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REVIEW

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Overview of Nrf2 as a target in ovary and ovarian dysfunctions focusing on its antioxidant properties

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Abstract

Female infertility is a common issue caused by various factors, such as hormonal imbalances, age-related decline in oocyte quality, and lifestyle choices. Ovarian dysfunction is a prevalent cause, impacting fertility by damaging cells and impairing functions. Oxidative stress (OS) is a condition resulting from an imbalance between natural antioxidants and the generation of oxidants. This phenomenon acts as a double-edged sword, playing a crucial role as a signaling mechanism in both physiological and pathological processes related to the female reproductive system. OS is linked to ovarian dysfunction, leading to cell damage and reduced fertility. Nrf2 is a key regulator in oxidative homeostasis, helping to defend against OS and improve ovarian function in women of reproductive age. Therefore, this review aims to highlight the role of Nrf2 in the female reproductive system, focusing on its antioxidant properties.

Keywords Nrf2, Infertility, Ovarian dysfunction, Oxidative stress

Introduction

Female infertility is a complex and often challenging issue that affects millions of women worldwide [1]. This condition can be attributed to a variety of factors, including hormonal imbalances, reproductive disorders, age-related declines in egg quality, and lifestyle choices [2]. Among the various causes of infertility, ovarian dysfunction represents a prevalent and significant challenge for women of reproductive age [3]. This condition can significantly hinder the ability to conceive, making it a critical concern in the field of reproductive health.

Oxidative stress (OS) is characterized by an imbalance between pro-oxidants, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the body's antioxidant defenses. This condition arises when the production of these harmful species exceeds the capacity of antioxidants to neutralize them [4].

OS is a significant factor influencing various physiological processes such as implantation, fertilization, pregnancy, and the normal course of parturition. Additionally, it is involved in the onset of preterm labor and contributes to the age-related decline in fertility [5, 6]. Numerous external factors, alongside physiological alterations, can contribute to OS in the ovaries. These factors include smoking, significant psychological stress, the natural aging process, superovulation associated with assisted reproductive technology (ART), diets high in sugar, chemotherapy medications, and exposure to industrial environmental pollutants [7].

The optimal concentration of OS is recognized as a significant signal for triggering apoptosis in the granulosa cells, thereby facilitating the onset of ovulation. However,

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research has demonstrated that the OS present in the ovarian microenvironment can lead to significant pathological consequences. These include apoptosis of granulosa cells, meiotic arrest in oocytes, and dysfunction of the corpus luteum, all of which contribute to the acceleration of ovarian aging. The implications of these findings are profound, as they highlight the critical role of OS in ovarian health. Understanding these mechanisms may provide insights into potential therapeutic strategies aimed at mitigating the effects of oxidative damage and preserving ovarian function over time [7].

Various studies have indicated that OS plays a critical role in the development of preeclampsia. It appears that the excessive generation of ROS, which occurs as a consequence of placental ischemia–reperfusion injury, is a key factor in the pathophysiology of this condition [6].

Recent findings indicate that OS is implicated in the development of ovarian dysfunction and contributes to the emergence of various related etiologies [7–9]. This encompasses a range of issues, including the shortening of telomeres, impairment of biomacromolecules, dysfunction of mitochondria, apoptosis, and the activation of inflammatory responses [6, 10]. OS has the potential to impact various cell types involved in fertility, including germ cells, somatic cells, oocytes, cumulus cells, and granulosa cells [11, 12]. This disruption can lead to reduced oocyte quality and significant damage to the metabolic and endocrine functions of the ovaries, ultimately resulting in a decline in female fertility [6].

A key strategy for enhancing the female fertility rate involves reducing or normalizing OS to physiologically optimal levels. This can be achieved by fostering a reproductive-friendly microenvironment through healthy lifestyle choices and antioxidant supplements [13, 14]. Antioxidants can eliminate, neutralize, or inhibit the production of ROS, thereby mitigating OS. This protective function is essential for preserving cellular integrity and preventing various conditions related to oxidative damage [15].

As a crucial regulator, nuclear factor erythroid 2-related factor 2 (Nrf2) plays a pivotal role in antioxidant defense mechanisms against OS. This transcription factor is instrumental in modulating a wide array of antioxidant enzymes that facilitate the detoxification and removal of OS and has been extensively studied, particularly concerning infertility disorders [16].

The Nrf2 signaling pathway is essential for sustaining ovarian proliferation and facilitating normal follicular development, while also contributing to the enhancement of ovarian function [17]. It is hypothesized that a relationship exists between the expression of the Nrf2 protein and ovarian reproductive function, suggesting that Nrf2 may play a significant role in safeguarding ovarian reproductive capabilities. Throughout the stages of youth, growth, and aging, as ovarian reproductive function initially rises, the levels of Nrf2 protein within the ovarian tissue demonstrate a pattern of increase followed by a subsequent decline [18].

The objective of the present study is to guide researchers regarding the role of the Nrf2 signaling pathway in regulating OS and influencing ovarian. This review aims to highlight the role of Nrf2 in the female reproductive system by emphasizing its crucial contribution to the enhancement of ovarian function in women of reproductive age.

Structure and mechanisms of nrf2 action

Nrf2 is a Cap 'n' Collar (CNC)-structured basic leucine zipper (bZIP) transcription factor comprising 605 amino acids. These amino acids are organized into seven highly conserved domains known as Nrf2-ECH homology (Neh) domains, each of which is assigned specific functional roles [19–21]. The Neh1 domain functions as a CNC-bZIP domain, facilitating the dimerization of Nrf2 with small muscle aponeurosis fibromatous (sMAF) proteins, specifically MAFK, MAFG, and MAFF, thus enabling DNA binding [22]. Furthermore, the Neh1 domain interacts with UbcM2, an E2 ubiquitin-conjugating enzyme, thereby regulating the stability of the Nrf2 protein [23]. Nrf2 associates with its cytosolic repressor, Kelch-like ECH-associated protein 1 (Keap1), through the Neh2 domain [24]. The transcriptional activation of genes containing an antioxidant response element (ARE) in their promoter regions is mediated by the Neh3, Neh4, and Neh5 domains [25]. The Neh3 domain interacts with components of the transcriptional machinery, serves as a transactivation domain, and contributes to the stability of the Nrf2 protein [26]. The Neh4 and Neh5 domains bind to the cAMP response element binding protein, which possesses intrinsic histone acetyltransferase activity, rather than to other proteins that also act as transactivation domains [27]. The Neh6 domain contains a serine-rich region involved in a redox-insensitive mechanism that regulates Nrf2 independently of Keap1 [28]. Lastly, the Neh7 domain plays a role in the suppression of Nrf2/ARE signaling pathway by interacting with the retinoid X receptor alpha (RXRα) [29] (Fig. 1).

NRF2 activity is primarily regulated by its interaction with Keap1. In homeostatic states, Nrf2 is inactive in the cytosol due to binding with Keap1. However, the Keap1-Nrf2 complex is disrupted under OS conditions, allowing Nrf2 to be transferred into the nucleus. There, Nrf2 initially interacts with small MAF proteins to form a heterodimer, which then binds to ARE and triggers the expression of phase II antioxidant genes, including CAT, PRDX1, SOD, and HO-1, to neutralize

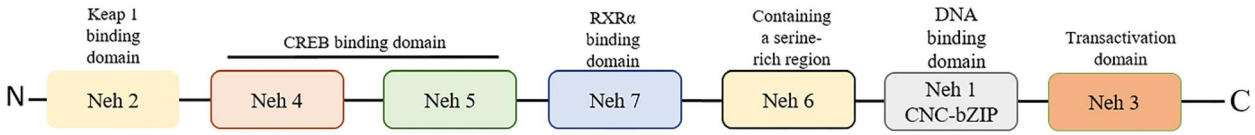

Fig. 1 Diagram of Nrf2 structure with Nrf2-ECH homology domains (Neh1-Neh7)

the effects of OS and promote survival under suboptimal environmental conditions [30–34].

