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Review

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The effects of *Citrus* on oxidative stress and lipid metabolism modulation: its potential for improving female reproductive health

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Abstract: *Citrus*, with a long history of consumption internationally, is widely used as a health food. *Citrus* and its active components exert significant effects on oxidative stress and lipid metabolism, factors closely associated with female reproductive health. Studies suggest that citrus-derived compounds may alleviate oxidative stress by activating signaling pathways such as Nrf2 and SIRT1, and improve lipid metabolism through the activation of pathways including PPARα. This review focuses on the effects of *Citrus* on oxidative stress and lipid metabolism, aiming to provide new insights for promoting female reproductive health, but further work is needed to elucidate the mechanisms involved and validate the therapeutic potential of *Citrus* bioactive components in clinical settings.

Key words: *Citrus*; Food; Female reproductive health; Oxidative stress; Lipid metabolism

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1 Introduction

The genus *Citrus* and its closely related genera—*Fortunella*, *Poncirus*, *Eremocitrus* and *Microcitrus*—are members of the Rutaceae family (subfamily Aurantioideae) of flowering plants (Wu et al., 2018). These taxa are predominantly found in monsoon regions stretching from western Pakistan to north-central China, as well as in areas like the East Indies, New Guinea, northeastern Australia, and parts of Polynesia (Wu et al., 2018).

Citrus species include *Citrus reticulata* (mandarin, tangerine), *Citrus grandis*, *Citrus aurantium* (sour orange), *Citrus sinensis* (sweet orange), and *Citrus medica* (citron). The countries with the largest production of *Citrus* are China, Brazil, and the USA (Spreen et al., 2020). *Citrus*-derived ingredients have been integral to both culinary traditions and healthcare practices globally. One study reported that citrus fruit consumption is associated with a reduced risk of endometriosis (Harris et al., 2018). Additionally, nobiletin, a polymethoxylated flavone extracted from citrus fruits, has been shown to promote oocyte maturation and subsequent embryo development (Cajas et al., 2020). Together, these findings suggest that citrus fruits may play a beneficial role in improving female reproductive health (Harris, et al., 2018; Cajas, et al., 2020). The different parts and preparations of *Citrus* plants transform into different food products, which are widely consumed around the world (Table 1).

In China, *Citrus*-based food and herbal beverages have a long history. For instance, *C. reticulata* is a versatile ingredient used in foods like the Xinhui Chenpi plum, Chenpi paste, cakes, duck dishes, and even wine, which not only neutralizes strong odors in meats but also enhances flavor. When included in desserts such as mung bean soup or red bean porridge, it imparts a distinct, aromatic taste (Su, 2011). The "Red Crown" Juhong herbal drink features *C. grandis* as a key ingredient, complemented by licorice, mesona, imperata root, chrysanthemum, honeysuckle, mulberry leaves, rock sugar, and granulated sugar (Liang et al., 2023). These

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drinks, known for their soothing and heat-reducing properties, are preservative-free and can be served hot or cold (Liang, et al., 2023). Today, *C. grandis*-based teas—such as Juhong-green fruit tea, Juhong-gardenia tea, and Juhong-Pu'er tea—continue this tradition, combining health benefits with the unique flavor of *C. grandis* (Liang, et al., 2023). Recent innovations have expanded the applications of *C. grandis*. For example, effervescent vitamin C tablets were developed, which suggests that these tablets have antioxidant properties. This highlights the ongoing exploration of the potential of *Citrus* for enhancing health and well-being. In China, *Citrus aurantium* is commonly consumed as an infusion to aid bowel movement and protect the gastric mucosa (Gao et al., 2021). In Iran, the mature fruits of *C. aurantium* are consumed as food (Hosseinimehr et al., 2003) and in Mexico they are used in table salt and chili paste (Fugh-Berman and Myers, 2004). In Turkey, their juice serves as a seasoning or acidulant in salads and appetizers (Karabiyikli et al., 2014). Additionally, *C. sinensis* is often made into orange juice in Turkey (Kelebek and Selli, 2011). In the 19th century, *C. medica* was used in savory dishes in the form of citron vinegar and ravigote vinegar with citron zest for a tinge of *Citrus* flavor, and the fruit is also used as different dishes (Chhikara et al., 2018).

