The study of sex steroid hormone compound in green algae (Chlorophyta) for female fertility: A literature review

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Abstract. Reproductive organ cell damage due to oxidants can cause problems in female fertility, this situation can be prevented and overcome by consuming antioxidants such as algae. Green algae Chlorophyta also contains a steroid that is thought to be useful for normal reproductive health in women. The purpose of this study was to determine the compounds of sex steroid hormones in green algae which are important for female fertility. The systematic review method was used in this study. Based on the results of studies, it shows that green algae contain sterols which through biochemical mechanisms will form sex steroid hormones in the target organ. These hormones play an important role in the regulation of the female reproductive system and the balance of these hormones is crucial for normal fertility in women. Based on this, women should be able to maintain their reproductive health well by consuming foods that contain lots of vitamins and natural fibers that are good for the body such as green algae. Women must also be able to maintain a healthy lifestyle, change bad lifestyles, and avoid environmental risk factors that can cause infertility.

Keywords: female fertility, green algae, healthy lifestyle, sex steroid hormone

1. Introduction

Impaired function and reproductive organs in women can cause serious problems in female fertility that can lead to infertility. Infertility in women can be caused by several factors, one of which is environmental factors like unhealthy lifestyle factors. Lifestyle and reproductive health are ways to control a woman's fertility. There are several other factors such as psychological stress, caffeine consumption, alcohol consumption and exposure to environmental pollutants that have been implicated in influencing women's reproductive health [1]. The previous study states that the risk factors for infertility are due to the influence of environmental exposure including heat, radiation including chemicals, and pesticides [2]. This gives the impression that harmful substances are oxidants or free radicals because they are the cause of oxidative stress. Free radicals are elements that can cause damage to cells, tissues and organs in the body or cause oxidative stress [3], including those that can occur in the female reproductive system, which ultimately results in disruption of normal female fertility.

Therapy for this female fertility problem is based on the causative factors either through pharmacological therapy, hormones or surgery [4]. One of the therapies for infertility that is still rarely used is a therapy that uses natural elements such as marine plants like marine algae. Algae consist of green algae (Chlorophyta), red (Rhodophyta) and brown algae (Phaeophyta), especially green algae are the most abundant algae found in shallow waters [5]. All types of algae contain antioxidant
compounds such as polyphenolic compounds, alkaloids, tannins, flavonoids and vitamins and minerals [6], which can prevent or inhibit cell damage from the effects of free radicals, where these antioxidant compounds are able to protect organ cells in the human body, and improve the function of cell organs [7], including the female reproductive organs which were initially damaged by exposure to oxidants.

The content contained in green algae in addition to being an antioxidant compound is also known to contain sterol or steroid elements [8]. The green algae extract had a fairly high antioxidant content and the phytochemical test found steroid-type sterols [9]. The steroid content contained in green algae can form hormones that play a role in female reproduction so that it can cause balanced hormonal regulation and the function of the female reproductive system can run optimally. Therefore, algae can be used as an alternative therapy made from herbs to overcome the toxic effects of free radicals that cause infertility in women as a result of disruption of hormonal regulation of the reproductive system. The purpose of this research is to study and find out more about the sex steroid hormone compounds of green algae for therapy for cases of infertility in women. Therefore, this fertility problem can be treated and even prevented, which has been studied through various previous expert studies.

2. Method

This research method uses a systematic review, with PRISMA (Preferred reporting items for systematic review 2020) flow diagram guidelines. The data obtained from previous studies were then analyzed descriptively regarding the contents of articles related to the effect of steroid content in marine algae Chlorophyta division for reproductive health and female fertility. The data used in this study were obtained through databases or secondary data through PubMed, Scopus, Google Scholar and Scient Direct were taken from 2010-2019. The journal inclusion criteria set by the researcher are open access journals and registered publications, providing full text and can be downloaded, in Indonesian and or English, reporting on the content in green algae. The data obtained through the database is then analyzed and concluded.