Previous reports have indicated that the MAPK and AMPK signaling pathways play a role in the upstream signaling of Nrf2 [35]. During OS, AMPK becomes active through phosphorylation at Thr172 and helps to increase antioxidants by activating the expression of genes such as Nrf2, DAF-16, FOXO factors, and SIRT [36]. Recently, it was demonstrated that over 85 miRNAs may target the Nrf2 gene. This suggests that the Nrf2 signaling pathway can be regulated through DNA methylation, histone modifications, interactions of microRNAs, and RNA-binding proteins [36, 37] (Fig. 2).

Nrf2 and ovary

The health of women's oocytes and ovaries plays the most important role in their reproductive capability. Various environmental and physiological factors are capable of eliciting detrimental effects on ovarian tissue. Extensive research has been conducted to recognize these factors and their underlying mechanisms.

The probable risks inquiry associated with environmental exposure to cadmium [38], the herbicide atrazine [39], carbon tetrachloride [40], and mercury chloride [41] in different species indicated the induction of OS and inflammatory responses in the ovary. This phenomenon is attributed to convoluted regulation occurring at multiple molecular levels and the activity of the Nrf2 signaling pathway and its associated genes. The activation of the apoptosis pathway and the overexpression of Keap1 and Nrf2 genes were observed following high-dose zinc oxide

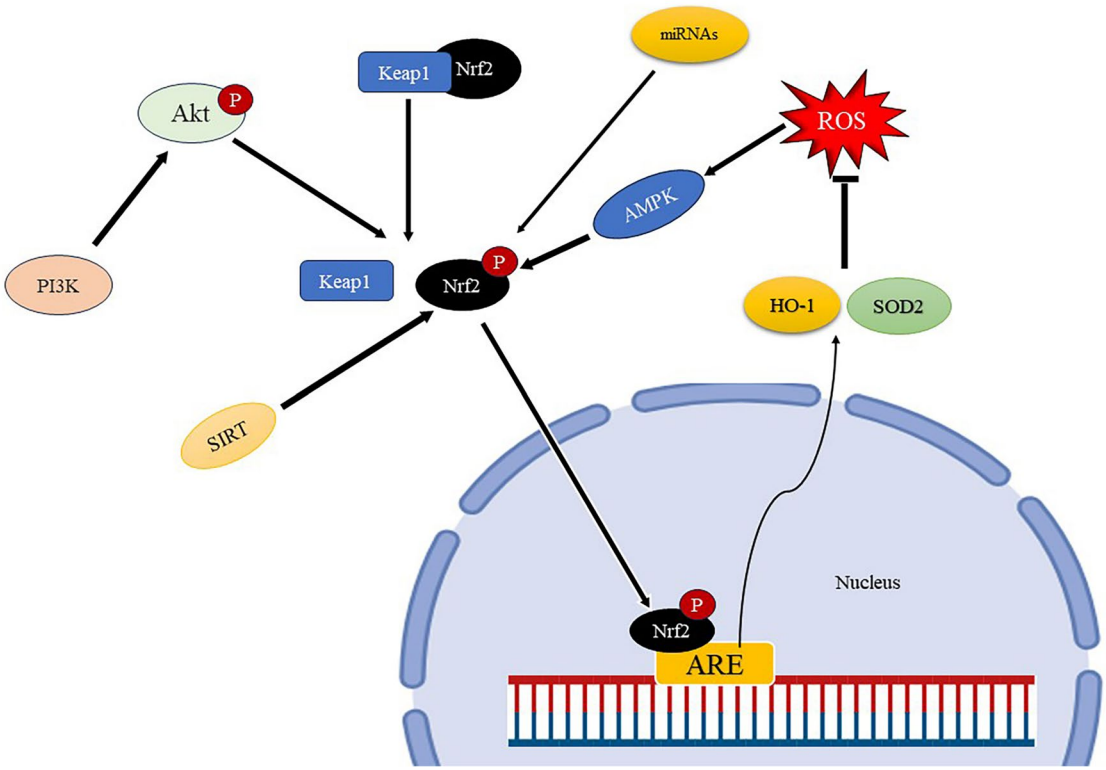

Fig. 2 The Keap1-Nrf2 antioxidant signaling pathway. Under basal conditions, Nrf2 is degraded by Keap1. However, the Keap1–Nrf2 complex is disrupted under OS, allowing Nrf2 to enter the nucleus. There, Nrf2 binds to ARE and triggers the expression of CAT, PRDX1, SOD, and HO-1 to neutralize the effects of OS and promote survival under suboptimal environmental conditions

(≥100) application in ovarian tissue. Zinc oxide toxicity can be mitigated by administering OS inhibitors, such as N-acetylcysteine (NAC) and salubrinal [42].

Oxidative damage to ovarian tissue has manifested as a consequence of contact with sodium fluoride (NaF) and dietary vanadium. Trying Vitamin C as a countermeasure proved ineffective in reversing the oxidative effects caused by NaF while analyzing the Keap1-Nrf2-sMaf antioxidant pathway, the researchers elucidated how epigallocatechin-3-gallate supplementation can alleviate the detrimental effects of vanadium and enhance overall antioxidant capacity [43, 44]. Raising environmental temperature and the induction of heat stress are considered suppressors of the Nrf2 signaling pathway and its associated proteins; however, capsaicinoid supplements reduce OS and boost antioxidant indicators [45]. A considerable portion of the research concentrates on protective antioxidants and dietary interventions aimed at mitigating ovarian dysfunction. Hydrogen-rich saline (HRS) and the inhibition of glycogen synthase kinase-3 (GSK-3) in countering chemotherapy-induced ovarian damage [46, 47], diselenonicotinamide (DSNA) against radiation-created damage [48], melatonin during cryopreservation [49, 50], and resveratrol [51] by targeting the OS pathway have shown promise for enhanced antioxidant production and diminished injuries originating from OS in the ovaries.

Age-related infertility represents a global concern, especially impacted by OS within ovarian tissue. Aging results in unusual upregulation of proteins involved in iron transport and storage: transferrin, ferritin, and IRP2-mediated transferrin receptor 1 (TfR1), which leads to OS and inflammatory responses in ovarian tissue. Intermediation in iron metabolism is a therapeutic approach that could alleviate aging-associated ovarian disorder [52]. Administration of dimethylfumarate and Tanshinone IIA as anti-aging interventions elevates Nrf2 and antioxidant markers, telomere length, and anti-Müllerian hormone levels in aged female mice [53, 54]. An experimental investigation elucidated that a deficiency in the transcription factor Nrf2 accelerates ovarian aging, particularly in response to exposure to toxic compounds [55]. According to recent findings, proteasome expression and activity decline meaningfully in aged somatic tissues, resulting in the aggregation of ubiquitinated and oxidized proteins. By contrast, proteasomes in gonadal tissues possess greater activity that is independent of age, enhancing these tissues' ability to withstand OS. Moreover, Nrf2 activation causes restoration of proteasome expression in aged somatic tissues, suggesting that age-related Nrf2 dysfunction is correlated with the diminished levels of proteasomes in these tissues [56]. Targeting pigment epithelium-derived factor (PEDF) may assist in the management of diseases related to ovarian oxidative damage. The factor is a multifunctional protein with antitumorigenic and neurotrophic properties. Mice lacking PEDF exhibit oxidative damage in the ovaries, evidenced by ROS accumulation and activation of the Nrf2 pathway [57]. Hypoxia-inducible factor-1 (HIF-1) mediates the activation of the HO-1 gene under hypoxic conditions. Over the past decades, Gong et al. explained that HO-1 gene expression is regulated by hypoxia and cobalt chloride (CoCl2) exposure through HIF-dependent and HIF-independent pathways. CoCl2 activates HO-1 gene expression via OS and the involvement of Nrf2 and MafG, whereas hypoxia employs a distinct pathway without involving these proteins in mutant Chinese hamster ovary (CHO) cells (Ka13), which lack HIF activity.

