovarian dysfunction and increases the mature oocyte, also it can protect the ovaries by decreasing the activation of 17 α-hydroxylase which is an enzymatic defect that leads to POF.

Declaration Sections:

Ethical Approval and Consent to Participate:

Experimental protocols and procedures were approved by Cairo University, Institutional Animal Care and Use Committee (CU-IACUC), **CU/I/F/49/21** for animal use in research.

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