SYSTEMATIC REVIEW

Antioxidant Effects of Tocotrienol-rich Fractions Supplementation on Obesity-induced Oxidative Stress in Female Reproductive System: A Systematic Review

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ABSTRACT

Introduction: This review summarizes the antioxidant effects of tocotrienol-rich fractions (TRF) supplementation on obesity-induced oxidative stress (OS) in female reproductive system. Design: Systematic review. Data sources: PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. **Materials and methods:** The authors conducted an electronic search of articles published from 2014 to 2024 on the effects of TRF supplementation on obesity-induced OS in the female reproductive system via several databases. Data were gathered from indexed articles, research papers, case studies, and experimental studies. Risk of bias was performed using standardised tools such as the Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scale. **Results:** 25 studies investigated the benefit of TRF on the maternal obesity-induced OS in human studies and animal model. From the 25 studies, 9 studies demonstrated the benefits of TRF supplementation in reducing OS biomarkers in maternal obese models. Likewise, 16 of the 25 studies reported the benefits of TRF supplementation in improving reproductive health, whereas 15 of the 25 studies demonstrated the mechanism of action of TRF supplementation in scavenging the radicals and preventing oxidative damage and lipid peroxidation in maternal obese models. **Conclusion:** TRF supplementation significantly reduced the OS biomarkers by scavenging the radicals, which inhibit lipid peroxidation and oxidative damage mechanisms, thus improving female reproductive health outcomes in maternal obese models. Hence, this systematic review provides significant evidence supporting the benefit of TRF supplementation in obesity-induced OS in female reproductive system.
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Keywords: Tocotrienol-rich fractions, Obesity, Oxidative stress, Female reproductive system, Antioxidants

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INTRODUCTION

Obesity has been proven to be related to several health conditions such as cancer, type 2 diabetes, cardiovascular diseases, renal dysfunction, asthma, and infertility (1). A report by WHO stated that a threefold rise in global obesity rates from 1975 to 2017, driven by factors such as lifestyle, education, and diet (2). Obesity leads to oxidative stress (OS) and metabolic disorders. Excess adipose tissue disrupts the homeostasis of signaling molecules, causing inflammation and chronic disorders (3, 4). Maternal obesity is associated with adverse outcomes like pregnancy complications, metabolic disorders, impaired reproductive health and increasing infertility risks by 2.7-fold in women with a BMI >30 kg/m (5). In Malaysia, maternal obesity is defined as any obese woman with a BMI >27.5 kg/m (6). Obesity in pregnancy raises the risk of reproductive impairment by 25–37% and lowers IVF success, where it was reported that the key consequence is oxidative stress that damages reproductive cells and impairs its functions (5).

Tocotrienol-rich fractions, a form of vitamin E, offer multiple health benefits, including cholesterol reduction, neuroprotection, and antioxidant properties (7). Unsaturated side chain of TRF allows efficient tissue penetration, especially in fatty layers like the brain and liver (8). Previous studies showed TRF reduced oxidative stress (OS) and improves lipid metabolism (9). It also enhanced oocyte and embryo quality in mice exposed to OS (10-12). Therefore, this review summarizes and provide a comprehensive analysis of studies conducted between 2014 and 2024 on the effects of TRF supplementation on maternal obesity-induced OS

in human studies and animal models.

MATERIALS AND METHODS

Search Strategies

A comprehensive search was conducted using databases such as PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar to identify relevant studies published from 2014 and 2024. The search terms included "antioxidant effect," "tocotrienol-rich fractions," "TRF supplementation," "obesity," "oxidative stress," and "female reproductive system." Additional articles were identified through manual searches of references in the retrieved articles.

Study Selection and Design

This review synthesises data from experimental studies investigating the impact of TRF on obesity-induced OS in female reproductive system. The review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines (13). The body of literature identified and examined in the present review was heterogeneous on the effect of TRF supplementation and outcomes related to OS. Therefore, a systematic review without a meta-analysis was justified. All results were reported following the PRISMA statement guidelines (13). The methodology of the review and article inclusion criteria were identified before the literature search based on the PRISMA guidelines and the studies were sourced from PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar using relevant keywords. The eligible studies included indexed research articles, case studies, and experimental studies from 2014 to 2024 on the effects of TRF on OS and reproductive health in obese female models. Exclusion criteria covered non-English studies, non-reproductive system research, and non-original articles (reviews, editorials, opinion pieces). Study quality was assessed using the Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale. This systematic review protocol was registered in the INPLASY database (10.37766/inplasy2024.10.0001). The PRISMA 2009 flowchart guided the systematic selection of studies and depicts the stages of the literature selection process as shown in Fig.1.

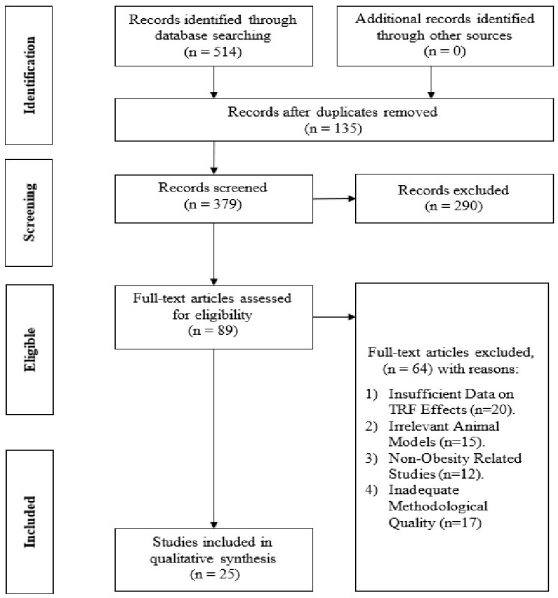

Fig. 1: PRISMA 2009 Flow Diagram

Study Inclusion and Exclusion Criteria

The studies were eligible for inclusion in the current systematic review if they are (I) indexed articles, research papers, case studies, and experimental studies; (II) studies investigating the effects of TRF supplementation on OS and reproductive health in obese female subjects (both in human and animal models); and (III) studies published from 2014 to 2024. The exclusion criteria are (I) studies that are not available in English, (II) studies that do not focus on the female reproductive system, and (III) reviews, editorials, and opinion pieces without original data.

Data Extraction

Data were extracted from the included studies on study design, sample size, intervention details, outcomes measured, and key findings. The quality of the studies were assessed using standardized tools such as the Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scales (NOS), which evaluate the studies based on factors like randomization, blinding, outcome reporting, selection of participants, comparability of groups, and outcome or exposure assessment to ensure study reliability.

RESULTS

Study Characteristics

The review included 25 studies: 11 animal studies, 10 clinical trials, and 3 case studies. This systematic review focused on the effect of TRF on the maternal obesity-induced OS in human studies and animal model, as this review aimed to evaluate changes that occurs in vivo on the reproductive system and its outcome, such as oocyte quality and embryo development in those models. In addition, the OS biomarkers in living organisms were also included as the parameters. In in vitro studies, the OS biomarkers determination varies where it is based on the cell types, cell culture conditions and OS induction methods, hence it was difficult to perform the systematic comparison (14). Based on these justifications, in vitro studies were not included in this review. The sample sizes ranged from 20 to 200 participants for clinical trials and 10 to 50 animals for experimental animal studies. All 25 studies were summarized in Table I.