Table 1 Different food products of *Citrus* used world widely

Latin name	Food products	Country
Citrus reticulata	Xinhui Chenpi plum, Chenpi paste, cakes, duck dishes, wine (Su, 2011)	China
Citrus grandis	Juhong-green fruit tea, Juhong-gardenia tea, Juhong-Pu'er tea, vitamin C effervescent tablets (Wang, 2012; Liang, et al., 2023)	China
Citrus aurantium	Health food products (Gao, et al., 2021)	China
	Food (Hosseinimehr, et al., 2003)	Iran
	Table salt and chili paste (Fugh-Berman and Myers, 2004)	Mexico
	A seasoning or acidulant in salads and appetizers (Karabiyikli, et al., 2014)	Turkey
Citrus sinensis	Orange juice (Kelebek and Selli, 2011)	Turkey
Citrus medica	Citron vinegar, ravigote vinegar, dishes (Chhikara, et al., 2018)	World

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Oxidative stress and lipid metabolism have a profound effect on ovarian and uterine functions. Oxidative stress arises from an imbalance in the body's antioxidant defense system, resulting in excessive accumulation of reactive oxygen species (ROS) (Sies, 2015). This condition not only damages cellular proteins and DNA but also significantly impacts lipid metabolism (Sies, 2015). Excessive ROS can trigger lipid peroxidation, compromising cellular membrane integrity and producing toxic byproducts like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) (Schieber and Chandel, 2014). Additionally, oxidative stress influences the expression of genes involved in lipid metabolism, affecting lipid synthesis, breakdown, and energy regulation (Spiteller, 2006). As a result, oxidative stress is a key factor in the development of various metabolic disorders.

Citrus contain naringenin, a dietary flavanone with strong antioxidant properties (Motallebi et al., 2022). Naringenin in *Citrus* fruits can scavenge free radicals, reducing oxidative damage (Alimohammadi et al., 2022). This helps prevent and ease oxidative stress-related diseases, making *Citrus* fruits a great dietary choice for antioxidant benefits (Alimohammadi, et al., 2022). Research has established a strong link between oxidative stress and various reproductive health issues, including polycystic ovary syndrome (PCOS) (Dubey et al., 2021) and endometriosis (Amini et al., 2021). As an essential component of overall health, female reproductive health significantly influences both fertility and the well-being of children. Oxidative stress, a condition marked by an imbalance between oxidative and antioxidant systems, leads to the excessive accumulation of ROS (Sies, 2015). Elevated ROS levels can damage oocytes and ovarian tissue, disrupt hormone secretion, and impair the quality of ova, ultimately interfering with normal reproductive functions (Agarwal et al., 2005). Similarly, lipid metabolism disorders are critical contributors to female reproductive health challenges (Dubey, et al., 2021). Abnormal lipid metabolism can result in obesity, insulin resistance, and inflammatory responses, all of which

negatively affect ovarian function and sex hormone regulation (Dubey, et al., 2021). These metabolic disturbances are frequently observed in conditions like PCOS and are closely associated with embryonic development (Ye et al., 2021).

In recent years, improving diet has gained increasing recognition due to its numerous advantages, including minimal side effects, safety, palatability, and ease of preparation (Shahid et al., 2022). The high prevalence of glucose metabolism disorders—reported in most individuals with ovarian dysfunction—underscores the role of excessive energy intake and imbalanced dietary patterns in the condition's onset and progression (Hu et al., 2023). Consequently, improving diet is increasingly recommended as a supportive treatment for obese or overweight individuals with ovarian dysfunction.

In addition, recent studies suggest that the bioactive components of *Citrus* may offer therapeutic benefits for female reproductive health. Compounds such as naringenin and hesperidin have shown promising effects. Naringenin has been linked to improved ovarian function through modulation of gut microbiota (Wu et al., 2022) and reductions in serum androgen levels (Gungor et al., 2014). Similarly, hesperidin has shown potential for improving ovarian dysfunction (Zarein et al., 2023). However, the mechanisms by which these compounds influence oxidative stress and lipid metabolism in female reproductive health remain underexplored. This review examines the potential of *Citrus*'s bioactive components to improve female reproductive health by targeting oxidative stress and lipid metabolism. By exploring these pathways, we aim to provide new insights into their therapeutic potential and their broader implications for developing functional foods in the future.

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2 Nutrition of *Citrus* Fruit

Citrus fruits are valued not only for their refreshing flavor but also for their rich nutritional content. They are an excellent source of essential vitamins, minerals, and dietary fiber, all of which support overall health and immune function (Lu et al., 2023). While best known for their high vitamin C content, *Citrus* fruits also provide key nutrients such as potassium, folate, calcium, and B vitamins, which contribute to energy production, nerve function, and bone health (Lu, et al., 2023).

Beyond their vitamin and mineral content, *Citrus* fruits contain beneficial phytochemicals, including flavonoids and carotenoids. These compounds have been linked to various health benefits, such as reducing the risk of chronic diseases, including cardiovascular conditions and certain cancers (Lu, et al., 2023). Additionally, *Citrus* fruits are naturally low in fat, sodium, and calories, making them a nutritious choice for those looking to maintain a healthy weight. Their combination of high nutrient density and low energy content makes them a valuable addition to a balanced diet, promoting both overall wellness and disease prevention (Lu, et al., 2023).

