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Therapeutic Effects of Garlic (*Allium Sativum*) Compounds from Different Pretreatment Processes on Women's Reproductive Health: A Narrative Review

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Abstract

Women's reproductive health disorders occur due to oxidative stress and can be treated with antioxidant intake. One of them is by utilizing the phytochemical content of garlic (Allium sativum). The semi-systematic review method helps authors to identify the pretreatment of garlic compound S-allyl cysteine (SAC) on women's reproductive health. The literature collection was adjusted to the study of the treatment of garlic compounds with search keywords used "Garlic", "Reproductive health", "S-allyl cysteine", and "Women". The sources used come from online publications from 2010 to 2024. The form of research in the literature review was carried out on test animals, test cells, and test treatments on humans. The selection of information in the reviewed article refers to the year of publication, test products, sample objects, research methods, results, and discussion. The interpretation of the results will be explained descriptively based on the review analysis. Ten study articles have a positive effect of garlic compounds on women's reproductive health. The pretreatment carried out was garlic extract, garlic powder, hexane extract of aged black garlic, dried garlic powder, and aged garlic (black) extract. This review shows that garlic has a main compound S-allyl cysteine (SAC). The bioactive components of garlic can stimulate antioxidant activity and increase the fertility of reproductive organs because it increases the metabolism of oocytes, hormonal regulation, and the maturation of the endometrium. The results of garlic pretreatment showed that aged garlic (black garlic) extract contained S-allyl cysteine (SAC) with more compounds, was more stable, soluble in water, and had minimal toxic content. It allows black garlic (SAC) to have prophylactic properties at the clinical level, so it is possible to develop research on black garlic's effects on women's reproductive health.

Keywords: Garlic, Reproductive Health, S-allyl cysteine, Women.

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1. INTRODUCTION

Women's reproductive health overall health condition includes physical, mental, and social life related to reproductive tools, functions, and processes functions and processes (Akbar, et al., 2021). Problems in reproductive health are a challenge that has a significant impact on life. The women's reproductive system is a complex organ system and plays a vital role in the reproductive process (Jafari, et al., 2023). Reproductive health disorders are often caused by oxidative stress, such as oocyte maturation disorders, ovarian steroidogenesis, ovulation, blastocyst formation and luteal maintenance in pregnancy. Regeneration from the menstrual cycle can also be disrupted due to low estrogen in the body, leading to implantation disorders (Ajiningrum, et al., 2020). Oxidative stress can be prevented and reduced by adding adequate and optimal antioxidant intake in the body. Antioxidants can inhibit or prevent the oxidation process in substrates by binding to free radicals and reactive molecules (Yoga and Komalasari, 2022). Naturally, antioxidants are formed in the body due to the physiological process of the emergence of free radicals called prooxidants balanced with endogenous defence. In certain circumstances, prooxidants and antioxidants will be in balance, and if there is an imbalance, oxidative stress conditions will be formed (Yusliani, 2018).

Garlic (*Allium sativum*) is the main ingredient that contains many phytochemicals. Several bioactive molecules have an essential role in maintaining human physiology and have the potential to reduce various diseases. Based on scientific research, garlic contains 65% water, 30% carbohydrates, and 5% other bioactive groups, especially sulfur-containing compounds (Suleria, et al., 2012). Therefore, Garlic is one of the herbal plants that is the prima donna in the health sector. The most beneficial benefits of garlic are its antioxidant, antimutagenic, antiproliferative, antimicrobial or immunomodulatory properties (Krumm, et al., 2012). Apart from being a therapeutic ingredient, organosulfur and phenolic compounds acting as antioxidants in garlic are important role holders in preventing cell and organ damage from oxidation (Prasonto, et al., 2017). Garlic contains γ-glutamyl-S-allylcysteine, which can be hydrolyzed and oxidised to form alliin. Alliin will be converted to allicin by the alliinase enzyme after crushing, cutting, chewing or heating. Warming causes the change of GSAC (γ-Glutamyl-S-allyl cysteine) to SAC (S-allyl cysteine) (Azhar and Yuliawati, 2021).

Meanwhile, as an antimicrobial, garlic significantly prevents various diseases, ranging from organ infections to heart disorders. Adding garlic powder to the treatment showed an increase in the hormone progesterone. Progesterone and oestradiol are hormones that control sexual and reproductive maturity (Hagag, et al., 2023). In addition, garlic extract (allicin) has been shown to increase the secretion of gonadotropins and hormones produced by the ovaries by activating the pituitary gland (Hajiuon, 2014).

