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Review

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

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Abstract: *Citrus*, which has been consumed internationally for a long time, is widely used as a health food. *Citrus* and its active components exert significant effects on oxidative stress and lipid metabolism, which are closely associated with female reproductive health. Studies suggest that citrus-derived compounds may alleviate oxidative stress by activating signaling pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2) and Sirtuin 1 (SIRT1), and improve lipid metabolism through the activation of pathways such as peroxisome proliferator-activated receptor α (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; however, further work is needed to elucidate the mechanisms involved and validate the therapeutic potential of *Citrus*'s bioactive components in clinical settings.

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

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 such as East Indies, New Guinea, northeastern Australia, and parts of Polynesia (Wu et al., 2018).

Citrus species include *Citrus reticulata* (mandarin or 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 are transformed 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, such as 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 liquorice, mesona, imperata root, chrysanthemum, honeysuckle, mulberry leaves, rock sugar, and granulated sugar (Liang et al., 2023). These 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

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Table 1 Different food products of *Citrus* used worldwide

Latin name	Food products	Country
Citrus reticulata	Xinhui Chenpi plum, Chenpi paste, cakes, duck dishes, and wine (Su, 2011)	China
Citrus grandis	Juhong-green fruit tea, Juhong-gardenia tea, Juhong-Pu'er tea, and 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 (Karabıyıklı et al., 2014)	Turkey
Citrus sinensis	Orange juice (Kelebek and Selli, 2011)	Turkey
Citrus medica	Citron vinegar, ravigote vinegar, and dishes (Chhikara et al., 2018)	World

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, vitamin C effervescent 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, *C. 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 (Karabıyıklı 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 in different dishes (Chhikara et al., 2018).

Oxidative stress and lipid metabolism have profound effects 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 such as 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, lipid breakdown, and energy regulation (Spiteller, 2006). As a result, oxidative stress is a key factor in the development of various metabolic disorders.

Citrus contains 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 such as 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 its modulation of gut microbiota (Wu et al., 2022) and decreased 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 broader implications for developing functional foods in the future.

2 Nutrition of *Citrus* fruit

Citrus fruits are valued not only for their refreshing flavor but also for their rich nutritional content. They serve as 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 contents, *Citrus* fruits contain beneficial phytochemicals, including flavonoids and carotenoids (Wang X et al., 2023). 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 (Zhang X et al., 2023).

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 (Pan et al., 2023), 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 such as 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, which are 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). An analysis of ethanol extracts from *C. aurantium* revealed a variety of bioactive compounds, including specific coumarins (Chen et al., 2012). Furthermore, research on different *Citrus* cultivated in Colombia revealed a diversity of coumarins that 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*.

4 Effects of *Citrus* on female reproductive health

4.1 Female reproductive system

Ovarian granulosa cells are essential for female reproduction, contributing to follicle formation and ovarian function. Alongside oocytes and theca cells, they form follicles, the fundamental units of the ovary. Granulosa cells facilitate follicle maturation by exchanging nutrients and small metabolites with oocytes through gap junctions, meeting up to 85% of the oocyte's metabolic needs during development (Zhang et al., 2010). PCOS is a common endocrine-metabolic disorder affecting women of reproductive age and is closely associated with female infertility (Wang JX et al., 2023). The most widely accepted diagnostic criteria are the Rotterdam criteria, which require the presence of at least two of the following three features: (1) hyperandrogenism, (2) oligoovulation or anovulation, and (3) polycystic ovarian morphology (Siddiqui et al., 2022). Hyperandrogenism contributes to insulin resistance and hyperglycemia, leading to increased ROS production, oxidative stress, and abdominal obesity (Siddiqui et al., 2022). Clinically, PCOS is often accompanied by insulin resistance, obesity, hirsutism, and acne (Wang JX et al., 2023).

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

Table 2 Health benefits of active components in *Citrus*

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

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.