Overall, the review underscores the critical role of OS and its regulators in maintaining ovarian health and presents potential therapeutic pathways to mitigate environmental and age-related damage (Table 1 and Fig. 3).

Ovarian steroidogenesis is the biochemical process through which ovarian cells synthesize hormones essential for maintaining reproductive tissues, regulating ovarian activities, facilitating ovulation, and establishing pregnancy. GCs are essential components of the ovaries, contributing significantly to steroid hormone production and oocyte maturation [72, 73]. The results indicate that Nrf2 enhances steroidogenesis through its influence on granulosa cells. Furthermore, the upregulation of Nrf2 led to an increase in the expression of genes associated with steroidogenesis, such as steroidogenic acute regulatory protein (StAR), cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1), 3 beta-hydroxysteroid dehydrogenase/isomerase (HSD3b1), all of which play a crucial role in promoting luteinization [74, 75].

Nrf2 and oocyte

In vitro maturation (IVM) is the technique of oocyte maturation to produce embryos in vitro. Additionally, it is an experimental in vitro method to study the effect of external intervention on oocyte cells. One problem with this technique is the rising OS. Researchers have added some components with antioxidative features to IVM culture to target signaling pathways related to Nrf2 to ameliorate the OS in IVM oocytes.

In this regard, astaxanthin was used to target the Nrf2 pathway and found the upregulation of Nrf2 and its downstream antioxidants like SOD1, SOD2, GPX4, and CAT, and reduced OS in IVM oocytes [76]. Similar to this study, [59] enriching the maturation medium of oocytes during IVM with epigallocatechin-3-gallate significantly enhanced the transcriptional level of Nrf2 and its downstream antioxidants in oocytes during IVM. The mechanism action of some interventions may be related to the

Table 1 The role of Nrf2 in ovary

Author et al	Animal type	Model	Component used to target Nrf2 signaling pathway	Outcomes
Zheng et al. [58]	zebrafish	In vivo	Cadmium	• Activated key transcription factors, Nrf2 and NF-kB • Increase Tumor Necrosis Factor-alpha (TNF-α)
Fan et al. [59]	Rat	In vivo	Atrazine	• Improved the oocyte maturation • Increased mRNA abundance of *NRF2*, *SOD1*, *CAT*, and *GPX4*
Xue et al. [60]	Mice	In vivo	Carbon tetrachloride	• Antioxidants such as SOD, NRF2, and HO-1 were decreased • Inflammation markers were increased
Ma et al. [61]	Laying Hens	In vivo	Mercury (Hg)	• Disrupted oocyte maturation through decreasing Nrf2-Cyclin B1 signaling pathway
Xu et al. [62]	Mice	In vivo	Zinc Oxide particle	• Upregulation of antioxidant-related genes, ER stress-related genes and genes related to apoptosis • increased atretic follicles and exfoliated follicular granulosa cells
Grzegorzewska et al. [63]	Chicken Embryonic Gonads	In vitro	Sodium florid	• disrupt normal antioxidant balance in developing reproductive organs • increase the intensity of immunolocalised antioxidant markers like CAT, SOD2, and Nrf1 in the ovary
Ma et al. [64]	Hens	In vivo	vanadium + epigallocatechin-3-gallate	• Vanadium exposure reduced antioxidant enzymes (SOD, CAT, GR, GSH-Px), but EGCG supplementation restored these enzyme activities • EGCG has ability to enhance Nrf2 and sMaf gene expression
Shain et al. [65]	Japanese quail	In vivo	Capsaicinoids supplement against heat stress	Heat Stress effects • Increases OS markers • Decrease levels of Nrf2**,** Akt**,** and HO-1 Capsaicinoids effects • Increase antioxidant markers Nrf2, Akt, and HO-1
Xing et al. [66]	Hens	In vivo	Resveratrol	• lower inflammation markers promotes antioxidant signaling pathways
Meng et al. [67]	Rat	In vivo	Co-administration Hydrogen-rich saline with Cisplatin	• improved ovarian function by reducing markers like MDA and increasing protective antioxidants SOD, CAT • elevated estrogen (E2) levels, reduced FSH
Niringiyumukiza et al. [68]	Mic	In vivo	Co-administration glycogen synthase kinase-3 inhibition with Doxorubicin	• increase the expression of Nrf2 and restored GSH-Px and SOD-1 levels • supporting ovarian recovery by restored AMH and E2 levels and lowered FSH
Sun et al. [69]	Rat	In vitro	Melatonin	• activation of antioxidative enzymes via the Nrf2 signaling Pathway • scavenge ROS

Table 1 (continued)

Author et al	Animal type	Model	Component used to target Nrf2 signaling pathway	Outcomes
Guo et al. [50]	Mic	In vitro	Melatonin	• melatonin regulates the expression of genes Nrf2, SOD1 and proteins Nrf2, HO-1 • Mitigating intracellular OS, consequently enhancing in vitro development of vitrified-warme germinal vesicle oocytes
Raghuraman et al. [48]	Chinese Hamster Ovary (CHO) cells and murine splenic lymphocytes	In vitro	Diselenonicotinamide (DSNA), 1.26	•. Increase antioxidant activity • Reduce radiation-induced DNA damage • Upregulation of repair gene RAD51
Sze et al. [52]	Rat	In vitro, in vivo	Aging and iron metabolism	• Nrf2 Downregulation • elevated expression of ovarian inflammatory factors such as (iNOS and TNFα) via NF-κB activation • iron accumulation and ferroptosis
Akino et al. [53]	Mic	In vivo	Dimethylfumarate 20 mg/kg, oral	• increase Nrf2 and antioxidant levels • reduce DNA damage, and OS in the ovary
Lim et al. [55]	Mic	In vitro	• deletion of Nrf2 and benzo [a] pyrene	• depletion of ovarian follicles in both Nrf2 + / + and Nrf2 − / − mic • ovarian aging accelerates in the absence of NRF2
Bai et al. [54]	Mic	In vivo	Tanshinone IIA	• enhances the ovarian reserve and attenuates ovarian OS
Tsakiri et al. [56]	Drosophila melanogaster	In vivo, in vitro	proteasome	• Unlike gonads, proteasome expression and activity decline in aged somatic tissues • age-related Nrf2 dysfunction is correlated with the diminished levels of proteasomes
Li et al. [57]	Mic	In vivo	Deletion of pigment epithelium-derived factor	• Increased the level of ROS and activated the Nrf2 pathway • Decrease ovarian reserve
Gong et al. [70]	CHO cells (Ka13)	In vitro	cobalt chloride and hypoxia	• CoCl2 ctivates Ho-1gen through OS and the involvement of Nrf2 and MafG • Hypoxia uses a distinct pathway without involving these proteins for Ho-1gen exprssion
He et al. [71]	CHOK1SV cells	In vitro	Altering the medium cell cultures	• reduce oxidation of monoclonal antibodies (mAbs), specifically tryptophan oxidation • reduce ROS through the Nrf2-mediated antioxidative response

upstream or downstream signaling pathway. For example, N-acetylcysteine as a potent antioxidant acts through protein kinase C (PKC) as an upregulated factor which disconnects Nrf2 from Keap-1 [58]. Another mechanism of Nrf2 function in oocyte maturation is described by Kim et al. [64]. They used melatonin as a Nrf2 activator and brutal as a Nrf2 inhibitor. They demonstrated that melatonin, by binding to the melatonin receptor 2, activates a series of cascades, leading to the detachment of Nrf2 from Keap1. Nrf2 is then translocated to the nucleus and targets ARE to express catalase, which prevents ROS accumulation and translocates to peroxisomes. In peroxisomes, catalase also prevents H2O2, which is produced in peroxisomes in porcine oocytes. Brutal reduced the detachment of Nrf2 from Keap1, thus reversing this signaling pathway and reducing oocyte quality. In contrast, it was shown that melatonin attenuated Nrf2 overexpression induced by heat stress in IVM of porcine oocytes