3 Chemical Composition of *Citrus*

Citrus contains four major active components: flavonoids (Zhao et al., 2020), essential oils (Dosoky and Setzer, 2018), alkaloids (Haaz et al., 2006), and coumarins (Ramírez-Pelayo et al., 2019). These components contribute to its diverse physiological and pharmacological properties, making it a valuable resource for both food and medicinal applications.

3.1 Flavonoids

Flavonoids are the most abundant active compounds in *Citrus* (Alam et al., 2022). Extensive research has revealed their broad physiological activities, including anti-cancer (Wang et al., 2000), antibacterial (Cushnie and Lamb, 2005), antioxidant, and lipid- and glucose-lowering effects (Khan et al., 2012). These properties underpin the therapeutic potential of flavonoids in addressing various health conditions.

3.2 Essential Oils

Essential oils are another key component, with limonene being the most prominent constituent (Lan et al., 2023). Limonene is abundant in *Citrus* plants like lemon and orange. (Anandakumar et al., 2021). It has been shown to exhibit expectorant and antibacterial effects (Vieira et al., 2018), further enhancing the medicinal value of *Citrus*.

3.3 Alkaloids

Citrus is also a source of alkaloids, particularly synephrine, a compound known for its hypertensive effects (Stohs et al., 2012). Synephrine increases cardiac output and peripheral vascular resistance, leading to elevated left ventricular pressure and arterial blood pressure (Koncz et al., 2022). These properties make alkaloids a significant component in understanding the physiological effects of *Citrus*.

3.4 Coumarins

Coumarins, characterized by their simple structures, high bioavailability, and low toxicity, are another important class of compounds in *Citrus*. These compounds, such as bergapten, exhibit analgesic, anti-inflammatory, and antibacterial activities, making them widely applicable in clinical settings (Annunziata et al., 2020; Garg et al., 2022). Analysis of ethanol extracts from *Citrus aurantium* has revealed a variety of bioactive compounds, including specific coumarins (Chen et al., 2012). Furthermore, research on different *Citrus* cultivated in Colombia has revealed a diversity of coumarins which have antibacterial effects (Ramírez-Pelayo, et al., 2019). These findings suggest the presence of additional, unexplored bioactive coumarins in *Citrus*, offering promising opportunities for future drug development. Table 2 lists the health benefits of the active components in *Citrus*.

Table 2 Health Benefits of Active Components in *Citrus*

Component Categories	Component	Health benefits
Flavonoids	Naringin (Shilpa et al., 2023)	Anti-inflammatory, antibacterial, lipid- and glucose-lowering, anti-tumor
	Hesperidin (Pyrzynska, 2022)	Antioxidant, anti-inflammatory, antibacterial, glucose-lowering
	Nobiletin (Moazamiyanfar et al., 2023)	Anti-tumor
	Naringenin (Uçar and Göktas, 2023)	Antioxidant, hepatoprotective
	Tangeretin (Ashrafizadeh et al., 2020)	Cardiovascular protection, glucose-lowering
Essential Oils	Limonene (Anandakumar, et al., 2021)	Antibacterial, anti-tumor, expectorant
	α-Pinene (Salehi et al., 2019)	Antibacterial, anti-infection, antioxidant
	β-Pinene (Salehi, et al., 2019)	Antibacterial
Alkaloids	Synephrine (Stohs, et al., 2012)	Promotes gastrointestinal motility, hypertensive, lipid-lowering
	N-methyltyramine (Stohs and Hartman, 2015)	Appetite stimulant, inhibits lipid breakdown
Coumarins	Umbelliferone (Da Cruz et al., 2020)	Antibacterial, Anti-ulcer
	Epoxyaurapten (Kuo et al., 2017)	Anti-inflammatory

The uterus relies on a highly dynamic structure that regenerates after each menstrual cycle or pregnancy. It consists of an epithelial lining, a stromal mesenchymal layer, and an underlying smooth muscle (myometrium) (Tempest et al., 2020; Yamaguchi et al., 2021). Endometriosis is an estrogen-dependent inflammatory disease of the pelvic cavity, characterized by the ectopic implantation and growth of endometrial tissue (including glands and stroma) outside the uterine cavity (Scutiero et al., 2017). Affected women commonly experience pelvic pain and infertility (Taylor et al., 2021). Endometriosis also alters metabolic functions in the liver and adipose tissue, contributing to systemic inflammation (Taylor, et al., 2021). Additionally, retrograde menstruation introduces macrophages, red blood cells, and apoptotic endometrial tissue into the peritoneal cavity—factors known to induce oxidative stress (Scutiero, et al., 2017). As a result, the generation of ROS within the peritoneal environment may play a crucial role in the pathogenesis of endometriosis (Scutiero, et al., 2017). The potential role of *Citrus* in improving the female reproductive system based on its effects on oxidative stress and lipid metabolism is summarized in Fig. 1.