4.2 Effects of *Citrus*-derived antioxidants 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,

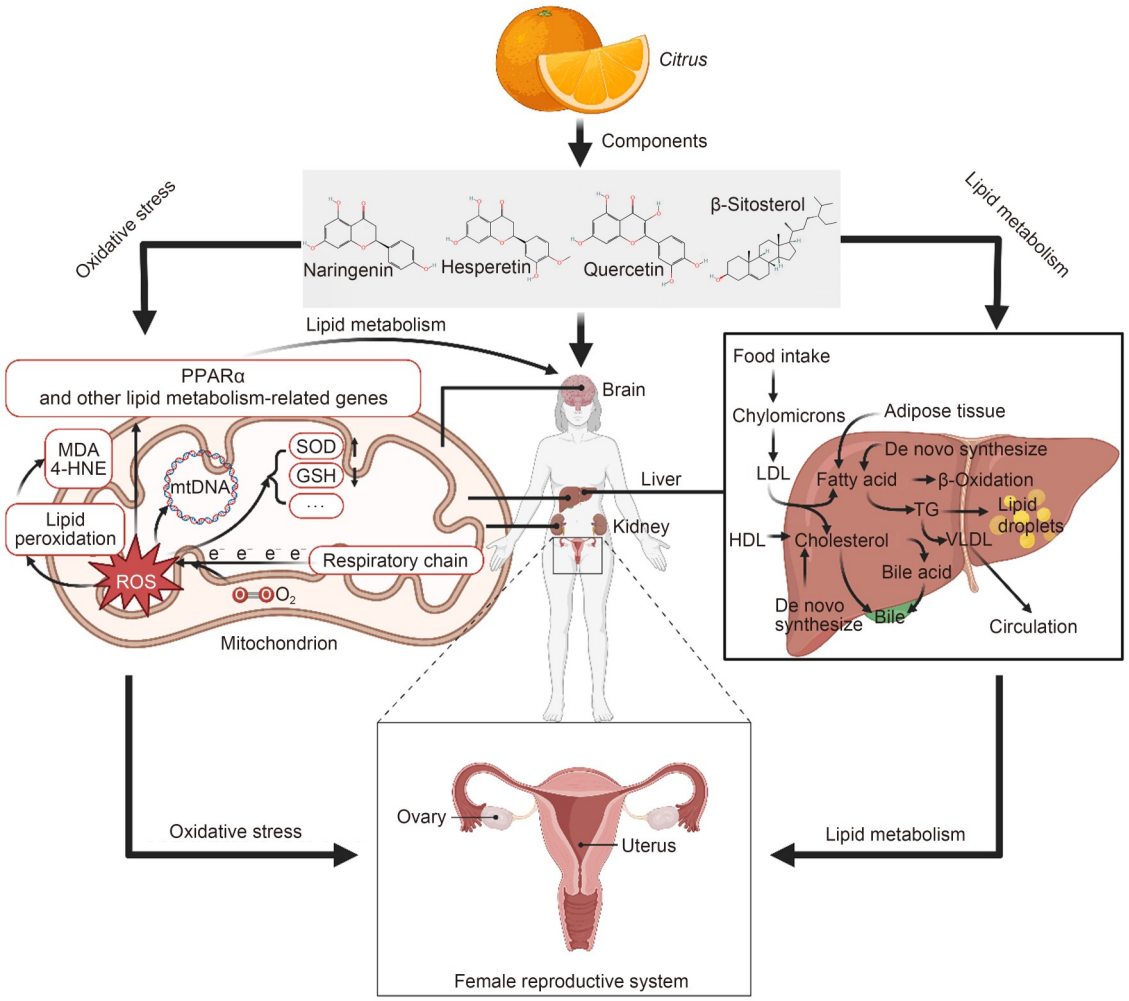

Fig. 1 Potential role of *Citrus* in improving the female reproductive system based on its effects on oxidative stress and lipid metabolism. PPARα: peroxisome proliferator-activated receptor α; MDA: malondialdehyde; mtDNA: mitochondrial DNA; 4-HNE: 4-hydroxynonenal; SOD: superoxide dismutase; GSH: glutathione; ROS: reactive oxygen species; TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein; VLDL: very low-density lipoprotein. Created with BioRender.com.

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 adenosine triphosphate (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).

To evaluate oxidative stress and mitochondrial function in affected tissues, researchers commonly measure ROS-related metabolites such as glutathione peroxidase (GPx/GSH-Px), catalase (CAT), superoxide dismutase (SOD), and MDA. 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-α (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 (Öner-İyidoğan et al., 2004). Studies have measured the activity of antioxidant enzymes and lipid peroxidation in ectopic endometrial tissue from ovarian endometriotic cysts. SOD activity was significantly higher in ectopic endometrium than in eutopic endometrium, with MDA levels showing a positive correlation with SOD activity. TNF-α has been shown to upregulate manganese SOD (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 nuclear factor-κB (NF-κB) pathway (Sugino et al., 2004). These findings highlight the intricate relationship among 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, CAT, GSH-Px, 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 has shown that naringin reduced MDA levels and elevated GPx and SOD activity in rat models treated with reserpine (Sadeghi Nejad et al., 2023). Further evidence demonstrated that naringin treatment significantly increased messenger RNA (mRNA) expression of antioxidant factors such as glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits in mice with liver dysfunction. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis suggested that naringin's effects were closely associated with the mitigation of oxidative stress (Ji et al., 2023). Moreover, other research indicated that naringin alleviated oxidative stress via the Sirtuin 1 (SIRT1)/forkhead box O1 (FoxO1) signaling pathway, resulting in reductions in ROS, MDA, and 4-HNE levels, alongside enhanced SOD, GSH-Px, and CAT activity (Zhao et al., 2023). These findings suggest that naringin may enhance cellular antioxidant capacity by modulating nicotinamide adenine dinucleotide (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 attenuated

