



## Review

### A Wonderful Hormone: Estrogen

Dhruvi Soni\*, Nikunj Patadiya

Department of Pharmacy, Shivam Pharmaceutical Studies and Research Center, Valasan, Gujarat, India

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#### ABSTRACT

Hormones play very important role in animal and plants. Estrogen is the hormone which present in male and females both and related to reproductive system of them. Estrogen also related with so many other body functions like Neuro-endocrine system, skeletal system, immune system. It's also related to many pathological conditions like infertility, osteoporosis, obesity, endometriosis and different kind of cancer. In human body two type of estrogen receptors (estrogen receptor alpha and estrogen receptor beta) present which is related to estrogen pharmacological action. Estrogen produces its pharmacological action via binding with DNA but currently its proof it can also produce its action without binding with DNA (non genomic method or indirect binding). Primary site of ER alpha receptor is uterus and pituitary gland and major site of ER beta receptor is granulose cells present in ovary. The studies of estrogen in mouse which proof that primary site of ER alpha is uterus and neuro endocrine system. As female mice lacking ER alpha are infertile due to impaired ovarian defects. The development of effective therapies for estrogen related diseases has relied on an understanding of the physiological roles and mechanistic functionalities of ER alpha and ER beta in various human health and disease.

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\*Corresponding author: Ms. Dhruvi Soni, Final Year B. Pharmacy, Shivam Pharmaceutical Studies and Research Center, Valasan, Gujarat, India. Contact: +91-7990076798, e-mail: [dhruvisoni05556@gmail.com](mailto:dhruvisoni05556@gmail.com)

## Introduction

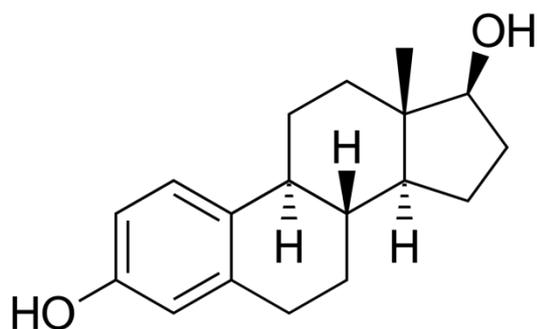
Estrogens are steroidal in nature and primary act as female sex hormones in human body. Estrogens are related with menstruation cycle and development of reproductive organs. Estrogen permeability is very high then they can

easily cross the biological membrane. For estrogen, in body special receptors called estrogen receptors are present and estrogen easily bind with it. When estrogen is bind with receptor, receptors is activated and modulate the expression of many genes and activate rapid

singling (Tripathi KD., 2008). The estrogen receptor antibody is directed against an located on the nucleus of an ER positive normal and neoplastic cells. Estrogen receptor is a ligand activated transcription factor belonging to the family of nuclear hormone receptors. ER protein is present in 50-70% of invasive breast cancers. ER receptor be assessed on all primary breast cancers (Ascenzi P. *et al.*, 2006).

### Classification

**Natural Estrogen-** As shown in name this type of estrogen synthesized in body. Estradiol is major estrogen and it's released by ovary. It's synthesized in graafian follicle, corpus luteum and placenta. Estradiol is synthesized from cholesterol. Estradiol is most potent estrogen. Minor quantity also shows in males which is produce by aromatization of testosterone. Eg. Estradiol, Estriol, Estrone (Tripathi, KD., 2008).



**Fig. 1: Common Structure of Estrogen**

**Synthetic Estrogen-** Naturally occurred estrogens are rapid metabolized in liver and orally inactive. To overcome this problem synthetic moiety produce which actions like estrogen and orally active (Tripathi KD., 2008). Eg. Steroidal - Ethinylestradiol, Mestranol; Non steroidal - Diethylstilbesterol, Hexestrol, Dinestrol.

### Pharmacokinetics

Naturally occurring estrogens are cannot given orally due to rapid hepatic metabolism, synthetic estrogens can give orally. Estrogens are well absorbed orally as well as transdermally. Esters of estradiol can be injected via intramuscular route; they are very slowly absorbed and give prolonged effect in body. Natural estrogens plasma protein binding is very high and majorly

bind with SHBG and albumin almost equally (Hess RA., 2003).

In liver Estrone can convert to estradiol and this action is vice versa. Estrone can freely convert to estriol in liver. Metabolism of all estrogens via conjugation with glucuronic acid and sulphate. Metabolites of estrogen excreted through human body via urine as well as bile. Ethinylestradiol is very slowly metabolized and orally active and potency is very high (Tripathi KD., 2008).