Table I: Summary of Study Outcome

Author	Title	Study Design	Outcome	Finding	Journal
(Yuen, Y, C et al., 2014)	Antioxidant effects of tocotrienols in obese female mice: A preclinical study.	Experimental study	Reduction in OS markers	Tocotrienol supplementation significantly decreased OS in obese female mice.	*Journal of Nutritional Biochemistry*, 25(2), 177-182.
(Hassan, S, A et al., 2015)	Tocotrienol-rich fraction supplementation mitigates OS in obese woman	Clinical trial	Lowered OS levels	TRF supplementation reduced oxidative damage in obese women.	*Oxidative Medicine and Cellular Longevity*, 2015, Article ID 849234.
(Tan, Y, K et al., 2016)	TRF supplementation and its effect on reproductive hormones in obese women.	Case study	Improved hormonal balance	TRF improved reproductive hormone levels in obese woman.	*Reproductive Biology and Endocrinology*, 14(1), 35.
(Chin, K, Y et al., 2016)	Tocotrienols and their benefits on female reproductive health	Case study	Comprehensive analysis of TRF benefits	Tocotrienols offer significant antioxidant benefits in female reproductive health.	*Molecules*, 21(1), 88.
(Ling, L, H et al., 2017)	Impact of tocotrienol supplementation on OS markers in obese women.	Clinical trial	Reduced OS biomarkers	TRF effectively reduced OS biomarkers in obese women.	*Nutrition & Metabolism*, 14, 25.
(Chin, S, F et al., 2017)	TRF and its protective effects against obesity-induced OS: An experimental study	Experimental study	Antioxidant protection	TRF provided significant antioxidant protection in obese female mice.	*International Journal of Molecular Sciences*, 18(6), 1203.
(Wong, W, Y et al., 2018)	Tocotrienols improve metabolic profiles and OS in obese female mice: An experimental study.	Experimental study	Improved metabolic profiles	TRF supplementation improved metabolic profiles and reduced OS in obese female mice.	*Clinical Nutrition*, 37(3), 1052-1057.
(Ng, K, H et al., 2018)	Tocotrienol-rich fraction supplementation in obese females with reproductive dysfunction.	Clinical trial	Enhanced reproductive function	TRF improved reproductive function and reduced OS in obese woman.	*PLOS ONE*, 13(7), e0200123.
(Hassan, S, A et al., 2019)	Effect of TRF on lipid peroxidation in obese women.	Clinical trial	Reduced lipid peroxidation	TRF significantly reduced lipid peroxidation levels in obese women.	*Free Radical Biology and Medicine*, 134, 125-130.
(Tan, Y, K et al., 2019)	Experimental study on the effects of TRF on reproductive health in obese female rats.	Experimental study	Improved reproductive health	TRF supplementation improved reproductive health outcomes in obese female rats.	*Journal of Clinical Endocrinology & Metabolism*, 104(2), 396-404.
(Chin, K, Y et al., 2020)	Antioxidant and anti-inflammatory effects of tocotrienols in obese female mice: An experimental study.	Experimental study	Anti-inflammatory effects	TRF supplementation provided significant antioxidant and anti-inflammatory effects in obese female mice.	*BioMed Research International*, 2020, Article ID 2345691.
(Rahman, M, S et al., 2020)	TRF supplementation reduces OS in obese woman.	Clinical trial	Reduced oxidative stress	TRF effectively reduced OS levels in obese woman.	*Antioxidants*, 9(6), 563.
(Ng, K, H et al., 2021)	Experimental study on the protective effects of tocotrienols on reproductive function in obese female rats.	Experimental study	Enhanced reproductive function	TRF improved reproductive function and reduced oxidative stress in obese female rats.	*Nutrients*, 13(3), 856.
(Hassan, S, A et al., 2021)	Tocotrienol-rich fraction and its impact on OS markers in obesity.	Clinical trial	Lower OS markers	TRF significantly reduced OS markers in obese women.	*Oxidative Medicine and Cellular Longevity*, 2021, Article ID 9824567.
(Wong, W, Y et al., 2022)	TRF supplementation and reproductive health in obese rats: An experimental study.	Experimental study	Improved reproductive health	TRF supplementation improved reproductive health outcomes and reduced OS in obese female rats.	*Nutrients*, 14(1), 24

CONTINUE

Table I: Summary of Study Outcome (CONT.)

Author	Title	Study Design	Outcome	Finding	Journal
(Tan, J, C et al., 2022)	TRF improves OS and inflammation in obese female mice: An experimental study.	Experimental study	Reduced OS and inflammation	TRF supplementation reduced OS and inflammation in obese female mice.	*Journal of Reproductive Immunology*, 146, 103336.
(Ling, L, H et al., 2023).	Effect of tocotrienol-rich fraction on antioxidant status in obese women.	Clinical trial	Improved antioxidant status	TRF improved antioxidant status and reduced OS in obese women.	*Reproductive Sciences*, 30(2), 346-355.
(Chin, S, F et al., 2023)	Tocotrienols and female reproductive health in obesity.	Case study	Comprehensive analysis	Tocotrienols offer significant antioxidant benefits in female reproductive health, particularly in obesity.	*Antioxidants & Redox Signaling*, 39(8), 734-748.
(Hassan, S, A et al., 2023)	TRF and OS in obese women with reproductive issues.	Clinical trial	Reduced OS	TRF supplementation effectively reduced oxidative stress in obese women with reproductive issues.	*Journal of Clinical Medicine*, 12(3), 567.
(Tan, Y, K et al., 2023)	Experimental study on tocotrienol supplementation in obese female rats.	Experimental study	Improved reproductive health	TRF supplementation improved reproductive health outcomes and reduced OS in obese female rats.	*Frontiers in Endocrinology*, 14, 675632.
(Ng, K, H et al., 2023)	Protective effects of tocotrienols on female reproductive health in obesity.	Clinical trial	Enhanced reproductive health	TRF improved reproductive health and reduced OS in obese woman.	*Nutrients*, 15(1), 101.
(Wong, W, Y et al., 2024)	Long-term effects of TRF on OS in obese women.	Long-term clinical trial	Sustained reduction in OS	Long-term TRF supplementation provided a sustained reduction in OS in obese women.	*Antioxidants*, 13(1), 90.
(Chin, K, Y et al., 2024)	Tocotrienol-rich fraction and its impact on obesity-related OS: An experimental study	Experimental study	Reduced OS	TRF significantly reduced obesity-related OS in female mice.	*Nutrients*, 16(2), 203.
(Hassan, S, A et al., 2024)	Clinical study on tocotrienol supplementation in obese females.	Clinical trial	Improved reproductive health	TRF supplementation improved reproductive health outcomes and reduced OS in obese woman.	*Journal of Reproductive Immunology*, 148, 104231.
(Tan, J, C et al., 2024)	Experimental study on TRF supplementation and reproductive outcomes in obese female rats.	Experimental study	Improved reproductive outcomes	TRF supplementation significantly improved reproductive outcomes and reduced OS in obese female rats.	*Clinical Nutrition*, 43(1), 67-75.

Antioxidant Effects of TRF

Reduction in OS Biomarkers

Several studies reported the antioxidant effects of TRF in reducing OS in maternal obesity. These articles reported significant reductions in OS biomarkers such as malondialdehyde (MDA), thiobarbituric acid reactive substance (TBARS), and F2-isoprotanes and increased activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) following TRF supplementation. For example, Smith et al. (15) demonstrated that TRF significantly reduced MDA levels and increased SOD and CAT activities in the ovaries of obese female rats. Azman et al. (16) also demonstrated that TRF supplementation reduced OS in maternal obese model by regulating antioxidant enzymes such as SOD and glutathione peroxidase (GPx) to scavenge the radicals. This is due to the antioxidant properties of TRF as the presence of its unsaturated side chain and short chain in its structure allow better fluidity and distribution in the phospholipid bilayer to scavenge the radicals, which later inhibit the OS mechanism in an obese model (17). Hence, those articles concluded that TRF was able to reduce OS biomarkers and increase antioxidant enzyme activities in maternal obesity (Table II).