Some studies show that garlic can be a beneficial compound in health. However, reviews regarding the use of garlic in women's reproductive health are still rare. Therefore, this review summarises and describes how the therapeutic effects of several garlic compounds (Allium sativum) produced from various garlic pretreatment processes for women's reproductive health. Thus, it can provide a broader picture of the use of garlic on women's reproductive health and can be developed in further research.

2. RESEARCH METHOD

The research method used in this study is the semi-systematic literature review method. However, this method could be a good map of theoretical approaches or themes and help identify knowledge gaps within the literature (Snyder, 2019). Data Collection This review article carried out a literature search for relevant studies on the effect of garlic compound extract on women's reproductive health with search keywords used “Garlic”, “Reproductive health”, “*S-allyl cysteine*”, and “Women”. The literature was found in national and international

journals and published in 2010-2024. The data search was carried out using an online platform. When writing this review article, the primary references were cited from trusted sources such as Google Scholar, Scopus, PubMed, and Science Direct. This study was chosen because an analysis was carried out on garlic's therapeutic effect on women's reproductive health in the form of research on test animals, test cells, and test treatments on humans. Total articles were selected ten articles from 1.039 articles. The selection of information in the reviewed article refers to the year of publication, test products, sample objects, research methods, results, and discussion. The interpretation of results is carried out descriptively based on the analysis of the review results (Jafari, et al., 2023).

3. RESULTS AND DISCUSSION

Semi-systematic reviews are conducted to provide a description and evaluate existing research. The study results are from a review and analysis of several studies regarding the therapeutic effects of garlic compounds (*Allium sativum*) from the difference in pretreatment on women's reproductive health. This semi-systematic review shows that garlic contains several compounds that have a role in the female reproductive system—a total of 10 research articles that meet the desired characteristics of review articles according to the method. An overview of the characteristics of the study can be seen in Table 1.

Table 1. Characteristics of included research in the review research

Author (Year)	Product Treatment	Component of the Research Method	Outcome
Kim, et al (2013)	Hexane extract of aged black garlic (raw garlic incubating at 75 dC and 70% relative humidity for two weeks)	• The type of research design is a clinical research study • Human Endometrial Stromal Cells (HESCs) from endometriotic tissue were obtained from 18 women (aged 25-45 years) with advanced endometriosis. • 5 types doses of HEABG (1, 10, 30, 50,70 µg/ml) • Statistical analysis using a two-tailed student's test	Hexane extract of black garlic inhibits the TNF-α-induced proliferation and cell cycle progression of HESCs by suppressing ERK/MAPK and JNK/MAPK activation. it is indicated that HEABG is effective in the prevention and treatment of endometriosis in humans
Amirsalari, et al (2021)	Supplement form dried powder garlic 400 mg (1100 µg of allicin	• The present study was a randomized placebo-controlled triple-blind clinical trial • 60 patients were aged between 20 and 45 years, being currently married, not being diagnosed	Garlic extract can reduce pelvic and back pain, dysmenorrhea, and dyspareunia, which are important symptoms of endometriosis.

Author (Year)	Product Treatment	Component of the Research Method	Outcome
		with severe physical or mental illness. • Doses of each tablet contain 400 mg of dried garlic powder (1100 μg of allicin). Each group received by garlic tablet per day. • Statistical analysis in pain scores using normality Kolmogorov–Smirnov test, plotting on histograms, and examining skewness. Between groups are measured by ANOVA and ANCOVA.	
Falahatian, et al (2022)	Residu 10 (R 10) from fraction garlic. It contains supernatants and is purified from the Amicon ultrafiltration system	• The type of research design is a clinical research study • 60 female Mice at eight weeks old and 25-30 gram weight, and divided into 5 groups • Treatment was performed by intraperitoneal injection with 20 mg/kg doses • Statistical analysis used by one-way ANOVA test with post hoc Tukey's test	R 10 fraction showed that hormone levels increased, altering the polarizing activity of T cells and increasing IL-4, lowering IL-7 and increasing IFN γ in PCOS patients
Minami, et al (2020)	Garlic powder was extracted in 25 ml of methanol and centrifuged. The supernatant was filtered (*S-allyl*	• The type of research design is a clinical research study • 33 female Wistar rats ten weeks old	garlic extract with S-allyl cysteine showed that it improved neurological symptoms due to ovariectomized in rats that caused menopause without the