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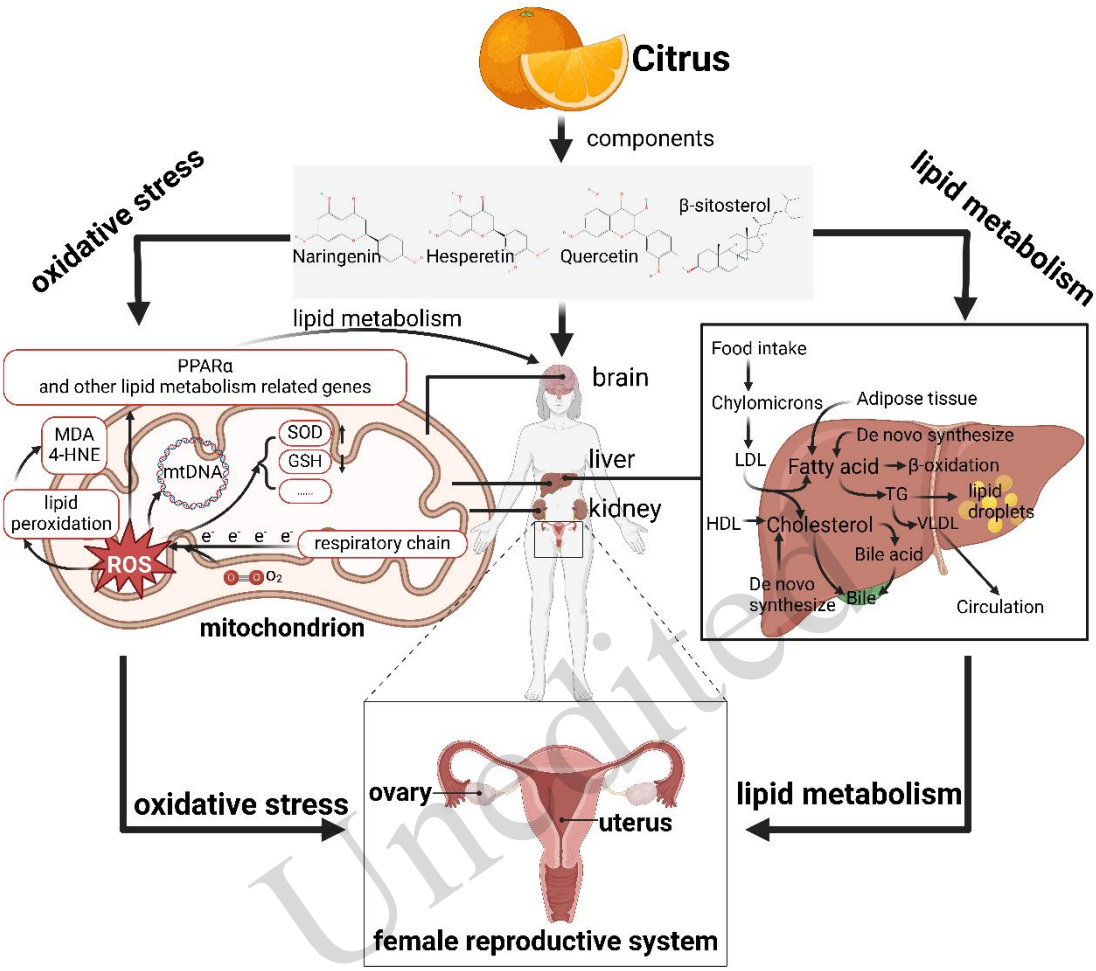

Fig. 1 Potential role of *Citrus* in improving the female reproductive system based on its effects on oxidative stress and lipid metabolism. MDA: Malondialdehyde; 4-HNE: 4-Hydroxynonenal; SOD: Superoxide Dismutase; GSH: Glutathione; TG: Triglyceride; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein. (created in BioRender. Yang, Y. (2025) https://BioRender.com/d73a999)

4.2 Effect of the antioxidant activities of Citrus on the female reproductive system

The antioxidant ability is the bridge connecting a variety of biological activities. *Citrus* flavonoids play an essential role in regulating oxidative stress and are an important source of the daily intake of antioxidant supplements. Many studies have shown that *Citrus* flavonoids promote health through antioxidation (Wang et al., 2022). Ovarian dysfunction is a significant contributor to endocrine abnormalities among women of reproductive age, with its high prevalence drawing substantial attention (Uyanikoglu et al., 2017). Research has identified mitochondrial dysfunction as a key feature in individuals with ovarian dysfunction, manifesting as structural abnormalities and mutations in mitochondrial DNA (mtDNA). Notably, the number of mtDNA copies in these individuals is significantly reduced, leading to impaired mitochondrial function (Uyanikoglu, et al., 2017). A critical factor in mitochondrial dysfunction is the overproduction of ROS by the electron transport chain within the mitochondrial inner membrane. This heightened oxidative environment exposes mtDNA to prolonged oxidative stress, resulting in a cascade of abnormalities. Studies have shown that mutations in mitochondrial transfer RNA disrupt mtDNA structure and aminoacylation capacity, impairing mitochondrial protein synthesis. This dysfunction inhibits the respiratory chain, reduces oxidative phosphorylation efficiency, and diminishes ATP production. The subsequent increase in ROS levels creates a feedback loop that exacerbates mitochondrial dysfunction, establishing conditions conducive to ovarian dysfunction (Zeng et al., 2020; Dabravolski et al., 2021).