3. Results and Discussion

From the results of journal searches that the author did through databases and articles and reports that have been registered online. The author can identify as many as 13 journals that match the research or inclusion criteria determined by the previous author; these journals will be analyzed into journal reviews. The sterol content of various types of green algae has also been analyzed, which is presented in the table 1.
Table 1. Identification of green algae (Chlorophyta).

| Ref | Algae sp.                | Assay                     | Sample                          | Sterol compounds                                      | Advantage                                                                 |
|-----|-------------------------|---------------------------|---------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------|
| [10] | Ulva lactuca L          | Invivo/ELISA              | *Rattus norvegicus* (12 weeks)  | Steroid (testosterone hormone)                         | Gonadal growth and development and fertility                              |
| [11] | Chlorella vulgaris      | Invivo/ELISA              | Male and female Rabbits         | Steroid (hormone estrogen, testosterone)               | Increased male fertility through increased seminal fluid volume and female fertility |
| [12] | Chlorella vulgaris plate| Invivo/ biochemistry hormone | Wistar albino female           | Steroid (hormone estrogen) and gonadotropin (LH and FSH) | Repair of damaged ovarian cells due to the influence of chemicals          |
| [13] | Chlamydomonas reinhardtii | GC-MS (Gas Chromatograph y-mass spectrometry) | Pellets Alga cell          | Ergosterol, 7-dehydroporiferasterol | Role in hormone biosynthesis                                               |
| [14] | Ulva australis          | Invitro/phytochemical     | Human recombinance              | Ethylcholesterol, isofucoterol,                        | Inhibits decreased enzyme activity that hold metabolic functions in the body which decline due to age, lifestyle and diet and exposure to environmental pollutants |
| [15] | Scenedesmus quadricauda & Chlamydomonas globosa | Invivo/ GC-MS (algae culture) | Zooplankton                     | Fungisterol, Chondrillasterol, 22-dihydrochondrillasterol | Reproductive growth; increased proliferation and differentiation of reproductive organs towards maturity |
| [16] | Dunaliella salina       | Invivo/ blood biochemistry | Goat                            | Steroid hormone (progesterone, estrogen, LH dan FSH)   | Role in ovarian activities such as the reproductive cycle and the estrus cycle |
| [17] | Ulva prolifera          | GC-MS                     | algal sediment                  | cholesterol, stigmasterol, β-sitosterol, fucosterol, 28-isofucosterol | Steroid hormone biosynthesis                                               |
| [18] | Prasiola crispa         | Invivo/ phytochemical-combined with HPC | Nauphoeta cinerea cockroaches | phytosterols                                           | Neurotransmission for the inner steroidal molecules                       |
| [19] | Spirogyra               | Invivo/ anti-inflammatory activities | Algae culture & Rats            | Sterol-enriched fraction                              | Reduction of reactive oxygen species (ROS) generation, cell death, and production of NO |
| [20] | Ulva clathrata          | Invivo/ GC/LS, histopathology and histochemical | Shrimp (Litopenaeus vannamei) | fucosterol and isofucosterol                          | Oocyte maturation, increasing transport of fatty acid during vitellogenesis, impacting the reproductive performance of shrimp |
| [21] | Chlorella vulgaris      | GC/LS                     | Pure alga culture               | steroid bioactive components                          | Supplements and natural medicinal sources                                 |
| [22] | Spirulina Arthrospira platensis sp. | Invivo | Female albino wistar rats       | -                                                   | Antioxidant for ovary, algae effective in protecting the harmful chemical agents that are exposed to tissues or reproductive organ, like as ovarian follicle in female |
Based on table 1 showed that several species of green algae which were studied based on the literature had sterol bioactive content as well as the form of steroid biosynthesis. Sterols and steroids produced by green algae species show good benefits for the health of reproductive organs and fertility from the research samples used.

3.1. The compounds of antioxidants in green algae (Chlorophyta)

The phytochemical analysis results showed that the green algae *Halimeda opuntia* sp. contained alkaloids, steroids, saponins, flavonoids, phenols, and tannins [23]. This active compound is thought to play a role in producing antioxidant activity. These active components are thought to have antioxidant activity in preventing oxidative stress because antioxidant enzymes function to protect cells and tissues from oxidative damage. According to [24], the class of flavonoid compounds, phenolic acids, tannins, and lignans belongs to the natural antioxidant group. Microalgae *Chlorella vulgaris* species contain phenolic compounds, tannins, flavonoids, cardiac glycosides, saponins and terpenoids [25]. Flavonoids can act as antioxidants by trapping free radicals. The antioxidant activity of most flavonoids is contributed by the phenolic hydroxyl group in its molecular structure and also through its scavenging power against free radicals, as well as its activity as a metal binder.