### Type of Receptors

**ER alpha receptor-** ER alpha known as NR3A1 (nuclear receptor, subfamily 3, group A member 1) is one of two main types of estrogen receptor, a nuclear receptor that is activated by the sex hormone estrogen, in humans ER alpha is encoded by the gene ESR1. Generally this receptors are majorly shows at vagina, uterus, blood vessels, hypothalamus and breasts (Ascenzi P. *et al.*, 2006; Couse JF, *et al.*, 1997). **ER beta receptor-** ER beta also known as NR3A2 (nuclear receptor subfamily 3, group membrane 2) is one of two main type of estrogen receptor a nuclear receptor which is activated by the sex hormones estrogen In human, ER beta is encoded by the ESR2 gene. Major site of these receptors is ovaries (female) and prostate gland (male) (Ascenzi P., 2006).

### Mechanism of Action

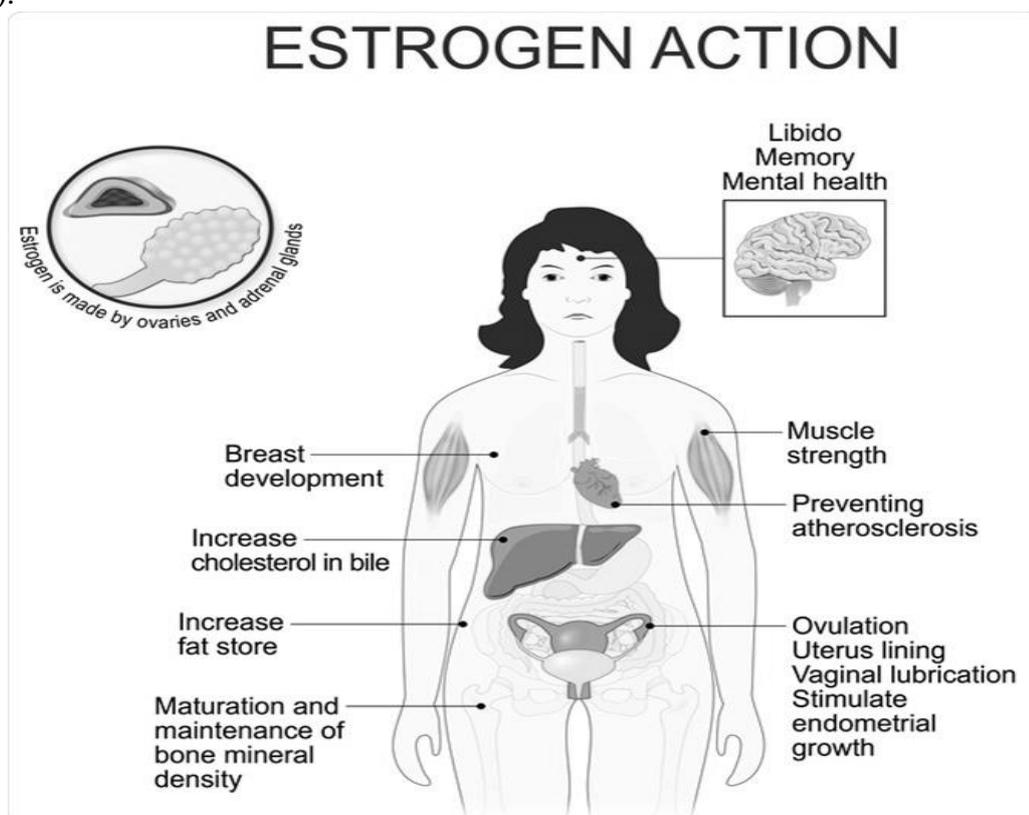
Estrogen receptors are distributed in female reproductive organs, pituitary gland, breasts, blood vessels, bones, and liver, central nervous system, heart and breast carcinoma cells. Estrogen receptors are similar to steroidal receptors. When agonist molecule bind to ligand binding domain cause dimerization of receptor. Its interact with 'estrogen response elements' (EREs) of target genes. Co activator proteins promote gene transcription (Tripathi KD., 2008). When antagonist binds, it interacts with co-repressor proteins which inhibiting gene transcription. Estradiol affinity for ER $\alpha$  and ER $\beta$  is same, but some ligand has different affinity. ER $\alpha$  and ER $\beta$  have different style to interaction with co-repressor and co activators. Non-genomic action of estrogens is also done through

same estrogen receptors (Couse JF, *et al.*, 1997; Nilsson S, 2001).

### Pharmacological Actions

1. On reproductive organs: Estrogen is responsible hormone for pubertal changes in females. Common changes are growth of vagina, fallopian tubes and uterus. Epithelium layer of vagina get thickened, cornified and stratified. In preovulatory phase estrogen cause endometrium proliferation. Estrogen alone can produce menstruation in absence of progesterone (Hess RA., 2003).