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To evaluate oxidative stress and mitochondrial function in affected tissues, researchers commonly measure ROS-related metabolites such as glutathione peroxidase, catalase, superoxide dismutase, and malondialdehyde. Alterations in these metabolites provide insight into redox imbalances associated with ovarian dysfunction, offering valuable evidence for further exploration of its underlying mechanisms (Jomova et al., 2024). In addition, in endometriosis, the activation of mononuclear phagocytes is triggered by factors such as damaged red blood cells and apoptotic endometrial cells. Research has shown that tumor necrosis factor (TNF)-α levels in peritoneal fluid are positively correlated with the severity of endometriosis (Bedaiwy and Falcone, 2003). Cytokines released by macrophages alter the redox state of ectopic endometrial tissue, contributing to the oxidative stress observed in endometriosis patients (Oner-Iyidogan et al., 2004). Studies have measured the activity of antioxidant enzymes and lipid peroxidation in ectopic endometrial tissue from ovarian endometriotic cysts. Superoxide dismutase (SOD) activity was significantly higher in ectopic compared to eutopic endometrium, with MDA levels showing a positive correlation with SOD activity. TNF-α has been shown to upregulate manganese superoxide dismutase (MnSOD) expression in endometrial tissue, suggesting that MnSOD acts as a protective mechanism to neutralize superoxide anions generated by TNF-α-induced oxidative stress (Sugino et al., 2002). Furthermore, hormonal fluctuations, such as estrogen and progesterone withdrawal, stimulate the production of prostaglandin F2α through ROS-mediated activation of the NF-κB pathway (Sugino et al., 2004). This highlights the intricate relationship between oxidative stress, inflammation, and hormonal regulation in the pathophysiology of endometriosis.

The active components of *Citrus* exhibit a range of biological activities, including anti-inflammatory, antioxidant, and apoptosis-regulating effects (Table 3). Naringin has been extensively studied for its antioxidant properties. Research indicates that naringin can enhance the activity of key antioxidants such as reduced glutathione (GSH), SOD, catalase (CAT), glutathione peroxidase (GPx), and glutathione-S-transferase (GST), which are often inhibited under stress conditions (El-Saad and Abdel-Wahab, 2020). For example, in high-fat diet (HFD) rat models, naringin was shown to reduce serum levels of MDA and nitric oxide (NO) while increasing SOD and GSH levels (Liu et al., 2022). Similarly, research shown that naringin reduced MDA levels and elevated GPx and SOD activity in rat models treated with Res (Sadeghi Nejad et al., 2023). Further evidence demonstrated that naringin treatment significantly increases mRNA expression of antioxidant factors like glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits in mice with liver dysfunction. KEGG pathway analysis suggested that naringin's effects were closely associated with the mitigation of oxidative stress (Ji et al., 2023). Moreover, other research indicates that naringin alleviates oxidative stress via the SIRT1/FoxO1 signaling pathway, resulting in reductions in ROS, MDA, and 4-HNE levels, alongside enhanced SOD, glutathione peroxidase (GSH-Px), and CAT activity (Zhao et al., 2023). These findings suggest that naringin may enhance cellular antioxidant capacity by modulating NAD^+ levels, thereby influencing the activity of the NAD^+-dependent deacetylase SIRT1 (Guan et al., 2025). This, in turn, promotes the deacetylation of FOXO3, a transcription factor that regulates the expression of antioxidant defense genes such as SOD and CAT (Guan, et al., 2025). Hesperidin, another active compound of *Citrus*, has also shown promise in reducing oxidative stress. One study has shown that hesperidin attenuates ROS overproduction in oleic acid-induced HepG2 cells by upregulating antioxidants (SOD etc.) through the activation of the PI3K/Akt-Nrf2 pathway (Li et al., 2021). Similarly, research found that hesperidin alleviates oxidative damage in H2O2-treated ARPE-19 cells via Nrf2 pathway activation, leading to reduced malondialdehyde/myeloperoxidase (MDA/MPO) levels and increased SOD/GSH activity (Chen et al., 2019). Additional studies confirmed that hesperidin could mitigate liver oxidative stress by activating the PI3K/Akt-Nrf2 pathway, thereby reducing ROS accumulation and suppressing NF-κB-mediated inflammation (Zhang et al., 2024). The above findings suggest that hesperidin may exert cytoprotective effects by activating Nrf2, which in turn upregulates the expression of genes encoding antioxidant and detoxifying enzymes (Luchkova et al., 2024). Alternatively, hesperidin may enhance antioxidant defense by increasing the availability of NADPH for glutathione regeneration via the pentose phosphate pathway (Luchkova, et al., 2024). Other bioactive components, such as β-sitosterol and quercetin, further highlight the therapeutic potential of *Citrus*. Studies have shown that β-sitosterol enhances ATP production by stimulating mitochondrial electron transport and activating the AMPK/PGC-1 signaling pathway (Wong et al., 2015; Wong et al., 2016). Quercetin, meanwhile, has been shown to reverse mitochondrial dysfunction, promote mitochondrial biogenesis via the PGC1-α pathway, and restore ovarian function by regulating the PI3K/Akt/FoxO3a pathway. These effects include enhanced expression of anti-Müllerian hormone (AMH), estradiol (E2), SOD, and GSH-Px, which collectively reduce oxidative stress and support