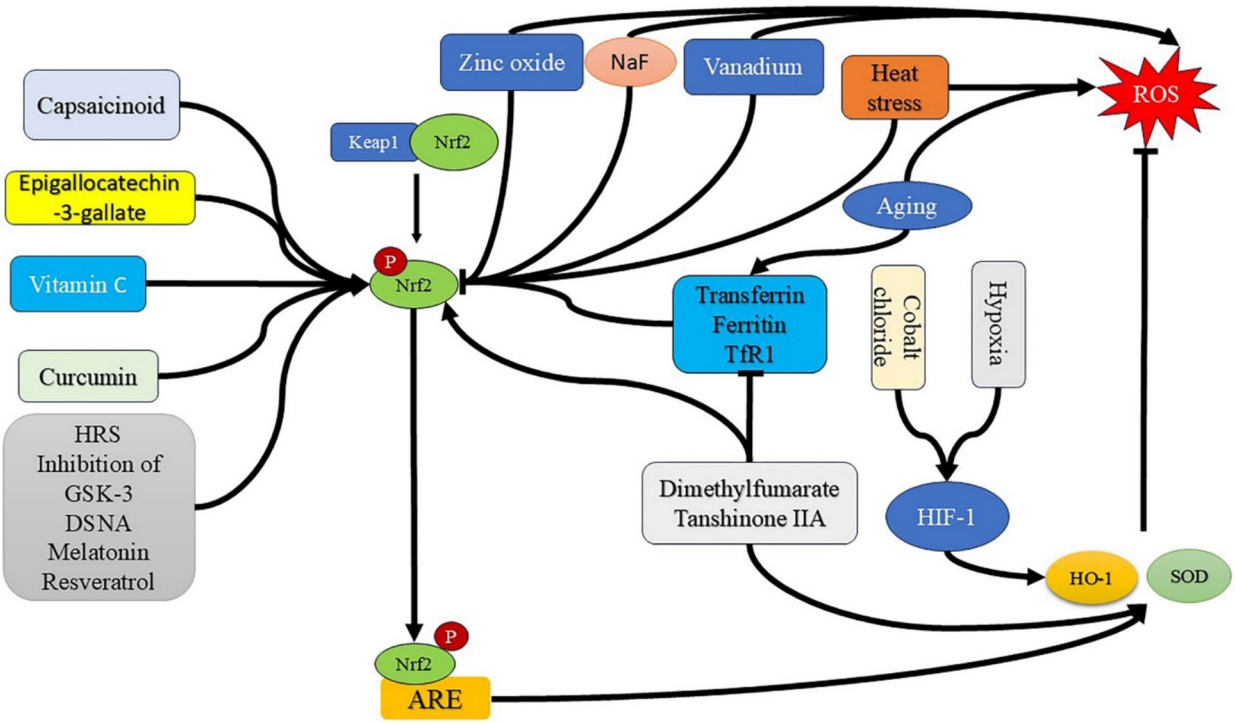

Fig. 3 Signaling pathways involved in Nrf2 inhibitors and simulators in ovary

[65]. This reverse effect of melatonin on the expression of Nrf2 may have originated from the neutralizing effect of heat stress. The mammalian target of rapamycin (mTOR) is another pathway that has been reported as a trigger for Nrf2 in oocyte cells. It was reported that targeting mTOR by rapamycin upregulated Nrf2 and its downstream antioxidant in IVM oocytes [66]. p38α MAPK is another regulator of Nrf2 that separates Nrf2 from Keap1 by Nrf2 phosphorylation. Myostatin acts through its upregulating factor [60].

Another intervention in IVM is cell therapy. One of the problems with the IVM process is the separation of the COC complex from follicular mural somatic cells. Mural cells have an essential function in protecting oocytes, such as myostatin production. To solve this miscommunication, the researchers added cumulus-derived somatic cells to IVM and observed modulation of ROS and enhancement of Nrf2 [63]. Furthermore, using equine amniotic fluid mesenchymal stem cell conditioned medium passages 7 to increase Nrf2 in cumulus cell-mediated oocyte maturation in IVM was to solve this phenomenon [67].

In vivo studies also confirm the essential effect of Nrf2 in oocytes. In this regard, it was reported that lead exposure increases ROS and MDA by reducing antioxidant activity in oocyte cells, and its effect was related to the Nrf2/Keap1 pathway [68]. Similarly, oral administration of isoniazid, (a synthetic first-line tuberculosis antibiotic) increased the level of ROS and activated the Keap1-Nrf2 pathway as an OS response [69]. This also led to apoptosis of oocytes and mitochondrial dysfunction.

Another function of Nrf2 is involvement in chromosome condensation. This role of Nrf2 is mediated through the Nrf2-Cyclin B1 signaling pathway. Cyclin B1 synthesis and degradation regulate maturation-promoting factor activity, which increases chromosome condensation and microtubule polymerization in prophase I oocytes. In support of this notion, it was reported that using brusatol as an inhibitor of the Nrf2-mediated signaling pathway disrupted oocyte maturation through the reduction of Nrf2. Reduced Nrf2 caused a reduction in Cyclin B1, thus disturbing proper spindle assembly and chromosome condensation in meiotic oocytes [61].

As a result, Nrf2 has a critical effect on oocyte maturation, especially in IVM. Its function is clarified by studies that used an activator or inhibitor intervention of the Nrf2 pathway (Table 2 and Fig. 4).

Nrf2 and granulosa cells

The follicular growth phase of mammalian folliculogenesis is characterized by the proliferation and differentiation of granulosa cells (GCs). These cells, which encase the oocyte, are crucial for the protection, support, and nourishment of maturing oocytes. GCs facilitate the

Table 2 The role of Nrf2 in oocyte cell

Author et al	Animal type	Model	Component used to target Nrf2 signaling pathway	Outcomes
Fan et al. [58]	Mouse	In vitro	N-acetyl-cysteine	• Promoted the nuclear translocation of Nrf2 • Activated the expression of superoxide dismutase and glutathione peroxidase, Removed excessive reactive oxygen species • Reduced mitochondria damage
Huang et al. [59]	Bovine	In vitro	Epigallocatechin-3-gallate (50 μM)	• Improved the oocyte maturation • Increased mRNA abundance of Nrf2, SOD1, CAT, and GPX4
Ma et al. [61]	Mouse	In vitro	Brusatol (200 nM)	• Disrupted oocyte maturation through decreasing Nrf2-Cyclin B1 signaling pathway
Mohammed et al. [60]	Buffalo		Myostatin inhibitor	• Downregulated the expression of Nrf2 and reduced the fertilization efficiency and cleavage and blastocyst rates
Yoon et al. [62]	Porcine		Myostatin	• Modulated oocyte maturation by regulating p38 MAPK phosphorylation following by regulating Keap1-Nrf2 mechanism, thus reduces intracellular ROS level during IVM
Yoon et al. [63]	Porcine	In vitro	Cumulus-derived somatic cells	• Increased expression of Nrf2 in oocyte and granulosa cells • Improved the developmental potential • of IVF- and PA-derived porcine
Park et al. [67]	Porcine	In vitro	equine amniotic fluid mesenchymal stem cell conditioned medium passages 7	• Increased Nrf2 in cumulus cell mediated oocyte maturation
Kim et al. [64]	Porcine	In vitro	Melatonin as Nrf2 activator Brusatol as Nrf2 inhibitor	• Melatonin upregulated Nrf2 signaling, resulting in the upregulation of catalase • Brusatol downregulated Nrf2, resulting in the downregulation of catalase
Yang et al. [65]	Porcine	In vitro	Heat stress as Nrf2 activator Melatonin as Nrf2 inhibitor	• Heat stress reduced maturation Rate, formation of α-tubulin, and F-actin, and expression of CDK1 and GDF9 and increased the expression of HSP70 and NRF2 • Melatonin increased maturation rate, formation of α-tubulin and F-actin, and expression of HSP70 and reduced the expression Nrf2
Yang et al. [66]	Mouse	In vitro	Rapamycin (10 nM)	• Increased the expression of Nrf2 in IVM oocytes
Xiang et al. [76]	Porcine	In vitro	Astaxanthin (2.5 μM)	• upregulated the SOD1, SOD2 GPX4 expression and alleviated OS • Enhanced maturation quality and subsequent embryo development of both fresh and vitrified porcine oocytes • Decreased cathepsin B activity, rescued lysosomal function, • Increased mitochondrial activity
Jiang et al. [68]	Mouse	In vivo	Lead	• Increased the transcription levels of Nrf2, CAT, GST, HO-1, GPX, GCLC, GCLM, and SOD • Enhanced ROS and MDA • Decreased antioxidant activity • Suppressed that of Keap1 • decreases the mitochondria
Qiao et al. [69]	Mouse	In vivo	Oral administration isoniazid (40 mg/kg/day)	• Increased the level of ROS and activated the Keap1-Nrf2 pathway • Caused apoptosis of oocytes and mitochondrial dysfunction