Only estrogen (without progesterone) gives to women, menstruation delayed but bleeding occur at specific intervals. Estrogen cannot suppress or stop bleeding at any dose. Estrogen increase uterus and fallopian tubes rhythmic contractions and cause secretion of watery alkaline solution, this secretion became sperm penetration comfortable. After menopause in female reproductive tract shows atrophic changes in condition of estrogen deficiency (Tripathi KD., 2008).



**Fig.2: Effects of Estrogen in Human**

2. Secondary sex characters: At puberty, estrogen produce many notable changes in female like, breast growth, in breast proliferation of ducts and stroma and fat accumulation. Estrogen promotes axillary and pubic hair growth, feminine body contours and effect on behavior. Acne is very common at this stage (Tripathi KD., 2008).

3. Metabolic effects: action of estrogen is anabolic like testosterone but in metabolism it is comparatively weaker. Epiphyses fusion promote by estrogen. Estrogen slows retarding bone resorption so it's very important to maintain bone mass. Estrogen inhibits formation of osteoclast

pit which result is increased bone matrix proteins (osteocalcin, osteonectin, alkaline phosphate and collagen) expression. Estrogen promotes positive calcium balance. (Tripathi KD., 2008; Hess RA., 2003)

4. Other effects: Normal dose of estrogen causes water retention and edema occurs in some patients. Blood pressure raised in many patients after prolong used. Estrogen increased high density lipids and triglycerides level in plasma and decreased low density lipids and cholesterol level in plasma which beneficial effect for human body. Estrogen also raised HDL: LDL ratio.

Ability of blood coagulation is increased by estrogen due to accelerate synthesis of coagulation factor (II, VII, IX, X). Increase plasma fibrinolytic properties due to estrogen. Estrogen increased secretion of cholesterol and reduce secretion of bile salt, so lithogenicity of bile is increased. Estrogen increased level of sex hormone binding globulin (SHBG), cortisol binding globulin (CBG) and thyroxin binding globulin (TBG), but no change in hormonal status. Estrogen precursor nitric oxide (NO) synthesis in vascular endothelium which promote vasodilatation at site (Tripathi KD., 2008; Hess RA., 2003).

### Causes of Low Estrogen

There are three main causes for low estrogen as shown in table 1.

**Table 1: Causes of Low Estrogen**

|                |  |
|----------------|--|
| <b>Natural</b> | Menopause. Premenopausal women can also suffer from it.              |
| <b>Induce</b>  | Hysterectomies and radiation treatments.                             |
| <b>Special</b> | Anorexia, genetic diseases, thyroid problem and inadequate body fat. |

Apart from above main three causes other some are,

Excessive exercise- The sports include Gymnastics, figure, skating and ballet distance running, diving and swimming.

Fat and calorie restriction- Low levels of circulating estrogen will halt the normal menstrual cycle in actively cycling women and may prevent the onset of first menstrual bleed in younger, preteen or teenage women (Hess RA., 2003).

Genetics and toxins- A women can have genetic reasons why her ovaries make insufficient levels of estrogen. A genetic condition known as Turner syndrome, which prevents the ovaries from developing normally, can lead to a delay of menstruation. In this genetic condition, altered genes determine internal and external sexual characteristics.

### Symptoms of Low Estrogen

Estrogen is responsible for the sexual development of girls when they reach puberty. Controls the growth of the uterine lining during

the menstrual cycle and at the beginning of a pregnancy causes breast changes in teenagers and women are who pregnancy is involved in bone and cholesterol metabolism regulates food intake, body weight, glucose metabolism, and insulin sensitivity (Hess RA., 2003).

### Common symptoms

- Painful sex due to lack of vaginal lubrication.
- An increase in urinary tract infections due to a thinning of the urethra.
- Irregular or absent periods
- Mood swings
- Hot flushes
- Breast tenderness
- Headaches or accentuation of pre-existing migraines.
- Depression
- Trouble concentrating
- Fatigue

### High Level Estrogen Symptoms

- Bloating
- Swelling and tenderness in the breasts
- Decreased sex drive
- Irregular menstrual periods
- Headaches
- Mood swings
- Fibrocystic developments in the breast
- Weight gain
- Hair loss
- Cold hands or feet
- Feeling tired or lacking energy.
- Difficulty with memory.
- Trouble sleeping
- Increased symptoms of premenstrual syndrome or PMS

### Therapeutic Uses

1. Contraception- Estrogen is widely use for contraception with progestin in different dosage form. Mostly ethinyl estradiol is use for this purpose. This combination is inhibit FSH, LH and shows anti-ovulatory effect and its contraceptive efficacy is very high.