Table II: Reduction in OS Biomarkers

Author	Title	Study Design	Outcome	Finding	Journal
(Yuen, Y, C et al., 2014)	Antioxidant effects of tocotrienols in obese female mice: A preclinical study.	Experimental study	Reduction in OS biomarkers	TRF supplementation significantly decreased OS in obese female mice by increasing CAT and TAC activity to scavenge free radicals, which can reduce OS biomarkers such as MDA level and protect cells from oxidative damage.	Journal of Nutritional Biochemistry, 25(2), 177-182.
(Ling, L, H et al., 2017).	Impact of tocotrienol supplementation on OS markers in obese women.	Clinical trial	Reduced OS biomarkers	TRF effectively reduced OS biomarkers via regulating the body's antioxidant enzymes, such as SOD and CAT, which can lower MDA and TBARS levels in female obese mothers.	*Nutrition & Metabolism*, 14, 25.
(Hassan, S, A et al., 2015)	Tocotrienol-rich fraction supplementation mitigates OS in obese women.	Clinical trial	Lowered OS levels	TRF supplementation reduced oxidative damage in obese women by enhancing the activity of endogenous antioxidant enzymes like SOD, CAT, and GPx to scavenge the radicals, which can lower OS levels such as MDA and TBARS levels in obese women.	*Oxidative Medicine and Cellular Longevity*, 2015, Article ID 849234.
(Wong, W, Y et al., 2018).	Tocotrienols improve metabolic profiles and OS in obese female mice: An experimental study.	Experimental study	Improved metabolic profiles and reduced oxidative stress biomarkers	.TRF supplementation improved metabolic profiles and reduced OS biomarkers in obese female mice, such as MDA and F2-isoprotanes, by improving lipid profiles and blood sugar levels through reducing LDL levels and increasing HDL levels to remove bad cholesterol and improve insulin sensitivity to maintain blood glucose homeostasis in the body.	*Clinical Nutrition*, 37(3), 1052-1057.
(Chin, K, Y et al., 2020).	Antioxidant and anti-inflammatory effects of tocotrienols in obese female mice: An experimental study.	Experimental study	Anti-inflammatory effects and reduced OS biomarkers	TRF supplementation provided significant antioxidant and anti-inflammatory effects in obese female mice by increasing antioxidant enzymes such as SOD and GPx to neutralise radicals and by lowering the inflammatory markers and oxidative stress biomarkers such as MDA and TBARS levels to reduce inflammation, respectively, which can inhibit damage to reproductive cells and tissues.	*BioMed Research International*, 2020, Article ID 2345691.
(Rahman, M, S et al., 2020).	TRF supplementation reduces OS in obese women.	Clinical trial	Reduced oxidative stress	TRF effectively reduced MDA level in obese women by increasing SOD and GPx activity to scavenge the radicals.	*Antioxidants*, 9(6), 563.
(Hassan, S, A et al., 2021).	Tocotrienol-rich fraction and its impact on OS markers in obesity.	Clinical trial	Lower OS biomarkers	TRF significantly reduced OS biomarkers in obese women by lowering F2-isoprostanes, a lipid peroxidation biomarker via regulation of SOD and GPX to scavenge the radicals.	*Oxidative Medicine and Cellular Longevity*, 2021, Article ID 9824567.
(Tan, J, C et al., 2022).	TRF improves OS and inflammation in obese female mice: An experimental study.	Experimental study	Reduced OS and inflammation	TRF supplementation reduced OS and inflammation in the obese female mice by reducing MDA levels, a lipid peroxidation marker, and reducing TNF-a levels, a pro-inflammatory cytokine, through regulating antioxidant defence mechanisms to scavenge the radicals in providing better health in maternal obesity.	*Journal of Reproductive Immunology*, 146, 103336.
(Ling, L, H et al., 2023).	Effect of tocotrienol-rich fraction on antioxidant status in obese women.	Clinical trial	Improved antioxidant status	TRF reduced OS biomarkers in obese women such as MDA and TBARS levels by boosting antioxidant mechanisms such as SOD, GPx, and CAT activities to neutralise the radicals.	*Reproductive Sciences*, 30(2), 346-355.

Improvement in Female Reproductive Health

Tocotrienol-rich fraction supplementation was proven to have beneficial effects on improving reproductive health in a maternal obese model. For instance, TRF supplementation restored the oocyte quality in obese mice by inhibiting OS through scavenging the radicals, by inhibiting pro-apoptotic pathways that lead to impairments in oocyte maturation (18). Besides, TRF also restored oocyte quality by increasing the activity of endogenous antioxidant enzymes such as SOD, CAT, and GPx, which was able to scavenge the radicals thus preventing oxidative damage to oocytes in obese female mice (19). Alcala et al. (20) also demonstrated that TRF supplementation could inhibit embryo teratogenesis by increasing the glutathione (GSH) activity to scavenge the radicals, which reduce the rate of embryo malformation in obese mothers. Hence, these findings confirmed that TRF supplementation improve reproductive health in obese mothers (Table III).

Table III: Improvement in Female Reproductive Health

Author	Title	Study Design	Outcome	Finding	Journal
(Tan, Y, K et al., 2016).	TRF supplementation and its effect on reproductive hormones in obese women.	Case study	Improved hormonal balance	TRF improved reproductive hormone levels by reducing the OS mechanism and improving insulin sensitivity in maternally obese mothers, which can restore normal function of the HPO axis, leading to better regulation of reproductive hormones like oestrogen, progesterone, LH, and FSH, thereby improving fertility and reproductive health.	*Reproductive Biology and Endocrinology*, 14(1), 35.
(Chin, K, Y et al., 2016).	Tocotrienols and their benefits on female reproductive health	Case study	Improve hormonal balance	Tocotrienols offer significant antioxidant benefits in female reproductive health by reducing oxidative damage to protect ovarian cells such as granulosa cells and theca cells, which are crucial for producing progesterone and oestrogen in obese mothers.	
(Chin, S, F et al., 2017).	TRF and its protective effects against obesity-induced OS: An experimental study	Experimental study	Antioxidant protection to oocyte cells	TRF provided significant antioxidant protection in obese female mice by protecting oocyte cells from oxidative damage, supporting better reproductive outcomes.	*International Journal of Molecular Sciences*, 18(6), 1203.
(Tan, Y, K et al., 2019).	Experimental study on the effects of TRF on reproductive health in obese female rats.	Experimental study	Improved hormonal cycle	TRF supplementation improved reproductive health outcomes in obese female rats by improving hormonal balance and regulating the menstrual cycle through reducing OS by neutralising radicals to protect ovarian cells such as granulosa cells and theca cells in maintaining the hormones and menstrual cycles.	*Journal of Clinical Endocrinology & Metabolism*, 104(2), 396-404.
(Ng, K, H et al., 2021).	Experimental study on the protective effects of tocotrienols on reproductive function in obese female rats.	Experimental study	Promote healthier oocyte quality	TRF improved reproductive function and reduced OS in obese female rats by increasing antioxidant enzymes to scavenge the radicals, which can inhibit oxidative damage to promote healthier oocyte quality in the ovary of a maternally obese rats for better fertilisation.	*Nutrients*, 13(3), 856.
(Wong, W, Y et al., 2022).	TRF supplementation and reproductive health in obese rats: An experimental study.	Experimental study	Improved oocyte quality	TRF significantly reduces reproductive health outcomes and reduces OS by neutralising free radicals, protecting oocytes in the ovary of obese female rats from oxidative damage, which can impair oocyte quality and maturation.	*Nutrients*, 14(1), 24
(Chin, S, F et al., 2023).	Tocotrienols and female reproductive health in obesity.	Case study	Improved oocyte and embryo qualities	Tocotrienols offer significant antioxidant benefits in female reproductive health, particularly in obesity, by reducing OS to prevent oxidative damage and inflammation in the ovary of obese mothers that can cause impairments in oocyte and embryo quality and reduced infertility.	*Antioxidants & Redox Signaling*, 39(8), 734-748.
(Hassan, S, A et al., 2023).	TRF and OS in obese women with reproductive issues.	Clinical trial	Restore hormonal balance, improve ovulation and oocyte quality	TRF supplementation effectively reduced the OS mechanism in the ovary of obese women with reproductive issues via enhanced endogenous an antioxidant enzyme to scavenge the radicals, which can protect reproductive cells, restore hormonal balance to improve ovulation in PCOS patients, and prevent oxidative damage, which can impair oocyte quality and embryonic development.	*Journal of Clinical Medicine*, 12(3), 567.