Previous research reported that green algae showed high antioxidant activity with an IC50 value of 6.17±0.10 mg mL⁻¹ [25]. The extract of the *Dictyosphaeria cavernosa* had antioxidant activity [26]. The effect of *Spirulina* as an antioxidant for the ovaries, which increases the SOD (superoxide dismutase) levels in the rat ovary, suggesting that it may be effective in protecting the harmful chemical agents (cyclophosphamide) that are exposed to tissues or reproductive organs in female for fertility [22].

3.2. The compounds of sterols in green algae (Chlorophyta)

Sterols in marine algae are the main source of many types of sterols found in the marine environment [27]. Sterols, also known as steroid alcohols, are a class of chemicals that play an important role in the body. The well-known human sterol is cholesterol, which serves as the precursor for steroid hormones and fat-soluble vitamins [28]. In addition to sterols in algae, found that marine algae contain a steroid fraction [29,30]. The green macroalgae (*Ulva sp, Enteromorpha sp, Chaulerphasp, Codium sp, Halimedasp*), contain secondary metabolites such as terpenoids and steroids [31]. The results of phytochemical tests, especially on *Ulva lactuca* species positive contain steroids and saponins and show that green algae contain natural sterols [32,33].

Based on the results of studies, it is known that *Chlorophyta* in several species like *Chlorella sp* contain various types of sterols and steroids and have many benefits such as a source of functional foods, nutraceuticals, and food supplements [34]. The role of algae in the reproductive system is based on both the content of sterols they have and steroids directly. Types of sterol algae such as cholesterol will undergo a biochemical process to form steroid derivative compounds in the process of steroid formation, namely steroidogenesis [13]. Therefore, green algae can be used as a source of therapy for female fertility problems and can be consumed directly or used as a basic ingredient for supplements. The *Chlorella vulgaris* has steroidal bioactive components that can be used as food supplements or sources of natural medicine [21]. The *Scenedesmus, Chlamydomonas* contain phytosterols; ergosterol & 7-dehydroporiferasterol which are useful as ingredients for good nutrition and can improve the quality of food [28]. Based on this, it shows that green algae can be used widely by the community because it has various benefits. *Spirulina* for sterol activity was not observed, only its antioxidant activity was observed, it had a similar effect as on sterols, namely for the development of female reproductive organs, especially development of ovarian follicles through antioxidant pathways that fight against toxicity in the ovaries for the normal fertility in women [22].

3.3. Formation of sex steroid hormones from algae sterols (biochemical hormones)

Cholesterol compounds are components of brain and nerve cells and form important steroids such as bile acids, folic acid, adrenal cortex hormones (androgens, estrogens, progesterone), and
vitamin D precursors [35,36]. The adrenal cortex hormone is useful for the survival of cells and tissues of the reproductive organs, especially in women. Steroidogenesis requires the process by which cholesterol is converted into biologically active steroid hormones, synthesis occurring in the steroidogenic glands (i.e., adrenal glands, gonads, and placenta) [37]. The end products of the synthesis of these steroid hormones are estradiol (a most potent estrogen) and testosterone. The estradiol hormone can also be produced through the aromatization process of the testosterone hormone with the help of enzymes that occur in the female reproductive organs of the ovaries [38,39].

The ovaries are the site of the synthesis of sex steroid hormones, which occur in theca and granulosa cells of the ovarian organ. In granulosa cells, there is a synthesis of cholesterol to form pregnenolone, progesterone, androstenedione and testosterone, and in theca cells, there is a synthesis of hormones from progesterone, androstenedione, testosterone is aromatized into 17β-estradiol and estrone [40], therefore green algae are known to have sex steroid hormone compounds which are the result of the synthesis of cholesterol [41]. Experimental studies on experimental animals proved that administration extract of *Ulva lactuca* species in young mice caused growth and development of the gonads and normal fertility [10]. *Ulva lactuca* is known to have a steroid compound in the form of 17β-estradiol and estrone [38,39]. Another study proved that the administration of *Chlorella vulgaris* species in rabbits caused an increase in fertility for both males and females [11]. This proves that the provision of green algae containing elements of sex steroid hormones can be beneficial for fertility [41].