transfer of essential nutrients and small molecules to oocytes via gap junctions and are integral to ovarian function due to their roles in steroidogenesis and oocyte development [33, 72]. Consequently, the quantity and morphology of GCs serve as important indicators for assessing the potential for embryo development and the success of pregnancy outcomes. Additionally, OS, which encompasses endoplasmic reticulum stress, significantly

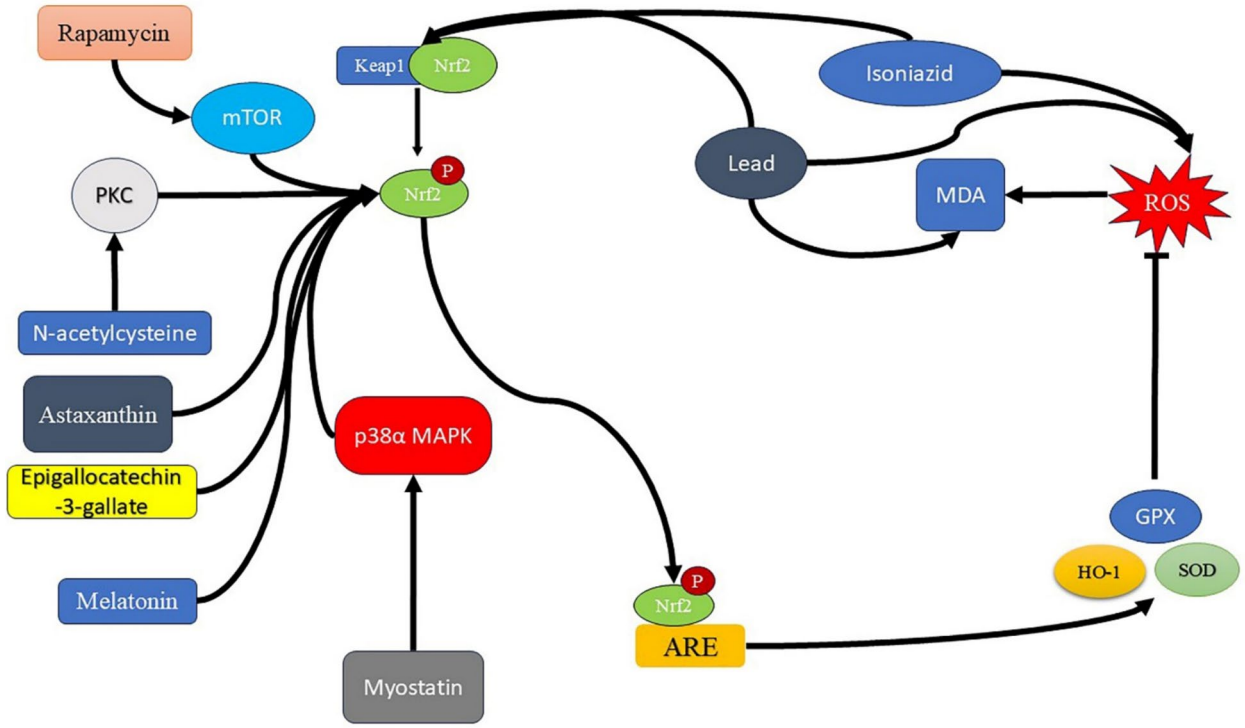

Fig. 4 Signaling pathways involved in Nrf2 inhibitors and simulators in oocyte

contributes to the apoptosis of GCs and oocytes, ultimately resulting in follicular atresia and infertility in women. Therefore, the management of OS in granulosa cells may enhance the outcomes of infertility treatments [33].

There are some studies designed in this context. In one of them, researchers isolated GCs and cultured them with H2O2, dimethylfumarate, and a Nrf2 activator. The objective was to investigate the interaction between Nrf2 and antioxidant mechanisms. The study concluded that Nrf2 activation contributes to the reduction of OS in GCs, highlighting its potential role as a protective factor against cellular damage caused by OS [74]. miR-28, miR-153, and miR-708 are endogenous regulators of the Nrf2 pathway in GCs. The findings indicated that OS triggers the activation of Nrf2 expression as a protective response while concurrently decreasing the levels of these specific miRNAs. Additionally, elevated levels of these miRNAs were associated with the downregulation of Nrf2 expression, resulting in increased ROS accumulation, decreased mitochondrial activity, and reduced cellular proliferation [37]. It was also shown that exosomal miR-27 could elevate ROS and promote apoptosis by downregulating the p-ERK/Nrf2 signaling pathway, which is negatively influenced by the regulation of SPRY2 [77].

Furthermore, recent studies have revealed that OS-suppressing compounds such as sulforaphane [30, 78–80], morroniside [81], astaxanthin [73], quercetin [82, 83], vitamin E [33, 75], and selenium [33] can alleviate the OS condition of GCs via the Nrf2 pathway.

By using sulforaphane, the elevation of the protein level of Nrf2 was demonstrated, which was followed by an increase in Nrf2 downstream factors like SOD, CAT, PRDX1, and TXN1. These factors improved GCs' defense mechanisms against OS. By ameliorating OS, sulforaphane improved the viability, apoptosis, and mitochondrial function in GCs exposed to H2O2 [30, 80]. This antioxidative effect of sulforaphane is achieved by stimulating the AMPK, AKT, and Nrf2 pathways, thereby providing protective effects against OS in GCs [78].

Another antioxidant is morroniside. It was reported that pretreatment of GCs with morroniside significantly reduced ROS, MDA, and 8-hydroxydeoxyguanosine (8-OHdG) in GCs. This effect of morroniside was achieved through upregulating the phosphorylation of Nrf2 and facilitating its translocation into the nucleus, leading to the transcriptional activation of antioxidant enzymes such as SOD and NQO1 [81].

Quercetin is another component with antioxidative properties. It was reported that quercetin upregulates

the messenger RNA expressions for Nrf2 and its associated downstream genes, which were also correlated with enhanced cellular viability. In addition, quercetin alleviated H2O2-induced steroidogenic dysfunction in goat GCs, a process that may be facilitated through the Nrf2 signaling pathway [83]. Also, its upregulating function on Nrf2 may occur through Thrx gene expression [82].

Various studies have indicated that administering vitamin E, both independently and alongside selenium, can substantially decrease intracellular ROS levels. These studies revealed that vitamin E influences GC dynamics, specifically their proliferation and apoptosis through a defense mechanism mediated by Nrf2 and its downstream antioxidants. This process is facilitated by the activation of the PI3K/AKT and ERK1/2 signaling cascades [33, 75]. Similarly, astaxanthin influenced GCs. Astaxanthin enhanced both gene and protein expression, as well as the nuclear localization of Nrf2, while simultaneously exerting an inhibitory influence on the protein levels of Keap1 [73].

In conclusion, the Nrf2 signaling pathway has a potential effect on the modulation of redox in GCs, and any downregulatory or upregulatory effect of this factor could have a potential impact on the GCs (Table 3 and Fig. 5).

