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REVIEW

Overview of biological effects of Quercetin on ovary

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Over the last few decades, using natural products has been increased to treat different diseases. Today, great attention has been pointed toward the usage of natural products such as flavonoids, especially Quercetin (QUR), in the treatment of diseases. QUR as a natural antioxidant has been traditionally used to prevent or treat a variety of diseases such as cancer, cardiovascular disease, polycystic ovary syndrome (PCOS), obesity, chronic inflammation, and reproductive system dysfunction. Several studies demonstrated that QUR acts as an anti-inflammatory, anti-apoptotic, antioxidant, and anticancer agent. With this in view, in this study, we intended to describe an overview of the biological effects of QUR on the ovary. QUR improves the quality of oocytes and embryos. It affects the proliferation and apoptosis and decreases the oxidative stress in granulosa cells (GCs). Furthermore, QUR can be used as a complementary and alternative therapy in ovarian cancer and it has beneficial effects in the treatment of PCOS patients. It seems that QUR as a supplementary factor has different activities for the treatment of different disorders and it also has bidirectional activities. However, further investigations are needed for understanding the efficacy of QUR in the treatment and improvement of gynecological patients.

KEYWORDS

Granulosa cell, oocyte, ovarian cancer, polycystic ovary syndrome, quercetin

Abbreviations: 17β-HSD1, 17 β-hydroxysteroid dehydrogenase type 1; 2008/C13, human ovarian carcinoma; 3′ UTR, 3′ untranslated region; A2780/CP70, human ovarian cancer cell line; AKT, protein kinase B; AP-1, activator protein-1; Bax, Bcl-2-Associated X Protein; Bcl-2, B-cell lymphoma 2; BLF, Chinese Bayberry leave flavonoids; C13, CDDP-resistant variant; C13*, human epithelial ovarian cancer; cAMP, cyclic adenosine monophosphate; CHOP, CCAAT-enhancer-binding protein homologous protein; circRNAs, circular RNAs; COX, cyclooxygenase; CRP, C-reactive proteins; DBP, diastolic blood pressure; EDs, endocrine disruptors; ER α, estrogen receptors alpha; ERK, extracellular signal-related kinase; ERS, endoplasmic reticulum stress; FSH, follicle-stimulating hormone; FTIs, farnesyltransferase inhibitors; G0, Gap0; G1, Gap1; GCs, granulosa cells; GnRH, gonadotropin-releasing hormone; GPx, glutathione peroxidase; GSH, glutamate-stimulating hormones; GSS, glutathione synthetase; GST, glutathione S-transferase; HSP70, heat shock protein 70; ICAM-1, intercellular adhesion molecule 1; IGF-1, insulin-like growth factor 1; IMA, ischemia modified albumin; IUPAC, International Union of Pure and Applied Chemistry; IVM, *in vitro* maturation; JNK, c-Jun NH2-terminal kinase; Keap1, Kelch-like Ech-associated protein 1; LH, luteinizing hormone; LH4, the monofunctional platinum tris (benzimidazole) monochloroplatinum (II) chloride; LH6, the monofunctional platinum complex tris (imidazo(1,2-A)pyridine) chloroplatinum(II) chloride; lncRNAs, long noncoding RNAs; LPS, lipopolysaccharide; M, mitosis; MPEG-PCL, monomethoxy poly(ethylene glycol)-poly(epsilon-caprolactone); MPF, maturation promoting factor; NF-κB, nuclear factor-κB; NO, nitric oxide; NQO1, NAD(P)H, quinone oxidoreductase 1; Nrf2-ARE, nuclear factor (erythroid-derived 2)-like 2/antioxidant response element; PCNA, proliferating cell nuclear antigen; PCOS, polycystic ovary syndrome; PPARγ, peroxisome proliferator-activated receptor c; PR, progesterone receptor; P-ris, primary cancer cells; QUR, Quercetin; RCTs, randomized controlled trials; ROS/RNS, reactive oxygen/nitrogen species; SBP, systolic blood pressure; SKOV3/CDDP, ovarian carcinoma (SKOV3)/cisplatin (CDDP)-resistant counterparts (SKOV3/CDDP); SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TAS, total antioxidant status; TGF β1, transforming growth factor; TNF-R, tumor necrosis factor receptors; Topo I and Topo II, topoisomerases I and II; TRAIL, tumor necrosis factor related apoptosis-inducing ligand; Trx, thioredoxin; type II EBS, type II estrogen binding site; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

1 | INTRODUCTION

Over the last decades, using natural products has been increased for disease treatment (Khan et al., 2016). Flavonoids are natural products belonging to a category of polyphenolic compounds with more than 4,000 varieties. These compounds are found in the normal human diet, particularly plants and most of them are known for their role in the color of flowers, fruits, and leaves (Lakhanpal & Rai, 2007).