The bioactive compounds of algae such as fucosterol and isofucosterol, which are types of sterols, function in oocyte maturation, increases fatty acid transport which is useful during the vitellogenesis process during the menstrual cycle and affects the reproduction process of experimental animals [20]. The phytosterols in green algae that function as neurotransmission in steroidal molecules, which are important for the synthesis of the necessary steroid hormones [18]. This shows that the content in green algae is very important for the continuity of the female reproductive system.

3.4. The benefits of sex steroid hormones in green algae for female fertility

Normal fertility in women is largely determined by the regulation of the hormonal system of the sex steroid hormones. The hormones are important for ovarian follicle maturation, cell proliferation in the endometrial wall and normal fertility in women, these hormone levels must be optimal to achieve optimal reproductive function [42]. The optimal reproductive function is characterized by the reproductive cycle and or the menstrual cycle of a woman who is in normal and regular conditions. The formation of sex steroid hormones derived from sterols contained in green algae can be useful for the normal course of the reproductive system, especially in a woman. Sex steroid hormones are secreted by the gonads or ovaries which are controlled by the hypothalamus, a gland located in the brain. The hypothalamus forms with the pituitary and the ovary called the HPO axis (hypothalamus, pituitary, ovary) [43].

The hypothalamus secretes GnRH (Gonadotropin Releasing Hormone) and stimulates the anterior pituitary gland to secrete gonadotropin hormones, namely luteinizing hormone (LH) and Follicle stimulating hormone (FSH) [44]. In women during ovulation, LH will be stimulating the ovary to produce estrogen and progesterone. FSH plays a role in stimulating the development of ovarian follicles and together with LH will stimulate estrogen and ovarian secretion. The secretion of LH and FSH is controlled by GnRH which is the control center for basal gonadotropins, ovulation time and puberty onset in each individual. Therefore, the HPO axis is a hormonal system that regulates follicular maturation, ovulation and the menstrual cycle. If the HPO axis and other hormones are disturbed, it can affect the regularity of the menstrual cycle and the normal function of the female reproductive cycle will also be disrupted [45], therefore the importance of the influence of sex steroid hormones for hormonal regulation during the female reproductive cycle.

Sex steroid hormones such as estradiol, are used as a diagnosis to determine the mechanism of the HPO axis, menopause and monitoring fertility treatment. Estrogen is responsible for the metabolic, behavioral, and morphological changes that occur during the various phases of reproduction. Estrogen
affects cell proliferation and differentiation, development and activity of tissues that participate in reproduction [46]. While the other steroid hormone is progesterone which is the main steroid in the corpus luteum [47]. Estrogen and progesterone play an important role in the regulation of female sex hormones. Progesterone plays a role in the reproductive organs including the mammary glands and the endometrium. Another target organ of progesterone is the uterus, where it aids in implantation of the ovum if fertilization occurs. During pregnancy, progesterone maintains the placenta, inhibits uterine contractility, and prepares the mother for lactation. Testosterone or androgens are the dominant sex steroid hormones in men, but in the female reproductive organs, the ovaries also secrete small amounts of testosterone, and most of it will be converted into estradiol [47].

4. Conclusion

Based on the results of studies in several journals, it shows that green algae (Chlorophyta), besides containing antioxidant compounds that are useful for repairing damaged cells, also contain sterols, namely cholesterol that is good for the body. Cholesterol in the reproductive organs is the main precursor in the synthesis of steroid hormones that play an important role in hormonal regulation in the reproductive system of both men and women, especially in women, directly or indirectly, the content in green algae can function to maintain female fertility in normal function and can be used as an alternative therapy for women who experience fertility problems. Therefore, for the next research, green algae can be used as the main ingredient for the manufacture of dietary supplements that are especially useful for women's reproductive health.

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