Author (Year)	Product Treatment	Component of the Research Method	Outcome
	cysteine and *cycloalliin)*	• Doses of garlic powder is 0.5% (w/w) • Statistical analysis using one-way ANOVA followed by Newman-Keuls multiple comparison test	risk of developing cancer cells due to ERα activation.
Wang, et al (2021)	*S-allyl cysteine* (SAC) extracted from aged garlic	• The type of research design is a clinical research study • Bovine mammary epithelial cell lines (BMECs) were cultured into six-well culture plates for each experiment with modified treatment • Concentration of SAC divided into 8 groups (0, 5, 10, 25, 50, 100, 150 and 200 μM) • Statistical analysis by one-way ANOVA using GraphPad Prism 8.0.1	SAC could protect BMECs from heat stress-induced injury by mediating the pathway, suggesting that SAC could be considered a therapeutic drug for attenuating heat stress-induced Nrf2/HO-1 signalling mammary gland diseases
Falahatin, et al (2024)	Residu 10 (R 10) from fraction garlic	• The type of research is experimental study • Sixty adult female NMRI mice (8 weeks old, 25-30 gr weight) • The use of the R10 fraction dose is 20 mg/kg weight • Statistical Analysis was performed with Prism GraphPad using ANOVA followed by post hoc Tukey's multiple comparison	Treatment R10 showed that garlic has a considerable therapeutic function in relieving the hormone PCOS symptoms. The graafian follicles have significantly increased and, implying reactivation of the normal ovulation process. So, R10 has the potential to modulate the hypothalamic-pituitary-gonadal axis, express crucial genes in oocyte development, and alleviate the histological abnormality of the ovary associated with PCOS.

Author (Year)	**Product Treatment**	**Component of the Research Method**	**Outcome**
Xu, et al (2018)	*S-allyl cysteine* (SAC)	• The type of research design is an experimental study • 6-well plate cultured by human epithelial ovarian cancer cell line A2780 • The concentration of SAC is 0 mmol/L; 2,5 mmol/L; 5 mmol/L; 10 mmol/L • Statistical analysis and data visualization were performed using IBM SPSS with two-tailed Student's test	SAC could inhibit the proliferation of human ovarian cancer A2780 cells and cause cell cycle arrest in the G1/S phase. SAC treatment decreased global DNA methylation levels and DNMT1 expression and reactivated CDKN1A.
Waseem, et al (2015)	Garlic extract	• The type of research design is an experimental study • 30 female BALB/c mice with 25-27 gr weight • The concentration of garlic extract is 500 mg/kg/day in group C for 60 days • Statistical analysis was determined by ANOVA and Post Hoc Tukey test.	Garlic extract plays a protective role in improving uterine tissue. It will be prevention for reducing infertility
Bronowicka-Adamska, et al (2020)	*S-allyl cysteine* (SAC) extracted from aged garlic	• The type of research design is an experimental study • The human breast adenocarcinoma cell line MCF-7 cell culture • SAC concentration is 800 µM, 1000 µM dan 2245 µM	Treatment SAC showed that MCF-7 cells have reduced viability from decreasing MPST and sulfate sulfur level reduction

Author (Year)	Product Treatment	Component of the Research Method	Outcome
		• Statistical analysis using the Mann-Whitney test	
Assayed, et al (2020)	Fresh garlic extract and *L-ascorbic acid* (vit C)	• The type of research design is an experimental study • 18 males and 36 pregnant females Wistar rats • The dose level of fresh garlic is 500 mg/kg body weight in IV • Statistical analysis using ANOVA with data was expressed as arithmetical mean±standar error of the mean (SEM)	Treatment of fresh garlic extract and vitamin C in male and pregnant female rats showed a significant decrease in the percentage of information fetal from the insecticide. it is verified that the treatment decreases reproductive toxicity and teratogenicity of cyprinid toxicity in rats

Table 1 shows that several studies used garlic with different pretreatments as a test of female reproductive therapy. Articles do pretreatment of dried, fresh, and aged (black) garlic to obtain several types of compounds. Different garlic pretreatments will result in different pharmacological properties (Kasuga, et al., 2001). Several studies explain that garlic's biological and pharmacological effects come from sulfur compounds. The sulfur compounds owned include *aliin*, *allicin*, *ajoene*, *allyl-propyl disulfide*, *diallyl trisulfide*, *S-allyl cysteine*, *vinyldithiines*, *S-allylmercaptocystein* (Hajiuon, 2014). Allicin compounds are commonly known as bioactive compounds (Balamurugan, et al., 2014).