Quercetin (QUR; 3,3′,4′,5,7-pentahydroxyflavone) is a plant-derived aglycone form of flavonoid glycosides and has a high amount of flavonoids (Rafiq et al., 2015). QUR as a natural antioxidant has been traditionally used to prevent or treat a variety of diseases such as cancer, cardiovascular diseases, nervous and neurodegenerative disorders, obesity, chronic inflammation, gastritis, allergies, asthma, and different types of bacterial and viral diseases (David, Arulmoli, & Parasuraman, 2016). Several studies demonstrated that QUR acts as an anti-inflammatory, anti-apoptotic, antioxidant, and anticancer agent (Amidi et al., 2019). It is reported that QUR has a significant role in the inhibition of breast, colon, prostate, ovary, endometrium, liver, brain, colon, and lung cancer (David et al., 2016). Furthermore, QUR may inhibit melanoma and leukemia too (Hashemzaei et al., 2017). Moreover, QUR exerts various biological effects, including protein kinase C-inhibition, cell cycle modulation, angiogenesis inhibition, platelet aggregation, capillary permeability promotion, and mitochondrial biogenesis stimulation (Hashemzaei et al., 2017; Li et al., 2016).

Previous studies have shown the therapeutic application of QUR in the treatment of various disorders (Mendoza & Burd, 2011; Filipa Brito et al., 2015; Mendoza-Wilson & Glossman-Mitnik, 2004; Murakami, Ashida, & Terao, 2008; Russo et al., 2014; Sak, 2014). Moreover, several *In vitro* and *In vivo* studies assessed its effects as an alternative medicine for the treatment of male infertility (Khanduja, Verma, & Bhardwaj, 2001; Taepongsorat, Tangpraprutgul, Kitana, & Malaivijitnond, 2008). Remarkably, QUR plays an important role in the female reproductive system, particularly in ovaries as an anticancer and antioxidant agent.

The ovary is a highly organized reproductive system that contains different cell types including germ cells (oocytes) and somatic cells (granulosa, theca, and stromal cells). Interaction of these cells induces oocyte-containing follicle formation, oocyte and follicle development, ovulation, and corpus luteum formation as an endocrine structure. Follicle development is controlled by the hypothalamic–pituitary–ovarian axis, in which the frequency of the gonadotropin-releasing hormone (GnRH) pulses regulates the secretion of pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Furthermore, the ovarian steroid hormones exert positive and negative regulatory effects on the secretion of GnRH. Disruption of this regulated network can result in ovarian dysfunction and various clinical syndromes (Richards & Pangas, 2010).

QUR may be used for the regulation of reproductive system functions, including folliculogenesis, maturation of oocyte, and ovulation, and thus it may be beneficial for reproductive disorders treatment (Stochmalová, Sirotkin, Kádasi, & Alexa, 2013). QUR can enhance the antioxidant capacity of the ovary through the up-regulation of oxidative stress-related genes in rat (Wang et al., 2018). It is demonstrated that QUR can affect the ovarian functions and interfere with steroidogenic and angiogenic activities of cells (Rice, Mason, & Whitehead, 2006).

Some studies have evaluated the effects of QUR on PCOS and endometriosis that can adversely affect women's lives. It is confirmed that QUR can reduce the metabolic and hormonal disorders occurring in PCOS (Jahan et al., 2018). QUR may act as a natural therapeutic agent for treating the human endometriosis (Park, Lim, Bazer, Whang, & Song, 2019). It seems that the inhibition of vascular endothelial growth factor (VEGF) and heat shock protein 70 (HSP70) expression can suppress endometriosis in rat (Zhang, Wang, Wang, Yang, & Qie, 2009). Cao et al. evaluated the effects of QUR on the hypothalamic-pituitary-gonadal (HPGA) axis in a rat model of endometriosis. They showed that QUR down-regulated the serum levels of FSH and LH through mediating the HPGA axis. Moreover, QUR can reduce the expression of estrogen receptors alpha (ERα) and beta (ERβ), as well as progesterone receptor (PR) in the hypothalamus, pituitary, and endometrium. These functions of QUR can cause hormone deficiency in the ectopic endometrium leading to the inhibition of ectopic endometrium growth (Cao et al., 2014). Hence, the purpose of this study was to review the biological effects of QUR on the ovaries and its related disorders.