Table 3 Antioxidant activity of *Citrus* active ingredients

Component	Target organ	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 ↓ (Sadeghi Nejad et al., 2023)	Not specified
	Liver	GCLC ↑, GCLM ↑, SOD ↑, GPx ↑, HO-1 ↑, inflammatory factors (TNF-α, 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 (TNF-α, 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, TNF-α) ↓ (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)	PGC-1α signaling pathway
		SOD ↑, GSH-Px ↑, CAT ↑, MDA ↓, hormone levels (E2 ↑, FSH ↓, LH ↓) (Zheng et al., 2022)	PI3K/Akt/FoxO3a signaling pathway

SOD: superoxide dismutase; GSH: glutathione; AST: aspartate transaminase; ALT: alaninetransaminase; GPx/GSH-Px: glutathione peroxidase; MDA: malondialdehyde; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ROS: reactive oxygen species; GCLC: glutamate-cysteine ligase catalytic; GCLM: glutamate-cysteine ligase modifier; HO-1: heme oxygenase-1; TNF: tumor necrosis factor; IL: interleukin; 4-HNE: 4-hydroxynonenal; GR: glutathione reductase; UCP3: uncoupling protein 3; AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; PGC-1: peroxisome proliferator-activated receptor γ coactivator-1; AMH: anti-Müllerian hormone; E2: estradiol; FSH: follicle stimulating hormone; LH: luteinizing hormone; CAT: catalase; STAT3: signal transducer and activator of transcription 3; LncRNA: long noncoding RNA; mRNA: messenger RNA; SIRT1: Sirtuin 1; FoxO1: forkhead box O1; PI3K: phosphoinositide-3 kinase; Akt: protein kinase B; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element.

ROS overproduction in oleic acid-induced human hepatocellular carcinomas (HepG2) cells by upregulating antioxidants (SOD, etc.) through the activation of the phosphoinositide-3 kinase (PI3K)/protein kinase B (Akt)-nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (Li et al., 2021). Similarly, research found that hesperidin alleviated oxidative damage in H_2O_2-treated ARPE-19 cells via the Nrf2 pathway activation, leading to reduced MDA/myeloperoxidase (MPO) level 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 nicotinamide adenine dinucleotide phosphate (NADPH) for GSH 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 adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1 (PGC-1) signaling pathway (Wong et al., 2015, 2016). Quercetin, meanwhile, has been shown to reverse mitochondrial dysfunction, promote mitochondrial biogenesis via the PGC-1α 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 ovarian health (Chen et al., 2022; Zheng et al., 2022).

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 CH et al., 2023). Research indicates that obesity, particularly abdominal obesity, exacerbates lipid metabolism disorders in individuals with ovarian dysfunction. The study on obese Chinese individuals with ovarian dysfunction has shown that 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 (TC). 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 such as atherosclerosis (Liu et al., 2022). In the study with LDL receptor (LDLR)-deficient 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, including *hmgcra*, *fasn*, and *fabp10α*, in zebrafish larvae (Lin et al., 2017). Research revealed that naringin regulates fat utilization by modulating AMPK, PPARα, and carnitine palmitoyltransferase type 1 (CPT-1), reducing triglyceride accumulation in adipose cells, and downregulating fatty acid uptake and synthesis through genes such as cluster of differentiation 36 (*CD36*) and acetyl-coenzyme A (CoA) carboxylase (*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 (macrophage scavenger receptor 1 (*MSR1*) and *CD36*) and enhancing cholesterol efflux via ATP-binding cassette transporter A1 (*ABCA1*), ATP-binding cassette transporter G1 (*ABCG1*), and scavenger receptor B1 (*SR-B1*) (Liu et al., 2024). Quercetin, another active compound in *Citrus*, has demonstrated lipid metabolism benefits. It activates the fragile X-related protein 1 (FXR1)/Takeda G-protein-coupled receptor 5 (TGR5) signaling pathway, reducing hepatic lipid accumulation (Yang et al., 2019). Studies showed that quercetin alleviates abnormal lipid metabolism by downregulating lipid-related genes such as prostaglandin G/H synthase 2 (*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 PPARα, sterol regulatory element-binding protein 1c (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 such as diacylglycerol acyltransferase (DGAT), fatty acid synthase (FAS), and cholesterol 7α-hydroxylase (CYP7A) are critical for lipid synthesis and breakdown