Throughout the processes of follicular development and ovulation, GCs activate an intrinsic defense mechanism that encompasses the NRF2-ARE pathway, which serves to protect against a range of stressors [80]. Recent research indicates that Nrf2 may serve as a significant factor in promoting the survival and maintenance of follicles. This finding highlights the potential role of Nrf2 in supporting the health and longevity of follicular structures [73, 74]. A significant presence of NRF2 protein has been identified within the follicular cells of the preovulatory follicle as well as in the newly developed corpus luteum. This localization plays a crucial role in initiating the activation of antioxidant mechanisms, which serve to safeguard the cells against apoptosis [86].

Nrf2 and polycystic ovarian syndrome

Systemic and ovarian imbalances of OS are critical characteristics of polycystic ovarian syndrome (PCOS). This evidence positions the Nrf2 pathway as a viable target for therapeutic intervention in the disease. Numerous comprehensive studies have been conducted to investigate beneficial strategies for modulating the Nrf2 pathway in order to alleviate symptoms associated with PCOS.

The combination administration of MitoQ10 and Vitamin D3 in induced PCOS reduced the expression of genes involved in OS, including Keap1, HO-1, and Nrf2 [87]. Another combination comprising linagliptin and I3C has revealed a positive impact on PCOS metrics by upregulating the Nrf2/HO-1 pathway and enhancing SOD and CAT antioxidant enzymes in ovarian tissue [88]. The utilization of diacerein, an IL-1β inhibitor, in the experimental PCOS model exhibited a pronounced protective effect against OS by effectively reducing elevated levels of MDA and total nitrite, while concurrently enhancing the production of SOD and CAT. The Keap-1/Nrf2/OH-1 signaling pathway is introduced for diacerein's ameliorating effect [89]. Luteolin (a naturally occurring flavonoid present in a diverse range of herbs) improved ovarian function by activating the PI3K/AKT signaling pathway. Also, luteolin enhanced antioxidant defenses by restoring the Nrf2 pathway and its downstream genes, specifically Nqo1 and Hmox1 in PCOS [90]. Astaxanthin and sulforaphane are commonly employed as advantageous dietary supplements. Both of them have been proposed as favorable candidates for mitigating OS in PCOS patients, which could respectively lead to increased levels of total antioxidant capacity (TAC) in the patient's serum and promote cell survival and growth in granulosa cells through activating the Nrf2 pathway and its relevant genes, AMPK/AKT [91, 92]. The traditional herbal formula known as Qi Gong Wan (QGW) has long been used in Ancient Chinese medicine as a remedy for obesity-induced infertility in women. The efficacy of QGW has been considered in PCOS, specifically in individuals with insulin resistance. QGW's therapeutic advantages are uncovered with improvements in ovarian health, insulin levels, and insulin resistance markers such as the HOMA-IR index. These beneficial effects are attributed to the activation of the Nrf2/HO-1/Cyp1b1 pathway, which plays an important role in protecting adipose tissue in cases of PCOS [93]. Humanin, a peptide biomarker derived from mitochondria, is well-known for its antioxidant properties. Humanin has yielded promising results in reducing OS and preventing PCOS by activating the Keap1/Nrf2 signaling pathway [32].

Some scientists have scrutinized the role of the unusual expression of miRNAs and unveiled an upregulation of miR-873-5p in patients with PCOS. Silencing of miR-873-5p activates the p38/Nrf2/HO-1 signaling pathway, thereby diminishing the generation of OS factors, including ROS and MDA. Histone deacetylase is an epigenetic regulator believed to contribute to ovarian dysfunction in PCOS. The hypothesis that sodium acetate, an inhibitor of histone deacetylase, could protect against ovarian dysfunction in PCOS, was examined recently. Acetate treatment illustrated positive outcomes, including reductions in body and ovarian weight, improvements in insulin sensitivity, and reconditioning of hormonal balance. Antioxidant response was determined by increasing ovarian levels of glutathione peroxidase and Nrf2 [94].

Table 3 The role of Nrf2 in granulosa cells

Author et al	Animal type	Model	Component used to target Nrf2 signaling pathway	Outcomes
Aglan HS et al. [84]	Bovine GCs	In-vitro	Lead	• Lead downregulate Nrf2, NF-κB, and antiapoptotic gene • Lead upregulates the expression of endoplasmic reticulum stress marker and the proapoptotic gene • Lead induces GCs cycle arrest and mediates apoptosis via disruption of Nrf2/NF-κB • Lead to decrease in the expression of cell proliferation marker genes in GCs
Sammad A et al. [72]	Bovine GCs	In-vitro	Acute Heat Stress	• Acute Heat Stress upregulate inflammatory, pro-apoptotic, caspase executioner genes, antioxidants and anti-apoptotic genes • High inflammatory responsible oxidative-stress-mediated apoptosis in GCs via NF-κB pathway and repression of the Nrf2 pathway • Acute Heat Stress induces transient cellular senescence and apoptosis in GCs via MAPK and p53 signaling pathway
Esfandyari S et al. [80]	Human GCs	In-vitro	Pretreatment of GCs with Sulforaphane	• SFN attenuated intracellular ROS production and apoptosis rate in the GCs • SFN increases the mRNA expression level of Nrf2, SOD, and CAT
Eslami M et al. [73]	Human GCs	In-vitro	Astaxanthin	• AST suppresses ROS generation and cell death in GCs • AST elevates gene and protein expression of Nrf2 and inhibits the protein of KEAP
Li M et al. [83]	Goat GCs	In-vitro	Quercetin	• Que decreased GCs apoptosis by downregulate expressions of BAX, BCL-2, Caspase 3, and Cleaved caspase 3 • Que increases cellular viability by upregulating Nrf2 and its downstream genes
Ma Y et al. [81]	Human GCs	In-vitro	Pretreatment with morroniside	• Morningside decreases the levels of ROS, MDA, and 8-OHdG in GCs • Morroniside upregulates p-Nrf2 and promoted the nuclear translocation of Nrf2, which transcriptionally activated antioxidant SOD and NQO1 • Morroniside regulates the levels of apoptosis-related proteins via the p38 and JNK pathways
Rashidi Z et al. [82]	Human GCs	In-vitro	Quercetin	• Que pretreatment decreases ROS production and apoptosis • Que increases the Nrf2 gene and protein expression and its nuclear translocation and decreases the level of Keap1 protein • Que protected GCs from OS by increasing Thrx gene expression and activity
Sohel MMH et al. [79]	Bovine GCs	In-vitro	Pretreatment of Sulforaphane	• SFN increases cell viability and reduces cytotoxicity in GCs • SFN increases the expression of Nrf2 and the relative abundance of the Nrf2 downstream target antioxidant genes
Sohel MMH et al. [30]	Bovine GCs	In-vitro	Pretreatment of Sulforaphane	• Higher concentrations of SFN have cytotoxic effects on GCs • SFN regulates Nrf2, genes downstream to Nrf2, and Keap1expression • SFN has concentration-dependent antioxidative and apoptotic effects on GCs
Wang M et al. [75]	Bovine GCs	In-vitro	Pretreated with Vitamin E	• VE decreases the intracellular ROS levels, increases the MDA content, and improves the antioxidant enzyme activity in a dose-dependent manner • VE promotes proliferation and inhibits apoptosis in GCs via the Nrf2 pathway
Wang M et al. [33]	Bovine GCs	In-vitro	vitamin E (VE) and selenium (Se)	• VE or Se could stimulate the GCs proliferation • VE or Se increased the secretion of estradiol and progesterone • VE or Se down-regulates the apoptosis-related gene expression, inhibits ROS and MDA generation, and increases T-AOC, and the activities of SOD, CAT, and GSH-Px • VE or Se alleviates the endoplasmic reticulum stress, activates the NRF2, and up-regulated the expression of its downstream genes

Table 3 (continued)