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ovarian health (Chen et al., 2022; Zheng et al., 2022).

Table 3 Antioxidant activity of *Citrus* active ingredients

Component	Target Organ	up/down regulation of detection Indicators	Target/Signaling Pathway
Naringenin	Liver	↑ SOD, ↑ GSH, liver enzymes (↓ AST, ↓ ALT) (El-Saad and Abdel-Wahab, 2020)	Not specified
	Kidney	↑ SOD, ↑ GPx, ↓ MDA, blood lipid parameters (↓ cholesterol, ↓ LDL, ↑ HDL) (Liu, et al., 2022)	STAT3 signaling pathway
	Brain	↓ ROS, ↓ MDA, neurodegeneration reduced(Sadeghi Nejad, et al., 2023)	Not specified
	Liver	↑ GCLC, ↑ GCLM, ↑ SOD, ↑ GPx, ↑ HO-1, inflammatory factors (↓ TNFα, ↓ IL-1β, ↓ IL-6) (Ji, et al., 2023)	lncRNA-mRNA axis
	Brain (ischemia-reperfusion injury)	↓ ROS, ↓ MDA, ↓ 4-HNE, inflammatory factors (↓ IL-1β, ↓ TNF-α) (Zhao, et al., 2023)	SIRT1/FOXO1 signaling pathway
Hesperetin	Liver	↑ SOD, ↑ GPx, ↑ GR, ↑ GCLC, ↑ HO-1, inflammatory factors (↓ TNFα, ↓ IL-6) (Li, et al., 2021)	PI3K/AKT-Nrf2-ARE signaling pathway
	Kidney	↑ SOD, ↑ GSH, ↓ MDA (Chen, et al., 2019)	Not specified
	Spinal Cord	↑ SOD, ↓ MDA, inflammatory factors (↓ IL-1β, ↓ TNFα) (Zhang, et al., 2024)	Not specified
β-Sitosterol	Skeletal Muscle	↑ mitochondrial ROS, ↑ mitochondrial function (↑ electron transport, ↑ membrane fluidity) (Wong, et al., 2016)	Mitochondrial uncoupling signaling pathway
		↑ ROS, ↑ UCP3, ↑ AMPK/PGC-1 activation (Wong, et al., 2015)	AMPK/PGC-1 signaling pathway
Quercetin	Ovary	↓ MDA, ↑ SOD, ↑ GSH-Px, hormone levels (↑ AMH, ↑ E2, ↓ FSH, ↓ LH) (Chen, et al., 2022)	PGC1-α signaling pathway
		↑ SOD, ↑ GSH-Px, ↑ CAT, ↓ MDA, hormone levels (↑ E2, ↓ FSH, ↓ LH) (Zheng, et al., 2022)	PI3K/Akt/FoxO3a signaling pathway

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4.3 Effect of *Citrus* on lipid metabolism disorder

Lipid metabolism disorders are significantly more prevalent in individuals with ovarian dysfunction than in healthy individuals, highlighting a strong association between impaired lipid metabolism and ovarian dysfunction (Lankarani et al., 2009; Roa Barrios et al., 2009; Zhang et al., 2023). Research indicates that obesity, particularly abdominal obesity, exacerbates lipid metabolism disorders in individuals with ovarian dysfunction. Studies on obese Chinese individuals with ovarian dysfunction have shown they have a notably higher incidence of dyslipidemia than their non-obese counterparts (Li et al., 2013). Abdominal obesity, in particular, appears to further increase susceptibility to these metabolic disturbances (Guo et al., 2022). These findings emphasize the critical role of lipid metabolism in ovarian dysfunction and suggest a need for targeted approaches to address obesity-related lipid imbalances in affected individuals. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) play pivotal roles in cholesterol metabolism, and balancing their levels is crucial for reducing total cholesterol. Research indicates that naringenin, a key active compound in *Citrus*, lowers cholesterol, triglycerides, and LDL while increasing HDL levels. This comprehensive effect helps maintain optimal blood lipid profiles, reduce arterial lipid buildup, and mitigate the risk of cardiovascular diseases like atherosclerosis (Liu, et al., 2022). In studies with Ldlr mice on isocaloric diets, naringenin treatment significantly reduced body weight and obesity compared to controls (Burke et al., 2019).