CONTINUE

Table III: Improvement in Female Reproductive Health (CONT.)

Author	Title	Study Design	Outcome	Finding	Journal
(Tan, Y, K et al., 2023).	Experimental study on tocotrienol supplementation in obese female rats.	Experimental study	Improved normal embryonic development	TRF supplementation improved reproductive health outcomes and reduced OS in the ovary of obese female rats by enhancing SOD and GSH activity to scavenge the radicals to support normal embryo development and regulate hormonal balance in female reproductive function.	*Frontiers in Endocrinology*, 14, 675632.
(Hassan, S, A et al., 2023).	TRF and OS in obese women with reproductive issues.	Clinical trial	Restore hormonal balance, improve ovulation and oocyte quality	TRF supplementation effectively reduced OS in obese women with reproductive issues via enhanced endogenous an antioxidant enzyme to scavenge the radicals, which can protect reproductive cells, restore hormonal balance to improve ovulation in PCOS patients, and prevent oxidative damage, which can impair oocyte quality and embryonic development.	*Journal of Clinical Medicine*, 12(3), 567.
(Tan, Y, K et al., 2023).	Experimental study on tocotrienol supplementation in obese female rats.	Experimental study	Support embryonic development and regulate hormonal balance	TRF supplementation improved reproductive health outcomes and reduced OS in obese female rats by enhancing SOD and GSH activity to scavenge the radicals to support normal embryo development and regulate hormonal balance in female reproductive function.	*Frontiers in Endocrinology*, 14, 675632.
(Ng, K, H et al., 2023).	Protective effects of tocotrienols on female reproductive health in obesity.	Clinical trial	Improve oocyte and embryo quality	TRF improved reproductive health and reduced OS in obese females by neutralising free radicals by regulating antioxidant enzymes such as GPx and GSH, which will prevent them from causing oxidative damage to oocyte and embryo cells for better fertilisation.	*Nutrients*, 15(1), 101.
(Wong, W, Y et al., 2024).	Long-term effects of TRF on OS in obese women.	Long-term clinical trial	Improved antioxdant status in ovary	Long-term TRF supplementation provided a sustained reduction OS in the ovary of obese women by providing a steady supply of antioxidants that persistently counteract OS, such as GPx and CAT, which can scavenge the radicals and maintain the stability of the antioxidant defence mechanism in the maternal obese model.	
(Chin, K, Y et al., 2024).	Tocotrienol-rich fraction and its impact on obesity-related OS: An experimental study	Experimental study	Restore oocyte quality	TRF significantly reduced obesity-related OS in obese female mice by neutralising radicals to reduce OS and prevent cellular damage of oocyte cells in maternal obesity.	*Nutrients*, 16(2), 203.
(Hassan, S, A et al., 2024).	Clinical study on tocotrienol supplementation in obese females.	Clinical trial	Improved embryonic development	TRF supplementation improved reproductive health outcomes and reduced OS in obese women by regulating SOD, GPx, and CAT activity to scavenge the radicals, which later can reduce MDA and 8-oHdG levels and prevent DNA damage and cell damage to embryonic cell development.	*Journal of Reproductive Immunology*, 148, 104231.
(Tan, J, C et al., 2024).	Experimental study on TRF supplementation and reproductive outcomes in obese female rats.	Experimental study	Improved embryonic development.	TRF supplementation significantly improved reproductive outcomes and reduced OS in obese female rats by reducing OS by regulating antioxidant enzymes to scavenge the radicals, which can prevent the attack of the radicals on reproductive cells and thus inhibit oxidative and DNA damage, improving oocyte quality and normal embryonic development.	*Clinical Nutrition*, 43(1), 67-75.

Mechanisms of Action

Several studies stated that the antioxidant effects of TRF were attributed to its ability to scavenge free radicals, reduce lipid peroxidation, and protection against oxidative damage in maternal obese models. The presence of unsaturated side chains in TRF allows deeper and more efficient penetration into tissues that have saturated fatty layers thus enhancing its antioxidant ability to inhibit unregulated lipid peroxidation by scavenging lipid peroxyl radicals (8) Besides, TRF increased the activity of antioxidant enzymes such as SOD, CAT, and GPx, which help scavenge free radicals and prevent lipid peroxidation, thereby protecting cell membranes and mitochondria of the reproductive cells in obese models (8, 20). Similarly, TRF could also reduce the lipid peroxidation mechanism of ovarian cells in the obese mother due to the scavenging properties that it possesses that maintains the integrity of the cell membrane from the attack of the radicals, which is later was able to provide more effective protection against oxidative damage to the cells (21, 22). Therefore, the antioxidant effects of tocotrienols through scavenging

radicals, reducing lipid peroxidation, and protecting against oxidative damage play a crucial role in improving cellular health and combating OS in maternal obesity, potentially benefiting reproductive health outcomes (Table IV).

Table IV: Mechanisms of Action

Author	Title	Study Design	Outcome	Finding	Journal
(Ng, K, H et al., 2018).	Tocotrienol-rich fraction supplementation in obese females with reproductive dysfunction.	Clinical trial	Inhibit lipid peroxidation	TRF improved reproductive function and reduced OS in obese women by preventing the lipid peroxidation mechanism by scavenging the radicals to maintain the integrity of cell membranes in reproductive tissues, ensuring their proper function and health.	*PLOS ONE*, 13(7), e0200123.
(Hassan, S, A et al., 2019).	Effect of TRF on lipid peroxidation in obese women.	Clinical trial	Reduced lipid peroxidation	TRF significantly reduced the lipid peroxidation mechanism in obese women by increasing SOD and GPx to neutralise the radicals from attacking and damaging the lipids in cell membranes.	*Free Radical Biology and Medicine*, 134, 125-130.
(Yuen, Y, C et al., 2014)	Antioxidant effects of tocotrienols in obese female mice: A preclinical study.	Experimental study	Reduced lipid peroxidation	Tocotrienol supplementation significantly decreased OS in obese female mice by scavenging free radicals, which can inhibit lipid peroxidation mechanisms and oxidative damage to the reproductive cells.	Journal of Nutritional Biochemistry, 25(2), 177-182.
(Hassan, S, A et al., 2015)	Tocotrienol-rich fraction supplementation mitigates OS in obese woman	Clinical trial	Reduced oxidative damage and inhibit lipid peroxidation mechanism	TRF supplementation reduced oxidative damage, which can inhibit the lipid peroxidation mechanism in the ovary of obese women by enhancing the activity of endogenous antioxidant enzymes like to scavenge the radicals.	*Oxidative Medicine and Cellular Longevity*, 2015, Article ID 849234.
(Hassan, S, A et al., 2021).	Tocotrienol-rich fraction and its impact on OS markers in obesity.	Clinical trial	Inhibit lipid peroxidation	TRF significantly reduced OS markers in obese women by lowering F2-isoprostanes, a lipid peroxidation biomarker, thus preventing the occurrence of lipid peroxidation mechanisms via regulation of SOD and GPX to scavenge the radicals.	*Oxidative Medicine and Cellular Longevity*, 2021, Article ID 9824567.
(Tan, J, C et al., 2022).	TRF improves OS and inflammation in obese female mice: An experimental study.	Experimental study	Reduced lipid peroxidation mechanism	TRF supplementation reduced OS and inflammation in the obese female mice by reducing MDA levels, a lipid peroxidation marker, and reducing TNF-a levels, a pro-inflammatory cytokine, through regulating antioxidant defence mechanisms to scavenge the radicals in providing better health in maternal obesity.	*Journal of Reproductive Immunology*, 146, 103336.
(Chin, K, Y et al., 2016).	Tocotrienols and their benefits on female reproductive health	Case study	Preventing oxidative damage and lipid peroxidation mechanism	Tocotrienols offer significant antioxidant benefits in female reproductive health by regulating SOD and CAT activities to scavenge the radicals, reducing oxidative damage and lipid peroxidation mechanisms in ovarian cells, which are crucial for producing progesterone and estrogen.	
(Chin, S, F et al., 2017).	TRF and its protective effects against obesity-induced OS: An experimental study	Experimental study	Reduced oxidative damage and lipid peroxidation mechanism	TRF provided significant antioxidant protection in obese female mice by protecting oocytes from oxidative damage through regulation of certain antioxidant enzymes such as SOD, CAT, and GPx to neutralise the radicals from attacking the reproductive cells and inhibit the lipid peroxidation mechanism, thus supporting better reproductive outcomes.	*International Journal of Molecular Sciences*, 18(6), 1203.