Fresh garlic and garlic extract in oil or powder can significantly boost immunity, have anti-tumor properties, and have antioxidant activity to protect the body from free radicals. Black garlic extract contains bioactive compounds in the form of sulfur compounds and saponins; fresh garlic, raw garlic, and garlic oil contain allicin; garlic contains antioxidant compounds; garlic extract has antioxidant and phenolic content (Verma, et al., 2023). Garlic powder can reduce the number of athretic follicles and oxidative stress due to its antioxidant content (Jafari, et al., 2021). Antioxidant activity can be seen from bioactive components in the form of polyphenol compounds. The primary mechanism of antioxidant activity is the regulatory flow of Nrf2-ARE, a transcription of redox-sensitive factors that can simulate the expression of antioxidant genes responsible for antioxidant enzymes and increased antioxidant enzyme activity (Zadoush, et al., 2023).

Garlic is indicated to have immunomodulatory activity. Immunomodulators are known as agents that affect the immune system. It refers to the immune response, which includes stimulation, amplification, expression, or inactivation of several stages of the immune response (Abood, 2017). The activation of immunomodulators that work as inhibitors are *ajoene* compounds and *saponins*. Garlic extract has a fractional protein with a low molecular weight known as R10. In vivo studies, the R10 fraction stimulated macrophage phagocytosis activity (Gamboa-León, et al., 2007). Treatment using the R10 fraction for polycystic ovary syndrome (PCOS) patients showed that there was a decrease in the expression of Gpx3 and Ptx3, which

could describe the presence of regular ovulation and increased fertility rate. In addition, the increase in IFN-γ and IL-17 levels indicates that the polarisation activity of T cells in PCOS occurs (Falahatian, et al., 2022).

Black garlic is known as fresh garlic that is fermented during a specific period with temperature (60-90°C) and humidity (80-90%). This process will change the physicochemical properties of black garlic so that it has higher biological activity than fresh garlic (Kimura, et al 2016). The compounds produced by black garlic have more stable and odorless characteristics, such as *S-allyl cysteine* (SAC), which then decomposes into organosulfur compounds such as *diallyl sulphide* (DAS), *diallyl disulphide* (DADS), *diallyl trisulphide* (DATS), *dithiins*, and *ajoene*. SAC is the dominant active compound produced by black garlic with high antioxidant content (Medina, et al., 2019). Reactive oxygen species (ROS) can cause the emergence of oxidative stress conditions, which then affect the development of obstetric complications. Oxidative stress at increased levels can lead to recurrent miscarriages, preeclampsia, limiting intrauterine growth (IUGR), and premature labour. ROS negatively affects the occurrence of embryonic attachment, the development of endometriosis, and preeclampsia. Therefore, antioxidants are needed to suppress oxidative stress in the body (Zadoush, et al., 2023).

The amount of SAC in black garlic is five to six times higher compared to fresh garlic. The aging and fermentation process of garlic causes *allicin* compounds to change into antioxidant components such as SACs, alkaloids, and flavonoids (Azhar and Yuliawati, 2021). As an antioxidant agent, SAC is a potential compound produced by black garlic that can dissolve in water and have minimal toxic content. It allows SAC to have prophylactic properties at the clinical level (Takemura et al., 2014).

Based on research on the differences in garlic pretreatment, namely raw garlic juice (RGJ), heated garlic juice (HGJ), dehydrated garlic juice (DGP), and aged garlic extract (AGE), showed an increase in NK activity and tumor cell killing. However, AGE can suppress tumor cell growth more than HGJ, RGJ, and DHP. Meanwhile, the antioxidant effect of AGE is an inhibitor of oxidative stress rate. AGE can significantly improve the spermatogenesis process compared to 3 other types of pretreatment (Kasuga, et al., 2001). Black garlic can reach almost 90%, inhibiting radicals and reducing power. In addition, black garlic has a higher antibacterial activity than fresh garlic, which is only around 15-34% (Chua, et al., 2022). It shows that AGE is an effective treatment to get the therapeutic effect of the compound to the maximum.

4. CONCLUSION

Garlic (Allium sativum) with various pretreatments has physicochemical properties that affect female reproductive health. The bioactive components of garlic can stimulate antioxidant activity in the female reproductive organs. Antioxidant activity can increase the fertility of reproductive organs because it increases the metabolism of oocytes, hormonal regulation, and the maturation of the endometrium. Antioxidant imbalances cause increasing oxidative stress and affect ovarian function, which then affects the development of health complications. Black garlic has a more complex compound group than other garlic precessions. The content of compounds in black garlic, such as S-allyl cysteine (SAC), is more obtaining five to six times, soluble in water, and has less toxic content. The production of black garlic compounds has a more stable character, so the effects from the treatment process will be more consistent and maximum. From these results, it is necessary to develop research on black garlic. So, it can be known how effective the treatment of black garlic is on women's reproductive health.

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