Author et al	Animal type	Model	Component used to target Nrf2 signaling pathway	Outcomes
Zou L et al. [85]	Human GCs	In-vitro	Copper model and pretreated with Hemin	• Copper decreases GCs viability and the mitochondrial membrane potential, increases the apoptosis rate, and induces OS • Hemin pretreatment induces HO-1 expression in GCs via the MAPK14-Nrf2 pathway, reduces the accumulation of ROS, and increases the levels of antioxidant enzymes

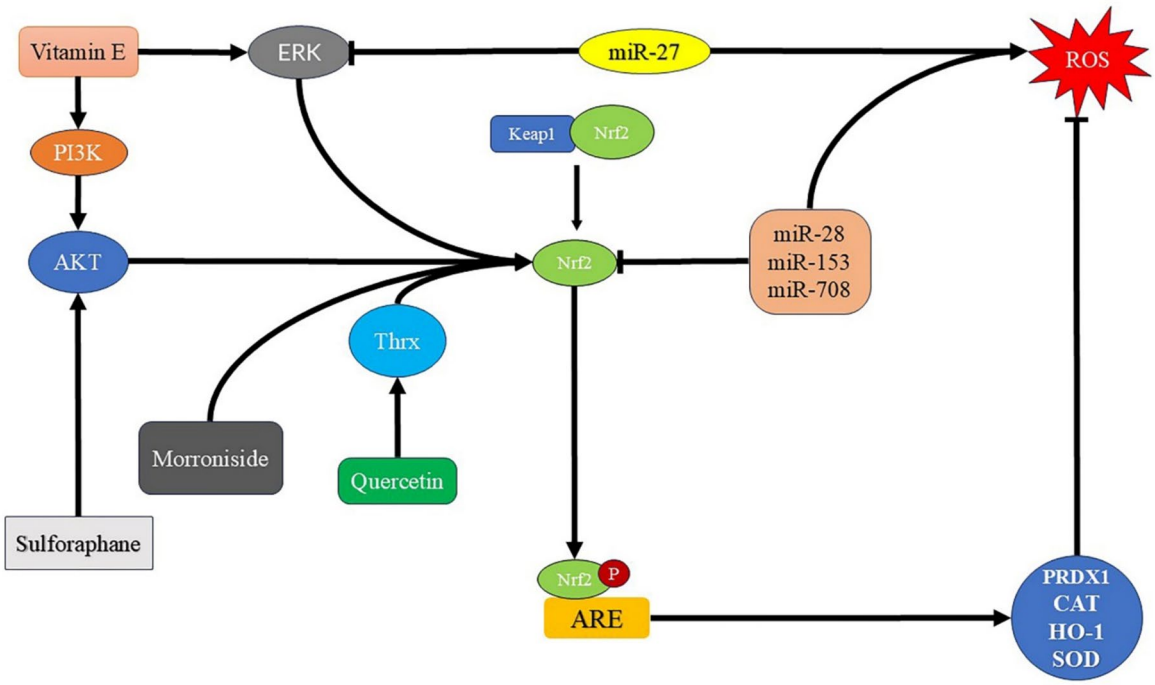

Fig. 5 Signaling pathways involved in Nrf2 inhibitors and simulators in granulosa cell

This extensive overview discusses recent advances in understanding and treating PCOS through targeted intervention in OS pathways, specifically focusing on the Nrf2 signaling pathway (Table 4).

Nrf2 and primary ovarian insufficiency

Primary ovarian insufficiency (POI) is a condition in which follicle development and sex hormone production in the ovaries are disrupted before the age of 40. One of the signaling pathways involved in POI is the Keap1-Nrf2-ARE pathway. In POI, the increase in OS and ROS inactivates this pathway, causing accumulated Nrf2 to be targeted by PKC, JNK, PIK3, and ERK and translocated to the nucleus. In the nucleus, Nrf2 induces the transcription of HO-1, NQO1, and SOD through ARE. These proteins are then transported to the cytoplasm to protect cells from OS damage [9, 95].

However, there are other interventions that can activate upstream proteins. For example, PI3K enhances the disconnection of the Keap1-Nrf2 complex by activating AKT [96]. Epicatechin [97], curcumin [98], and EGF [99] have been shown to alleviate POI by upregulating PI3K. Additionally, it has been suggested that EGF may directly activate Nrf2 or inhibit PTEN, which is an upregulator of PI3K. SESN2 is another protein that disrupts the Keap1-Nrf2 complex by promoting the autophagic degradation of Keap1 in POI [100]. Some components with antioxidative activity, such as chitooligosaccharide-zinc, have a therapeutic effect on POI by activating SESN2 [101]. PKC and HDAC-2 act as upregulators and downregulators, respectively, of the Nrf2 signaling pathway [102]. A study by Liu et al. found that squid ink polysaccharide positively affects POI by reducing Keap1 and HDAC-2 while increasing PKC, Nrf2, and downstream factors like SOD, HO-1, and NQO-1 [103]. SIRT1 is another upregulator of Nrf2 [104]. It was indicated that icariin influences POI by activating the Nrf2/HO-1/Sirt1 axis in an animal model [105]. Foxo3a is a downstream factor in the Nrf2

Table 4 the role of Nrf2 on polycystic ovarian syndrome

Author et al	Animal type	Model	Intervention used to target Nrf2 signaling pathway	Outcomes
Kyei et al. [58]	Mice	In vitro	Vitamin D3 + MitoQ10	• Decrease serum MDA, SOD, and hormone levels* • Reduction in steroidogenesis-related enzymes and OS-associated mRNA Nrf2 pathway
Kabel et al. [59]	Rat	In vivo	linagliptin and I3C	• Reduced levels of markers like TGF-β1, TNF-α, and IL-10, as well as hormone levels • Antioxidant enzyme activity (Nrf2/HO-1) increased • Reduced body weight, fasting blood glucose, insulin levels and improved ovarian morphology
Ibrahim et al. [61]	Rat	In vivo	Diacerein 50&25 mg/kg	• Reducing elevated levels of MDA and total nitrite • Enhance the protective proteins Keap-1, Nrf2, and OH-1 level • Inhibit the elevated mRNA levels inflammatory cytokines • Decrease body and ovarian weight, cyst formation, insulin, glucose, hormone levels
Akin et al. [60]	Human	In vitro	amphiregulin	• Promoted the maturation rate of oocytes • The expression Change of genes involved in steroidogenesis, ovulation, and metabolism
Huang et al. [62]	Rat	In vivo	Luteolin	• Reduces insulin resistance by activating the PI3K/AKT signaling pathway • Preserving oocytes and corpus luteum • Normalized the hormone imbalances
Gharaei et al. [63]	Human	In vivo	Astaxanthin	• Increase expression of Nrf2, HO-1, and NQ-1 in GCs • Raises of serum level CAT and TAC
Taheri et al. [64]	Human	In vivo	Sulforaphane	• Reduced intracellular ROS and apoptosis in GC • Activation of the AMPK/AKT/NRF2 signaling pathway
Zheng et al. [65]	Mic	In vivo	Qi Gong Wan (QGW)	• Improve cystic follicles, fasting insulin, and HOMA-IR index • By activating the Nrf2/HO1/Cyp1b1 pathway to improve adipocyte hypertrophy and inflammation
Wang et al. [66]	Rat, COV434 cell lines	in vivo and in vitro	Humanin	• Humanin Supplementation reduced body weight gain, Improved ovarian morphology and endocrinological disorders • Modulation of Nrf2/HO1/Cyp1b1 pathway
Zhang et al. [76]	KGN cells	in vitro	miR-873-5p inhibitor	• suppressed cell apoptosis, decrease in OS, and reduced production of ROS and MDA • activated the p38/Nrf2/HO-1 signaling pathway
Tan et al. [68]	KGN cells	In vitro	miR-93-5p	• miR-93-5p upregulated in the GCs • Overexpression of miR-93- promoted apoptosis and ferroptosis GCs • Silencing of miR-93-5p protects against GC dysfunction
Olaniyi et al. [69]	Rat	In vivo	Sodium acetate (200 mg/kg), oral	• Normal follicular development and improved circulating 17-β estradiol levels • Increasing ovarian levels of glutathione peroxidase, and Nrf2 • Reductions in body and ovarian weigh

pathway. It was reported that 4-Vinyl Cyclohexene Diepoxide reduces OS damage in an animal model of POI by upregulating Nrf2, Foxo3a, and HO-1 [106]. Another study identified the Nrf2/SOD2 pathway as a target for the antioxidative effect of puerarin in POI [107]. Additionally, daphnetin was introduced as another promoter of Nrf2 in D-galactose-induced POI [108]. Some antioxidative interventions, such as preventive electroacupuncture, alleviate POI by directly interfering with the Keap1-Nrf2 complex [109].