2. Hormone replacement therapy- Estrogen + Progestin HRT or 'Menopausal hormone therapy' is very useful treatment for postmenopausal women and very much beneficial in condition of vasomotor instability,

atrophic changes, mood disturbance, and many more problems related to menopause. Estrogen amount for this purpose is 0.625 mg/day which is less than contraceptive purpose.

Estrogen alone use in hysterectomised women, also alone use when progestin is not tolerated or is contraindicated. When estradiol given via transdermal route is have many advantages, so mostly preferred this.

### 3. Dysmenorrhoea-

First line drugs is prostaglandin synthesis inhibitor but estrogen cyclic therapy is also use. Estrogen inhibits ovulation and decreasing prostaglandin synthesis in endometrium.

### 4. Senile vaginitis-

Estrogen is very useful for this purpose. It can change vaginal cytology to premenopausal pattern. It is use with antibiotic in combination for this purpose. Generally topical preparations are more use than oral preparations.

### 5. Delayed puberty in girls-

It may be due to Turner's syndrome (Ovarian agenesis) or hypopituitarism. In both case estrogen given to patient with small amount of androgens. Cyclic treatment given, treatment start with small dose and increased dose gradually until reaches to full replacement dose.

### 6. Acne-

Acne is very common show in girls and boy at puberty due to more androgen secretion. Theoretically estrogen is useful in this condition by inhibiting Gn release from pituitary gland. This treatment not use for boys and for girl's only topical application with antimicrobial agents and tretinoin is preferred. Treatment patent is cyclic (Tripathi KD., 2008)

### Adverse Effect (Tripathi KD., 2008)

#### Serious side effects

- Overdose of estrogen preparation can cause leg vein thrombosis and pulmonary thrombosis.
- coronary thrombosis
- cerebral thrombosis
- Estrogen can cause irregular bleeding in postmenopausal women.
- Increased Blood pressure
- Estrogen can increased high density lipids (HDL)/ Low density lipids (LDL) ratio.

-Increased risk of vaginal cancer, cervical cancer, and breast cancer.

-Estrogen increased excretion of biliary cholesterol.

- Suppression of libido.

- Suppression of gynaecomastia

- Feminization developed when it gives to man.

-Fusion of epiphyses and reduction of adult stature when it gives to children's.

#### Non- serious side effects

-Nausea and vomiting which is similar to morning sickness in pregnancy.

- Mild headache is shown and sometimes migraine observed.

-Breast discomfort

#### Side effects that appear later

-Weight gain

-Acne

-Increased body hair

-Pigmentation of nose, cheeks and forehead (chloasma).

-Pruritus vulvae are infrequent.

-Mood swing or mood disturbance.

-abdominal distention

-Estrogen increased risk of endometrial carcinoma

- In very rare case, Estrogen increased risk of epilepsy.

### Conclusion

After the study all articles and available information, we conclude that,

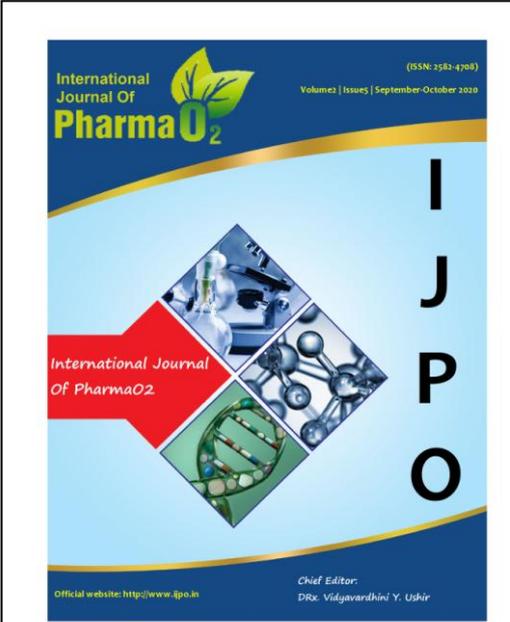
Estrogen is very much important hormone which plays different roles in human body. Without estrogen females cannot be imagine, its give feminine to females. It's also shown in men also but in very low amount. Lower level or higher level of estrogens can causes different pathogenic condition in humans, so its level in body is very important. Estrogens can imagine for treatment for the condition like hormone replacement therapy (HRT), acne, and other problems but it's only and widely use for contraception. Due to its magical action we can say estrogen is wonderful hormone.

### Conflict of Interest

The authors declare no conflict of interest.

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