The active components of *Citrus* influence lipid metabolism through their effects on various pathways and gene expression (Table 4). For example, naringenin reduces the expression of lipid metabolism-related genes in zebrafish larvae, including hmgcra, fasn, and fabp10α (Lin et al., 2017). Research revealed that naringin regulates fat utilization by modulating AMPK, PPARα, and CPT-1, reducing triglyceride accumulation in adipose cells and downregulating fatty acid uptake and synthesis through genes like CD36 and ACC. It also enhances fatty acid oxidation by increasing PPARα and CPT-1 levels (Alam et al., 2014; Zhang et al., 2021). Additionally, naringin supports lipid homeostasis in macrophages by suppressing genes for lipid uptake (MSR1, CD36) and enhancing cholesterol efflux via ABCA1, ABCG1, and SR-B1 (Liu et al., 2024). Quercetin, another active compound in *Citrus*, has demonstrated lipid metabolism benefits. It activates the FXR1/TGR5 signaling

pathway, reducing hepatic lipid accumulation (Yang et al., 2019). Studies showed that quercetin alleviates abnormal lipid metabolism by downregulating lipid-related genes like PTGS2, while improving glucose and lipid dysregulation via SIRT1 activation and its influence on the Akt signaling pathway (Peng et al., 2017; Zhu et al., 2024). Furthermore, β-sitosterol, another bioactive component, modulates fatty acid oxidation by influencing pathways involving PPAR-α, SREBP-1c, and CPT-1 (Abo-Zaid et al., 2023). These findings suggest that citrus-derived compounds may exert beneficial effects on lipid and cholesterol transport by activating PPARα (Bougarne et al., 2018). Activation of PPARα influences lipoprotein metabolism by reducing the production of very low-density lipoprotein (VLDL) and enhancing the catabolism of triglyceride-rich particles, thereby indirectly decreasing levels of small dense low-density lipoprotein (sdLDL) and promoting the formation of HDL particles (Bougarne, et al., 2018). Additionally, PPARα agonists have been shown to increase the activity of lipoprotein lipase (LPL), a key enzyme in triglyceride hydrolysis, leading to a reduction in circulating triglyceride-rich lipoproteins and improved hepatic clearance of excess cholesterol (Bougarne, et al., 2018).

Other studies have highlighted the regulatory potential of flavonoids in lipid metabolism. Enzymes like diacylglycerol acyltransferase (DGAT), fatty acid synthase (FAS), and cholesterol 7α-hydroxylase (CYP7A) are critical in lipid synthesis and breakdown (Table 5). Research has shown that *Citrus* flavonoids inhibit key enzymes like FAS, HMGR, and DGAT in triglyceride and cholesterol synthesis while enhancing lipid catabolism enzymes like CYP7A (Su et al., 2019; Sun et al., 2021). Another study showed that flavonoids from *Citrus* peel reduce lipid accumulation in HepG2 cells by suppressing miR-122 and miR-33, thereby regulating target mRNAs like FAS and CPT1α (Su, et al., 2019). Similar findings have highlighted the ability of flavonoids to modulate lipid metabolism and amino acid flux through enzymes like glyceraldehyde-3-phosphate dehydrogenase (Samec et al., 2023).

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Table 4 Researches on Lipid Metabolism Related to Active Components of *Citrus*