Furthermore, Nrf2 has been shown to regulate angiogenesis through the HO-1-mediated HIF-1α/VEGF signaling axis [110]. Supporting this idea, one study demonstrated that Si-Wu-Tang (a traditional Chinese

medicine) promoted angiogenesis by targeting the Nrf2/HO-1 pathway in POI [111] (Table 5).

Nrf2 and ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome (OHSS) is a significant complication that can occur following gonadotropin-driven ovarian stimulation, particularly when human chorionic gonadotropin (hCG) is administered to promote the development of multiple ovarian follicles. One of the critical issues associated with OHSS is OS, which can adversely affect oocyte quality and overall reproductive health. Nrf2 is crucial for regulating the expression of antioxidant enzymes, which help protect cells from oxidative damage.

In a study by Fan et al., the effects of N-acetyl-cysteine (NAC) on OS induced by repeated controlled ovarian hyperstimulation were examined in mice. Their findings demonstrated that NAC enhances Nrf2 activity and PKC, a regulator that activates Nrf2, while simultaneously suppressing Keap1, a negative regulator of Nrf2. The authors concluded that NAC alleviates OS in oocytes during controlled ovarian hyperstimulation and improves oocyte quality by upregulating the Nrf2 signaling pathway, thereby increasing the activity of various antioxidant enzymes [58]. Similarly, Guan et al. investigated Kunling Wan, a traditional Chinese herbal formulation comprising 31 components with antioxidant properties. Their study found that Kunling Wan activates Nrf2, leading to the upregulation of antioxidant enzymes such as SOD and GSH-Px. This activation helps counteract OS and prevents mitochondrial damage in oocytes and ovaries during controlled ovarian hyperstimulation. The formulation enhances oocyte quality by modulating the PKC/Keap1/Nrf2 pathway, effectively inhibiting oxidative damage associated with repeated stimulation [112].

In contrast, Liu et al. identified a different mechanism involving microRNA-27 (miR-27) that may contribute to reduced Nrf2 function in OHSS. Their research indicated that miR-27 mimics increase ROS levels by downregulating the phosphorylated ERK/Nrf2 pathway in granulosa cells. They noted that SPRY2 acts as an upregulator for the ERK/Nrf2 signaling pathway, and miR-27 increases OS by downregulating SPRY2, subsequently leading to decreased p-ERK/Nrf2 signaling in an OHSS model [77].

Overall, these studies underscore the complex interplay between OS and the Nrf2 signaling pathway in the context of OHSS, highlighting potential therapeutic

Table 5 The role of Nrf2 on primary ovarian insufficiency

Author et al	Animal type	Model	Intervention or component used to target Nrf2 signaling pathway	Outcomes
Chen et al. [107]	Mice	In vivo	Puerarin	• Increased follicle number and the primordial follicle ratio • Decreased the atresia ratio • Recovered the expression levels of Oct4, Mvh, Wnt1, β-catenin, cyclin D1, SOD2, and Nrf2 • Improved the Bcl-2/Bax ratio
Chen et al. [109]	Rat	In vivo	Preventive Electroacupuncture	• Sex hormones recovered to normal levels • reducing OS in rats • Increasing SOD and GSH levels and decreased MDA levels • Dropping Keap1 protein expression • Increasing protein expressions of Nrf2 and HO-1
Ding et al. [99]	Mice	In vitro	EGF (epidermal growth factor)	• EGF suppressed OS by upregulating the expression of the NRF2/HO-1 pathway AND inhibited the apoptosis by regulating the PTEN/PI3K/AKT pathway
Hu et al. [106]	Mice	In vivo	4-Vinyl Cyclohexene Diepoxide	• 4-Vinyl Cyclohexene Diepoxide reduces OS damage in model of POI by upregulating Nrf2, Foxo3a, and HO-1
Jia et al. [101]	Mice	In vivo	Chitooligosaccharide-zinc	• Improves the ovarian and follicular development through regulating the SESN2/NRF2 signaling pathway • Elevates SOD2 protein
Liu et al. [103]	Mice	In vivo	Sepia esculenta ink polysaccharide	• Reducing Keap1 and HDAC-2 • Increasing PKC, Nrf2 • Downstream factors like SOD, HO-1, and NQO-1
Chen et al. [105]	Mice	In vivo	Icariin	• Influenced POI by activating the Nrf2/HO-1/Sirt1
Yan et al. [98]	Mice	In vivo	Curcumin	• Inhibited D-gal-induced OS, apoptosis, and ovarian injury via a mechanism involving the Nrf2/HO-1 and PI3K/Akt signaling pathways in POI model
Zhang et al. [108]	Mice	In vivo	Daphnetin (a Nrf2 activator)	• Alleviated POI through Nrf2/TXNIP/NLRP3 axis
Zhou et al. [107]	Mice	In vivo	Si-Wu-Tang (a traditional Chinese medicine)	• Enhanced OS and promotes angiogenesis by targeting the Nrf2/HO-1 pathway in POI

strategies to mitigate oxidative damage and improve oocyte quality.

Nrf2 and ovarian cancer

There is an overview discussing Nrf2 and ovarian cancer [113]. Briefly, Nrf2 controls how cells respond to DNA damage [113, 114]. Recent studies have shown that Nrf2 levels are significantly increased in ovarian cancer, demonstrating a positive correlation with ovarian lesions. Additionally, the Keap1/Nrf2/ARE pathway interacts with essential components of the endogenous antioxidant and detoxifying systems in ovarian cancer. By activating the Keap1/Nrf2/ARE signaling pathway, Nrf2 can prevent ROS-induced apoptosis. By regulating proteins such as ERα, CD99, EGFR, ErbB2, AKR1C1, AKR1C2, and ABCF2, Nrf2 can influence the apoptotic process in ovarian cancer cells. It can also regulate the cell cycle and the proliferation of cancer cells [113, 115–117].

About the role of Nrf2 in ovarian health, it is worth noting that most of the ovarian tissue protectors during chemotherapy, including GSK-3 inhibitors, epigallocatechin gallate, resveratrol, melatonin, and theaflavins, exert their positive effects by activating Nrf2 signaling to preserve female fertility [113]. Comprehensive studies have confirmed that miRNAs, such as miR-141 and miR-181d, can influence the expression of Nrf2 in breast and ovarian cancer, which, in turn, affects chemoresistance. According to the data, Nrf2 activation increases chemoresistance to chemotherapy by inhibiting drug-mediated OS (such as platinum drugs), which usually leads to cancer cell death [19, 115].

Conclusion

In conclusion, Nrf2 plays a significant role in the pathogenesis of ovarian dysfunction. The studies indicate that interventions affecting the Nrf2 signaling pathway may influence OS and redox balance within cells. The evidence reviewed suggests that the primary signaling pathway involved in mitigating OS is the Keap/Nrf2 signaling pathway. Various antioxidants that provide protective effects against ovarian disorders target this signaling pathway or its upstream regulatory factors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been approved by the Ethics and Research Committee of Qazvin University of Medical Sciences (IR.QUMS.REC.1403.496).

Competing interests
The authors declare no competing interests.

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