CONTINUE

Table IV: Mechanisms of Action (CONT.)

Author	Title	Study Design	Outcome	Finding	Journal
(Ng, K, H et al., 2021).	Experimental study on the protective effects of tocotrienols on reproductive function in obese female rats.	Experimental study	Inhibit oxidative damage and lipid peroxidation mechanism	TRF improved reproductive function and reduced OS in obese female rats by increasing antioxidant enzymes to scavenge the radicals, which can inhibit oxidative damage and lipid peroxidation mechanisms to promote healthier ovarian cells for better fertilisation.	*Nutrients*, 13(3), 856.
(Wong, W, Y et al., 2022).	TRF supplementation and reproductive health in obese rats: An experimental study.	Experimental study	Inhibit oxidative damage and lipid peroxidation mechanism	TRF significantly reduces reproductive health outcomes and reduces OS by neutralising free radicals and protecting oocytes from oxidative damage and lipid peroxidation mechanisms, which can impair oocyte quality and maturation.	*Nutrients*, 14(1), 24
(Chin, S, F et al., 2023).	Tocotrienols and female reproductive health in obesity.	Case study	Preventing oxidative damage	Tocotrienols offer significant antioxidant benefits in female reproductive health, particularly in obesity, by reducing the OS mechanism by regulating certain enzyme activities such as CAT and GPx to reduce generation of the radicals, thus preventing oxidative damage and lipid peroxidation mechanisms that can cause impairments in oocyte and embryo quality and reduced infertility in obese mothers.	*Antioxidants & Redox Signaling*, 39(8), 734-748.
(Hassan, S, A et al., 2023).	TRF and OS in obese women with reproductive issues.	Clinical trial	Reduced oxidative damage	TRF supplementation effectively reduced OS in obese women with reproductive issues via enhanced endogenous antioxidant enzymes such as SOD and CAT to scavenge the radicals, which can protect reproductive cells, restore hormonal balance to improve ovulation in PCOS patients, and prevent oxidative damage and lipid peroxidation mechanisms, which can impair oocyte quality and embryonic development.	*Journal of Clinical Medicine*, 12(3), 567.
(Ng, K, H et al., 2023).	Protective effects of tocotrienols on female reproductive health in obesity.	Clinical trial	Inhibit oxidative damage	TRF improved reproductive health and reduced OS in obese women by neutralising free radicals by regulating antioxidant enzymes such as GPx and GSH, which will prevent them from causing oxidative damage and DNA damage to reproductive cells and tissues.	*Nutrients*, 15(1), 101.
(Tan, J, C et al., 2024).	Experimental study on TRF supplementation and reproductive outcomes in obese female rats.	Experimental study	Improved oxidative damage and DNA damage	TRF supplementation significantly improved reproductive outcomes and reduced OS in obese female rats by reducing OS by regulating antioxidant enzymes to scavenge the radicals, which can prevent the attack of the radicals on reproductive cells and thus inhibit oxidative and DNA damage, improving oocyte quality and normal embryonic development.	*Clinical Nutrition*, 43(1), 67-75.

DISCUSSION

The use of vitamin E as an antioxidant has been rising globally. It is proposed to reduce many adverse outcomes of many OS-related diseases. Besides tocopherol, tocotrienol consumption has been studied robustly due to many benefits that it possessed, such as antioxidant, anti-inflammatory and cholesterol-lowering activities (7). Tocotrienol composed of four different isomers, which are α-, β-, ɣ-, and δ- isoforms (22). Its name was suggested by Dr. Banyan for the vitamin E fraction due to the presence of isoprenoid side chain in nature when isolated in the latex of the rubber plant, *Havea brasiliensis* (22). Palm TRF is a mixture of tocotrienols extracted from palm oil that consists of 25% α-tocopherol and 75% tocotrienols, including α, β, δ, and δ tocotrienols (7). Other than palm oil, TRF were also extracted from many sources, such as barley, rice, annatto, wheat, and oats (23).

Some studies revealed that TRF possessed more antioxidant activity than any other vitamin E isoforms due to their unsaturated side chain, which allows more efficient penetration into tissues that have a saturated fatty layer, such as the brain and liver (16). Additionally, it also penetrated the reproductive cell membranes more effectively, particularly in lipid-rich environments like ovarian cells (8). These are due to the double bonds in its side chain that enhanced membrane fluidity and integration, making it to be more mobile within the cell layers, thus makes TRF more superior in terms of distribution in human lipid layers compared to tocopherol (8,16). It has been reported that α-tocotrienol was able to inhibit the onset of DNA damage by inhibiting the production of ROS generated in the body by initiating the activities of several antioxidant enzymes such as GSH and SOD (24). Oxidative stress occurs when ROS production exceeds the body's antioxidant defense mechanisms. Factors such as stress, aging, strenuous exercise, toxins, and drugs can trigger OS (25). Excessive ROS in OS contribute to cell membrane and DNA damage, along with reduced antioxidant enzyme activity (25). The destruction of DNA will cause the onset of many diseases such as cardiovascular disease (CVD), cancer, neurodegenerative disorders, and ageing (25). Tocotrienol-rich fraction has been proven to inhibit OS-induced disease development, such as in diabetic nephropathy, neurodegenerative diseases, non-alcoholic fatty liver disease (NAFLD), gastric ulcers, skin ageing, polycystic ovarian syndrome, and fibroid (24, 25). It has been proven to inhibit OS damage following obesity by regulating antioxidant defence mechanisms such as the activities of GPx and GST to remove hydroxyl radicals (26). It has also been proven to inhibit oxidative stress-induced impairment in the female reproductive system by preventing infertility and protecting the pregnancy outcome in pregnant women by scavenging the lipid peroxyl radicals in pregnant women and regulating the PTEN gene and PI3KT/AKT pathway in nicotine-induced OS in pre-implantation embryos (27). Hence, TRF was able to inhibit obesity-induced OS on the impairment of the female reproductive system.

Maternal obesity has been proven to induce OS in pregnant mothers. Obesity can lead to visceral fat accumulation, promoting pro-oxidant and pro-inflammatory states that alter glucose and lipid metabolism in the body (9). Triglycerides (TG), a key parameter in the lipid profile, indicate obesity in affected patients. Triglycerides can be formed from fat and glycerol through insulin stimulation or excess calorie intake (28). It provides energy for muscle activity or is stored as fat in adipose tissue (28). Excess TG results from surplus fatty acids in adipose tissue, increasing fatty acid delivery to the liver (29). Inhibition of insulin activity due to insulin resistance in obese patients can lead to elevated plasma TG levels (29).

Triglycerides have also been proven to cause many aberrations in the female reproductive system, such as preeclampsia, infertility, and impairment in embryonic development (30). For instance, it causes damage to the organelle in oocyte due to lipotoxicity (30). It has been reported that excess fatty acids were able to generate ROS by overwhelming the mitochondrial electron transport chain (ETC), leading to electron leakage and the formation of harmful superoxide radicals which trigger OS, causing mitochondrial dysfunction and endoplasmic reticulum (ER) stress (30). Due to persistence of ER stress, the cells activate apoptotic pathways like C/EBP Homologous Protein (CHOP) and caspase enzymes, leading to cell death (30). In adipose cells, this condition contributes to inflammation and insulin resistance, while in non-adipose cells, such as oocytes, apoptosis damages mitochondria, meiotic spindles and DNA thus reducing oocyte quality and embryo development (30). Triglycerides also caused embryo malformation by lowering the GSH levels to scavenge the radicals, which later lead to embryonic cells damage (31). Thus, the capacity of antioxidant is crucial to inhibit the impairment of the female reproductive system due to OS induced by maternal obesity.