Component	Target Organ	up/down regulation of detection Indicators	Target/Signaling Pathway
Naringenin	Liver	Alcohol-induced liver injury ↓, lipid metabolism-related genes (cyp2y3, cyp3a65, hmgcra, hmgcrb, fasn, fabp10α, fads2, echs1) ↓, apoptosis markers (chop, gadd45αa, edem1) ↓ (Lin, et al., 2017)	Inhibits steatosis and liver damage, reduces apoptosis and DNA damage
		Fatty acid oxidation ↑ (Alam, et al., 2014)	Activates PPARα and PGC-1α pathways, reduces SREBP-1c-mediated lipogenesis
Naringin	Liver	Total cholesterol, triglycerides ↓ (Alam, et al., 2014)	Inhibits HMG-CoA reductase activity, activates AMPK, increases the expression of PPARα, CPT-1, and UCP-2
	Liver (tissue-engineered model)	Triglycerides (TG) ↓, lipogenic enzymes, pyruvate dehydrogenase kinase 4 ↓, PPAR-α, carnitine palmitoyltransferase 1 (CPT-1) ↑ (Zhang, et al., 2021)	Improves lipid metabolism disorder, targets CD36 and PPAR-α
	Macrophages	Lipid uptake genes (MSR1, CD36) ↓, cholesterol efflux genes (ABCA1, ABCG1, SR-B1) ↑, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) ↓, anti-inflammatory cytokine (IL-10) ↑ (Liu, et al., 2024)	Maintains lipid homeostasis, inhibits foam cell formation, improves inflammation
Quercetin	Neurons	Lipid metabolism-related gene (PTGS2) ↓, ferroptosis markers (total Fe, Fe2+, MDA, ROS) ↓, CD4+/CD8+ T cell ratio ↑ (Zhu, et al., 2024)	Inhibits neuronal ferroptosis, regulates lipid metabolism, promotes immune response
	Liver	Serum transaminases (ALT, AST) ↓, fat accumulation ↓, antioxidant indicators (SOD, CAT, GSH) ↑, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) ↓ (Yang, et al., 2019)	FXR1/TGR5 signaling pathway activation, improves lipid metabolism
		Blood glucose, lipid metabolism indicators (FBG, TG, TC, LDL-C) ↓, HDL-C ↑, SIRT1 and Akt activity ↑ (Peng, et al., 2017)	Increases SIRT1 and Akt signaling pathway activity, improves glucose and lipid metabolism
β-sitosterol	Liver	Triglycerides (TG) ↓, transaminases (ALT, AST) ↓, inflammatory factors (IL-1β, iNOS) ↓, lipid oxidation-related factors (PPAR-α, SREBP-1c, CPT-1) regulation (Abo-Zaid, et al., 2023)	Reduces oxidative stress, ER stress, and inflammation, improves lipid metabolism

Table 5 Key enzymes in metabolic pathways associated with lipid metabolism.

Chinese Name	English Name	Abbreviation	Metabolic Pathway
Diacylglycerol Acyltransferase	Diacylglycerol acyltransferase	DGAT(Bhatt-Wessel et al., 2018)	Triglyceride synthesis metabolism
Fatty Acid Synthase	Fatty acid synthase	FAS(Gunenc et al., 2022)	Fatty acid synthesis metabolism
3-Hydroxy-3-Methylglutaryl-CoA Reductase	3-hydroxy-3-methylglutaryl coenzyme A reductase	HMGR(Gunasekaran and Shukor, 2020)	Cholesterol synthesis metabolism
Cholesterol 7α-Hydroxylase	Cholesterol 7α-hydroxylase	CYP7A(Ge et al., 2019)	Cholesterol breakdown metabolism

5 Future directions and challenges in the use of *Citrus* for improving female reproductive health

Future studies should prioritize investigating bioactive compounds in *Citrus* with demonstrated effects on female reproductive health. For enhanced delivery, these compounds could be encapsulated in nanocarriers such as liposomes (for improved membrane permeability), polymeric micelles (for sustained release), or dendrimers (for precise targeting). Critical research questions include: (1) How do surface modifications of these carriers affect the efficiency of ovarian tissue targeting? (2) What are the optimal stimulus-responsive mechanisms (e.g., pH-sensitive or enzyme-triggered release) for reproductive tract-specific delivery? The development of biocompatible, uterus-targeting delivery systems should be coupled with rigorous pharmacokinetic studies to maximize local effects while minimizing systemic exposure. High-quality evidence should be generated through multicenter, randomized controlled trials focusing on standardized *Citrus* extracts to reduce heterogeneity. Priority should be given to: (a) identifying the single most potent bioactive compound through systematic screening, (b) establishing dose-response relationships using validated biomarkers, and (c) elucidating long-term effects on ovarian function through longitudinal studies. Mechanistic research should address how *Citrus* compounds interact with hormonal signaling pathways and the ovarian follicle microenvironment.

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6 Conclusions

Citrus, a food with medicinal properties, contains active components such as naringenin, quercetin, and β-sitosterol, which have shown potential in improving lipid metabolism and reducing ROS levels, and offer promising avenues for dietary therapy in managing ovarian dysfunction. However, further research is needed to elucidate the mechanisms involved and validate the therapeutic potential of such compounds in clinical settings.

Data availability statement

This review article does not present new experimental data. The information synthesized herein is derived from publicly available studies, whose datasets are described in the respective original publications. Readers are referred to the Data Availability Statements of the cited studies for specific access details.

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Author contributions

Jue ZHOU determined the topic of the article, proposed this program, reviewed and revised the manuscript. Yiyan YANG collected the literature, wrote the manuscript, summarized and drew the tables and pictures. Both authors have read and approved the final manuscript.

Compliance with ethics guidelines

Yiyan YANG and Jue ZHOU declare that they have no conflict of interest.

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