(Table 5). Research has shown that *Citrus* flavonoids inhibit key enzymes such as FAS, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), and DGAT in triglyceride and cholesterol synthesis while enhancing lipid catabolism enzymes such as CYP7A (Su et al., 2019; Sun et al., 2021). Another study showed that

Table 4 Research on lipid metabolism related to active components of *Citrus*

Component	Target organ	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	TC ↓, TG ↓ (Alam et al., 2014)	Inhibits HMGR activity; activates AMPK; increases the expression of PPARα, CPT-1, and UCP2
	Liver (tissue-engineered model)	TG ↓, lipogenic enzymes ↓, pyruvate dehydrogenase kinase 4 ↓, PPARα ↑, CPT-1 ↑ (Zhang et al., 2021)	Improves lipid metabolism disorder; targets CD36 and PPARα
	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, Fe^{2+}, 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)	Activates FXR1/TGR5 signaling pathway; improves lipid metabolism
		Blood glucose and 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	TG ↓, transaminases (ALT, AST) ↓, inflammatory factors (IL-1β, iNOS) ↓, lipid oxidation-related factors (PPARα ↑, SREBP-1c ↓, CPT-1 ↑) regulation (Abo-Zaid et al., 2023)	Reduces oxidative stress, ER stress, and inflammation; improves lipid metabolism

TC: total cholesterol; TG: triglycerides; PPARα: peroxisome proliferator-activated receptor α; CPT-1: carnitine palmitoyltransferase type 1; *MSR1*: macrophage scavenger receptor 1; *CD36*: cluster of differentiation 36; *ABCA1*: ATP-binding cassette transporter A1; *ABCG1*: ATP-binding cassette transporter G1; *SR-B1*: scavenger receptor B1; IL: interleukin; TNF: tumor necrosis factor; *PTGS2*: prostaglandin G/H synthase 2; MDA: malondialdehyde; ROS: reactive oxygen species; ALT: alaninetransaminase; AST: aspartate transaminase; SOD: superoxide dismutase; CAT: catalase; GSH: glutathione; FBG: fasting blood glucose; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SIRT1: Sirtuin 1; Akt: protein kinase B; iNOS: inducible nitric oxide synthase; SREBP-1c: sterol regulatory element binding protein 1c; PGC-1α: peroxisome proliferator-activated receptor γ coactivator-1α; HMGR: 3-hydroxy-3-methylglutaryl coenzyme A reductase; AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; UCP2: uncoupling protein 2; FXR1: fragile X-related protein 1; TGR5: Takeda G-protein-coupled receptor 5; ER: endoplasmic reticulum.

Table 5 Key enzymes in metabolic pathways associated with lipid metabolism

Enzyme name	Abbreviation	Metabolic pathway
Diacylglycerol acyltransferase	DGAT (Bhatt-Wessel et al., 2018)	Triglyceride synthesis metabolism
Fatty acid synthase	FAS (Günenc et al., 2022)	Fatty acid synthesis metabolism
3-Hydroxy-3-methylglutaryl-coenzyme A reductase	HMGR (Gunasekaran and Shukor, 2020)	Cholesterol synthesis metabolism
Cholesterol 7α-hydroxylase	CYP7A (Ge et al., 2019)	Cholesterol breakdown metabolism

flavonoids from *Citrus* peel reduce lipid accumulation in HepG2 cells by suppressing microRNA-122 (miR-122) and miR-33, thereby regulating target mRNAs such as *FAS* and *CPT-1α* (Su et al., 2019). Similar findings have highlighted the ability of flavonoids to modulate lipid metabolism and amino acid flux through enzymes such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Samec et al., 2023).

5 Future directions and challenges

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: (1) identifying the single most potent bioactive compound through systematic screening; (2) establishing dose-response relationships using validated biomarkers; and (3) 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.

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.

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Author contributions

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

Compliance with ethics guidelines

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

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