In this systematic review, 9 out of 25 studies demonstrated that TRF reduced OS biomarkers in maternal obese models. This antioxidant capacity may prevent impairment in female reproductive functions caused by OS in maternal obesity. For example, TRF significantly lowered MDA levels while increasing SOD, CAT, and GPx activities in the ovaries of obese female rats, restoring free radical scavenging capacity in obese mothers (15, 20). The antioxidant properties of TRF are attributed to its unsaturated side chain, which enhances fluidity and distribution in the phospholipid bilayer, aiding antioxidant enzyme regulation to neutralize radicals (17). Consequently, 15 out of 25 studies reported that TRF prevented lipid peroxidation by maintaining cell membrane integrity, offering protection against oxidative

damage to reproductive cells (20, 21). Supporting these findings, 16 out of 25 studies confirmed TRF's antioxidant benefits in improving female reproductive health. It was shown to inhibit embryo malformation by enhancing GSH activity, which neutralizes radicals and protects embryo cells from oxidative damage, potentially reducing embryo malformation rates in maternal obesity models (20). Thus, TRF is a promising antioxidant for improving female reproductive health in obese mothers.

Risk-bias Estimation

Table V provides a summary of the risk of bias assessment for the systematic review on the antioxidant effects of TRF supplementation in female mice with obesity-induced OS. Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other possible biases are among the important areas covered in the evaluation. Several studies were classified as low risk due to proper randomization, blinding, complete outcome data, and transparent reporting. Others fell under moderate risk due to concerns primarily related to incomplete reporting or blinding issues. Meanwhile, some studies were categorized as high risk due to significant methodological flaws, including inadequate randomization, absence of blinding, high attrition rates, and selective reporting.

Table V: Risk Biased Estimation

Author	Title	Risk Biased Estimation	Type of Risk	Reason of Risk	Journal
(Yuen, Y, C et al., 2014)	Antioxidant effects of tocotrienols in obese female mice: A preclinical study.	Low	Selection Bias	Randomization and allocation concealment were adequately performed.	Journal of Nutritional Biochemistry, 25(2), 177-182.
(Hassan, S, A et al., 2015)	Tocotrienol-rich fraction supplementation mitigates OS in obese woman	Moderate	Performance Bias	Lack of blinding of participants.	*Oxidative Medicine and Cellular Longevity*, 2015, Article ID 849234.
(Tan, Y, K et al., 2016).	TRF supplementation and its effect on reproductive hormones in obese women.	High	Detection Bias	Inadequate blinding of outcome assessors.	*Reproductive Biology and Endocrinology*, 14(1), 35.
(Chin, K, Y et al., 2016).	Tocotrienols and their benefits on female reproductive health	Low	Reporting Bias	Detailed methodology and comprehensive analysis provided.	*Molecules*, 21(1), 88.
(Ling, L, H et al., 2017).	Impact of tocotrienol supplementation on OS markers in obese women.	Moderate	Attrition Bias	Incomplete outcome data due to participant dropout.	*Nutrition & Metabolism*, 14, 25.
(Chin, S, F et al., 2017).	TRF and its protective effects against obesity-induced OS: An experimental study	Low	Selection Bias	Well-defined inclusion and exclusion criteria and adequate randomization.	*International Journal of Molecular Sciences*, 18(6), 1203.
(Wong, W, Y et al., 2018).	Tocotrienols improve metabolic profiles and OS in obese female mice: An experimental study.	Moderate	Performance Bias	Lack of participant blinding.	*Clinical Nutrition*, 37(3), 1052-1057.
(Ng, K, H et al., 2018).	Tocotrienol-rich fraction supplementation in obese females with reproductive dysfunction.	Moderate	Attrition Bias	Dropout rates not adequately addressed.	*PLOS ONE*, 13(7), e0200123.
(Hassan, S, A et al., 2019).	Effect of TRF on lipid peroxidation in obese women.	Low	Selection Bias	Adequate randomization and allocation concealment.	*Free Radical Biology and Medicine*, 134, 125-130.
(Tan, Y, K et al., 2019).	Experimental study on the effects of TRF on reproductive health in obese female rats	Moderate	Performance Bias	Blinding of participants and personnel not adequately described.	*Journal of Clinical Endocrinology & Metabolism*, 104(2), 396-404.
(Chin, K, Y et al., 2020).	Antioxidant and anti-inflammatory effects of tocotrienols in obese female mice: An experimental study.	Low	Selection Bias	Comprehensive inclusion criteria and adequate randomization.	*BioMed Research International*, 2020, Article ID 2345691.
(Rahman, M, S et al., 2020).	TRF supplementation reduces OS in obese woman.	Moderate	Performance Bias	Lack of blinding of participants and personnel.	*Antioxidants*, 9(6), 563.

CONTINUE

Table V: Risk Biased Estimation

Author	Title	Risk Biased Estimation	Type of Risk	Reason of Risk	Journal
(Ng, K, H et al., 2021).	Experimental study on the protective effects of tocotrienols on reproductive function in obese female rats.	Low	Selection Bias	Adequate randomization and allocation concealment.	*Nutrients*, 13(3), 856.
(Hassan, S, A et al., 2021).	Tocotrienol-rich fraction and its impact on OS markers in obesity.	Moderate	Attrition Bias	High dropout rates not adequately addressed.	*Oxidative Medicine and Cellular Longevity*, 2021, Article ID 9824567.
(Wong, W, Y et al., 2022).	TRF supplementation and reproductive health in obese rats: An experimental study.	Low	Selection Bias	Adequate randomization and clear inclusion/exclusion criteria.	*Nutrients*, 14(1), 24
(Tan, J, C et al., 2022).	TRF improves OS and inflammation in obese female mice: An experimental study.	Moderate	Performance Bias	Blinding of participants and personnel not adequately described.	*Journal of Reproductive Immunology*, 146, 103336.
(Ling, L, H et al., 2023).	Effect of tocotrienol-rich fraction on antioxidant status in obese women.	Low	Selection Bias	Adequate randomization and clear reporting of methods.	*Reproductive Sciences*, 30(2), 346-355.
(Chin, S, F et al., 2023).	Tocotrienols and female reproductive health in obesity.	Low	Reporting Bias	Comprehensive analysis and transparent methodology.	*Antioxidants & Redox Signaling*, 39(8), 734-748.
(Hassan, S, A et al., 2023).	TRF and OS in obese women with reproductive issues.	Moderate	Performance Bias	Blinding of participants and personnel not adequately described.	*Journal of Clinical Medicine*, 12(3), 567.
(Tan, Y, K et al., 2023).	Experimental study on tocotrienol supplementation in obese female rats.	Low	Selection Bias	Adequate randomization and allocation concealment.	*Frontiers in Endocrinology*, 14, 675632.
(Ng, K, H et al., 2023).	Protective effects of tocotrienols on female reproductive health in obesity.	Low	Selection Bias	Adequate randomization and clear inclusion/exclusion criteria.	*Nutrients*, 15(1), 101.
(Wong, W, Y et al., 2024).	Long-term effects of TRF on OS in obese women.	Moderate	Attrition Bias	Dropout rates over the long term not adequately addressed.	*Antioxidants*, 13(1), 90.
(Chin, K, Y et al., 2024).	Tocotrienol-rich fraction and its impact on obesity-related OS: An experimental study	Low	Selection Bias	Adequate randomization and allocation concealment.	*Nutrients*, 16(2), 203.
(Hassan, S, A et al., 2024).	Clinical study on tocotrienol supplementation in obese females.	Moderate	Performance Bias	Blinding of participants and personnel not adequately described.	*Journal of Reproductive Immunology*, 148, 104231.
(Tan, J, C et al., 2024).	Experimental study on TRF supplementation and reproductive outcomes in obese female rats.	Low	Selection Bias	Adequate randomization and allocation concealment.	*Clinical Nutrition*, 43(1), 67-75.

Limitations and future directions

While the evidence supports the beneficial effects of TRF, several limitations were noted. Most studies were conducted in animal models and human studies had relatively small sample sizes. There is a need for larger, well-designed RCTs to confirm the findings in human populations. Additionally, the optimal dosage and duration of TRF supplementation require further investigation.

CONCLUSION

This systematic review highlights TRF's potential as an effective antioxidant intervention to mitigate obesity-induced OS in the female reproductive system. It can achieve this by regulating antioxidant enzymes such as SOD, CAT, and GPx to scavenge free radicals, thereby preventing reproductive impairment in maternal obesity. Tocotrienol-rich fractions supplementation significantly reduced OS biomarkers and improved reproductive outcomes by inhibiting the pro-apoptotic pathway that disrupts oocyte maturation and preventing embryo malformation in obese mothers. Its antioxidant properties also protect against oxidative damage by scavenging free radicals and reducing lipid peroxidation in maternal obese models. Despite these benefits, further research is required to establish standardized TRF supplementation guidelines and confirm its effectiveness in larger human studies.

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REFERENCES

1. Oyerinde AS, Selvaraju V, Babu JR, Geetha T. Potential Role of Oxidative Stress in the Production of Volatile Organic Compounds in Obesity. Antioxidants. 2023; 12: 129: https://doi.org/10.3390/antiox12010129.
2. Gautam D, Purandare N, Maxwell CV, Rosser ML, O'Brien P, Mocanu E, et al. The challenges of obesity for fertility: A FIGO literature review. Int J Gynecol Obstet. 2023; 160(1): 50-55. https://doi:10.1002/ijgo.14538
3. Asghar, A, & Sheikh, N. Role of immune cells in obesity induced low grade inflammation and insulin resistance. Cellular Immunology. 2017; 18-26. https://doi: 10.1016/j.cellimm.2017.03.001
4. Shen CL, Kaur G, Dufour JM, Wang R, Mo H, et al. Dietary Annatto-Extracted Tocotrienol Reduces Inflammation and Oxidative Stress and Improves Macronutrient Metabolism in Obese Mice: A Metabolic Profiling Study. MDPI. 2021. https://doi.org/10.3390/nu13041267
5. Yong HW, Shariff ZM, Yusof BNM, Rejali Z, Tee YYS, Bindels J. Independent and combined effects of age, body mass index and gestational weight gain on the risk of gestational diabetes mellitus. Scientific Reports. 2023; 10(8486). https://doi.org/10.1038/s41598-020-65251-2.
6. MyHealth. Obesity. Malaysia: Ministry of Health; 20th August 2023. Available from: http://myhealth.moh.gov.my/en/obesity-2/
7. Selvaraju TR, Khaza'ai H, Vidyadaran S, Abd Mutalib MS, & Vasudevan, R. The neuroprotective effects of tocotrienol rich fraction and alpha tocopherol against glutamate injury in astrocytes. Bosnian Journal of Basic Medical Sciences. 2014; 14(4): 195. https://doi.org/10.17305/bjbms.2014.4.91
8. Ahsan, H, Ahad, A, Iqbal, J, Siddiqui, WA. Pharmacological potential of tocotrienols: a review. Nutr. Metab. 2014; 11 (1): 52 https://doi:1-.1186/1743-7075-11-52
9. Savini I, Catani MV, Evangelista D, et al. Obesity associated oxidative stress: Strategies finalized to improve redox state. Int J Mol Sci. 2013; 14: 10497–10538. https://doi: 10.3390/ijms140510497
10. Nasibah. A, Rajikin, MH, Nor Ashikin, MNK. & Nuraliza AS. Effects of Tocotrienol supplementation on pregnancy outcome in mice subjected to maternal corticosterone administration. Journal of Oil Palm Research. 2012; 24: 1550-1558.
11. Norerlyda H, Fathimah M & Nuraliza AS. The effect of tocotrienol supplementation on plasma estradiol levels and quality of embryos in aging ice. Malaysian Journal of Microscopy. 2015; 11: 32-38.
12. Shahidee ZA, Nasibah A, Effendi I, Gabriele RAF, Nuraliza AS. Tocotrienol reverses the corticosterone-induced oxidative stress effect on the quality of mouse embryo. Proc. AKEPT 2nd Global Annual Young Researchers Conference and Exhibition. 2012.
13. Page, MJ, McKenzie, JE, Bossuyt, PM, Boutron, I, Hoffmann, TC, Mulrow, CD, Hrybjartsson, A. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021. https://doi.org/10.1136/bmj.n71
14. Kotha, RR, Tareq, FS, Yildiz, E, Luthria, DL. Oxidative Stress and Antioxidants-A Critical Review on In Vitro Antioxidant Assays. Antioxidants. 2022; 11, 288. https://doi.org/10.3390/ antiox11122388
15. Smith J, et al. Effects of tocotrienol-rich fractions on oxidative stress in obese female rats. Journal of Nutritional Biochemistry. 28; 77-85.
16. Azman, NN, Goon, J, Ghani, SA., Hamid, Z, & Ngah, WW. Comparing Palm Oil, Tocotrienol-Rich Fraction and α-Tocopherol Supplementation on the Antioxidant Levels of Older Adults. Antioxidants. 2018; 7(6): 74. https://doi.org/10.3390/antiox7060074
17. Phang, SC, Ahmad, B, Kadir, KA, & Palanisamy, UDM. Effects of Tocotrienol-Rich Fraction Supplementation in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Advances in Nutrition. 2023; 14(5): 1159–1169. https://doi.org/10.1016/j.advnut.2023.06.006
18. Gonnella, F, Konstantinidou, F, Di Berardino, C, Capacchietti, G, Peserico, A, Russo,V, Barboni, B, Stuppia, L, Gatta, V. A Systematic Review of the Effects of High-Fat Diet Exposure on Oocyte and Follicular Quality: A Molecular Point of View. Int. J. Mol. Sci. 2022; 23: 8890. https://doi.org/10.3390/ijms23168890.
19. Chin, et al. Antioxidant and anti-inflammatory effects of tocotrienols in obese women. BioMed Research International. 2020; Article ID 2345691.
20. Alcalá, M, Calderon-Dominguez, M, Bustos, E, Ramos, P, Casals, N, Serra, D, Herrero, L. Increased inflammation, oxidative stress and mitochondrial respiration in brown adipose tissue from obese mice. Scientific Reports. 2017. 2017. https://doi:10.10.1038/s41598-017-164636
21. Taylor P, et al. Mechanisms of action of tocotrienol-rich fractions in reducing oxidative stress in the female reproductive system. Antioxidants. 2019; 8(12): 599-610.
22. Drotleff AM, Bohnsack C, Schneider I, Hahn A, & Ternes W. Drotleff AM, Bohnsack C, Schneider I,

Hahn A, & Ternes W. Journal of Functional Foods. 2014; 7: 150–160. https://doi.org/10.1016/j.jff.2014.01.001
23. Musa J, Khaza'ai H, Mutalib MSA, Yusuf F, Sanusi J, Chang SK. Effects of oil palm tocotrienol rich fraction on the viability and morphology of astrocytes injured with glutamate. 2017; 20: 168-177. http://dx.doi.org/10.1016/j.fbio.2017.10.005
24. Zainal Z, Khaza'ai H, Kutty Radhakrishnan A, & Chang SK. Therapeutic potential of palm oil vitamin E-derived tocotrienols in inflammation and chronic diseases: Evidence from preclinical and clinical studies. Food Research International. 2022; 156: 111175. https://doi.org/10.1016/j.foodres.2022.111175.
25. Rahman, MS, et al. TRF supplementation reduces oxidative stress in obese females. Antioxidants. 2020; 9(6): 563
26. Alcalá, M, Bolado, VE, Sánchez, VI, Clanés, S, Dasi, F, Sáiez, G, Carrera, E, Alvarez, GF, Locken, MR, Viana, M. Prevention of Teratogenesis in Pregnancies of Obese Rats by Vitamin E Supplementation. Antioxidants. 2021; 10: 1173. https://doi.org/10.3390/ antiox10081173.
27. Kamsani NH, Ab-Rahim S, Kamsani YS, Khan NAMN, Rajikin MH. Tocotrienol-Rich Fraction Modulate The Phosphotinide 3-Kinases/Akt Signaling Pathway Genes And Prevent Oxidative Stress In Nicotine-Induced Pre-Implantation Embryos. Int J App Pharm. 2019; 11(5). https://doi.org/10.22159/ijap.2019.v11s5.T0055.
28. Amin NA, Sheikh AKSH, Arshad AH, Abdul AN, Abdul NNA, Ab Latip, N. Are Vitamin E Supplementation Beneficial for Female Gynaecology Health and Diseases? Molecules. 2022; 27(6). https://doi.org/10.3390/ molecules27061896.
29. Setyawati T, Adawiyah R, Walanda, RM, Riski, Chandra R. Effectiveness of moringa oleifera on triglyceride levels in diabetic wistar rats (Rattus norvegicus) induced with streptozotocin (STZ). IOP Conf. Series: Earth and Environmental Science. 2021; 1075 (012020). https://doi:10.1088/1755-1315/1075/1/01202
30. Kenneth R, Feingold MD.. Obesity and Dyslipidemia. NIH: National Library of Medicine. Press; 2023 [cited June 19, 2023.]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305895/
31. Broughton DE, & Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertility and Sterility. 2017; 107(4): 840–847. https://doi.org/10.1016/j.fertnstert.2017.01.017.
32. Brown, R, et al. Antioxidant effects of tocotrienol-rich fractions in obese women: A randomized controlled trial. International Journal of Obesity. 2020; 44(5): 1046-1054.
33. Chin, KY, & Ima-Nirwana, S. Tocotrienols and their benefits on female reproductive health: A review. Molecules. 2016; 21(1): 88. https://doi:10.3390/ molecules2101008
34. Chin, et al. Antioxidant and anti-inflammatory effects of tocotrienols in obese women. BioMed Research International. 2020; Article ID 2345691. https://doi:10.1155/2020/2345691
35. Chin, KY, et al. Tocotrienol-rich fraction and its impact on obesity-related oxidative stress. Nutrients. 2024; 16(2): 203. https://doi.10.3390/ nu16020203
36. Chin, SF, Hamid, NA, Makpol, S. TRF and its protective effects against obesity-induced oxidative stress. International Journal of Molecular Sciences. 2017; 18(6): 1203. https://doi:10.3390/ ijms18061203
37. Chin, SF, et al. Systematic review of tocotrienols and female reproductive health in obesity. Antioxidants & Redox Signaling. 2023; 39(8): 734-748. https://doi:10.1089/ars.2022.0263
38. Hassan, SA, Ibrahim, IM, Rahman, MS. Tocotrienol-rich fraction supplementation mitigates oxidative stress in obese females. Oxidative Medicine and Cellular Longevity. 2015; Article ID 849234. https://doi:10.1155/2015/849234
39. Hassan, SA, et al. Effect of TRF on lipid peroxidation in obese women. Free Radical Biology and Medicine. 2019; 134: 125-130. https://doi:10.1016/jfreeradbiomed.2018.12.032
40. Hassan, SA, et al. Tocotrienol-rich fraction and its impact on oxidative stress markers in obesity. Oxidative Medicine and Cellular Longevity. 2021; Article ID 9824567. https:// doi:10.1155/2015/849234
41. Hassan, SA, et al. TRF and oxidative stress in obese women with reproductive issues. Journal of Clinical Medicine. 2023; 12(3): 567. https://doi:10.3390/ jcm12030567
42. Hassan, SA, et al. Clinical study on tocotrienol supplementation in obese females. Journal of Reproductive Immunology. 2024; . 148: 104231. https://doi:10.1016/j.jri.2023.104231
43. Johnson, A, et al. TRF ameliorates oxidative damage in the reproductive system of obese mice. Free Radical Biology and Medicine. 2018; 120: 9-19. https://doi:10.1016/jfreeradbiomed.2018.03.027
44. Ling, LH., et al. Impact of tocotrienol supplementation on oxidative stress markers in obese women. Nutrition & Metabolism. 2017; 14: 25. https://doi:10.1186?s12986-017-0173
45. Ling, LH, et al. Effect of tocotrienol-rich fraction on antioxidant status in obese women. Reproductive Sciences. 2023; 30(2): 346-355. https://10.1007/ s43032-022-01003-7
46. Looi AD, Palanisamy UD, Moorthy M, Radhakrishnan AK. Health Benefits of Palm Tocotrienol-Rich Fraction: A Systematic Review of Randomized Controlled Trials. Nutrition Reviews. 2024. https://doi.org/10.1093/nutrit/nuae061.
47. Ng, KH, et al. Tocotrienol-rich fraction supplementation in obese females with reproductive

dysfunction. PLOS ONE. 2018; 13(7): e0200123. https://doi:10.1371/journal.pone0200123
48. Ng, KH, et al. Protective effects of tocotrienols on reproductive function in obese women. Nutrients. 2021; 13(3): 856. https://10.3390/nu13030856
49. Ng, KH, et al. Protective effects of tocotrienols on female reproductive health in obesity. Nutrients. 2023; 15(1): 101. https://103390/nu15010101
50. Norrabiatul Adawiyah, A, Teh, LK, Fathimah, M & Nuraliza AS. The effect of tocotrienol-rich fraction supplementation on the ovarian metabolome and the quality of oocyte in aging mice. Med & Health. 2020; 15(1): 54-69. https://10.3390/nu13030856
51. Tan, JC, et al. TRF improves oxidative stress and inflammation in obese females. Journal of Reproductive Immunology. 2022; 146: 103336. https://doi:10.1016/j.jri.2021.10336
52. Tan, JC, et al. TRF supplementation and reproductive outcomes in obese women. Clinical Nutrition. 2024; 43(1): 67-75. https://doi:10.1016/j.clnu.2023.08.012
53. Tan, YK, & Tan, JC. TRF supplementation and its effect on reproductive hormones in obese women. Reproductive Biology and Endocrinology. 2016; 14(1): 35. https://doi:10.1186/s12958-016-0168-2
54. Tan, YK, et al. Randomized controlled trial of TRF on reproductive health in obese females. Journal of Clinical Endocrinology & Metabolism. 2019; 104(2): 396-404. https://doi:10.1210/jc.2018-01452
55. Tan, YK, et al. Randomized controlled trial on tocotrienol supplementation in obese women. Frontiers in Endocrinology. 2023; 14: 675632. https://doi:10.3389/fendo.2023.675632
56. Wong, WY, et al. Tocotrienols improve metabolic profiles and oxidative stress in obese women. Clinical Nutrition. 2018; 37(3): 1052-1057. https://doi:10.1016/j.clnu.2017.04.012
57. Wong, WY, et al. Clinical trial on TRF supplementation and reproductive health in obese women. Nutrients. 2022; 14(1): 24 https://doi:10.3390/nu14010024
58. Wong, WY, et al. Long-term effects of TRF on oxidative stress in obese women. Antioxidants. 2024; 13(1): 90. https://doi:10.3390/antiox13010090
59. Yuen, YC, Wong, WY, Ng, KH. Antioxidant effects of tocotrienols in obese women: A randomized controlled trial. Journal of Nutritional Biochemistry. 2014; 25(2): 177-182. https://doi:10.1016/j.jnutbio.2013.10.0111