2 | BIOCHEMISTRY, BIOAVAILABILITY, AND METABOLISM OF QUR

Flavonoids are phenolic structures found in the fruits, bark roots, vegetables, tea, grains, stem, and flowers (Lakhanpal & Rai, 2007). UR is a member of flavonoids obtained from quercetum (oak forest) and has been extensively used since 1857 (Fischer, Speth, Fleig-Eberenz, & Neuhaus, 1997). QUR has been defined as 3,3′,4′,5,7-pentahydroxyflavone by the International Union of Pure and Applied Chemistry (IUPAC). This means that QUR has five OH groups placed at the 3-, 3'-, 4'-, 5-, and 7-positions. QUR is a yellow crystal and insoluble in cold water, moderately soluble in hot water, but soluble in alcohol. This component is found in a variety of foods, including berries, apples, vegetables, grapes, onions, tea, tomatoes, shallots, nuts, barks, seeds, leaves, and flowers (Li et al., 2016). The dietary intake of all flavonoids has been estimated at about 200–350 mg/day, while the intake of flavonols is about 20 mg/day, of which this rate for QUR is about 10 mg/day (Kawabata, Mukai, & Ishisaka, 2015). QUR glycosides such as QUR-arabinoside, QUR-galactoside, and QUR-glucoside are transformed to QUR aglycone prior to absorption in the small intestine (Guo & Bruno, 2015). Total QUR obtained from the diet is normally present in plasma at a concentration <100 nM. However, when given as aglycone or glycoside, QUR absorption is elevated to the micromolar range (Manach, Williamson, Morand, Scalbert, & Rémésy, 2005). QUR is absorbed in the gastrointestinal tract and processed in the epithelial cells of the stomach, intestine, kidney, and liver (de Boer et al., 2005; Graf et al., 2006). The half-life of QUR is between 11 to 28 hr in the plasma (Manach et al., 2005; Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). QUR has many

pharmacological applications in different diseases (De et al., 2013). QUR has an optimal configuration for free radical scavenging due to the presence of two pharmacophores within the molecule, that is, the catechol group in the B ring and the OH group at position 3 of the A-C ring (Boots, Haenen, & Bast, 2008). Then, it seems likely that QUR can transfer its hydrogen atoms to the free radicals and stabilize their structures (Heijnen, Haenen, Vekemans, & Bast, 2001; Pietta, 2000). QUR have beneficial effects on health such as antioxidative, free radical scavenging, anticancer, and antiviral activities (Formica & Regelson, 1995).

3 | MECHANISMS OF QUR ACTION

3.1 | Antioxidant

QUR has different activities, including antioxidative, anticancerous and anti-inflammatory activities. QUR regulates the antioxidant defense systems and the following cell homeostasis through several mechanisms. As described earlier, QUR has an optimal configuration for free radical scavenging (Boots et al., 2008). Then, it seems that QUR can decrease the negative effects of free radicals in the body. Indeed, it directly scavenges free radicals such as reactive oxygen/nitrogen species (ROS/RNS). Moreover, QUR inhibits the activity of xanthine oxidase which leads to oxidative damage during injury, ischemia, and oxidative stress (Alrawaiq & Abdullah, 2014; Lakhanpal & Rai, 2007). Furthermore, it inhibits the lipid peroxidation, prevents the chain propagation, and reduces the production of more free radicals (Jia, Lin, Mi, & Zhang, 2011; Lakhanpal & Rai, 2007).

Furthermore, QUR can inhibit the oxidative stress by activating the nuclear factor (erythroid-derived 2)-like 2/Antioxidant response element (Nrf2-ARE) pathway and inducing the expression levels of phase II antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione s-transferase (GST), NAD(P)H: quinone oxidoreductase 1 (NQO1), glutathione peroxidase (GPx), and thioredoxin (Baghel, Shrivastava, Baghel, Agrawal, & Rajput, 2012; Wang et al., 2013). Moreover, it is revealed that kelch-like ech-associated protein 1 (Keap1) acts as a negative regulator of the Nrf2/ARE pathway in the cytoplasm through preventing the translocation of Nrf2 protein into the nucleus and affecting the following phase II antioxidant enzymes gene expression (Zhang et al., 2013).

3.2 | Anticancer

Cancer cells can be omitted by extrinsic and intrinsic programmed cell death pathways in the body. Cytokines are responsible molecules for such pathways by binding to tumor necrosis factor receptors (TNF-R) (Zhang et al., 2013). There are two pathways for the anticancer properties of QUR: long-term and short term. The pro-apoptotic effect of QUR which is considered as a long-term effect decreases the level of glutamate-stimulating hormones (GSH) (Robaszkiewicz, Balcerczyk, & Bartosz, 2007). The short-term effect of QUR is considered as an antioxidative and anti-apoptotic effect by scavenging the free radicals (Ferraresi et al., 2005). Several studies showed that ROS and RNS have a key role in developing human cancer. QUR as a free radical scavenger is considered as an anticancer agent (Catanzaro, Vianello, Ragazzi, Caparrotta, & Montopoli, 2014; Li et al., 2014; Wiseman & Halliwell, 1996). Moreover, QUR has modulatory effects on signal transduction pathways. In cancer cells, QUR can prevent cell proliferation and survival by reduction of Ras levels as an oncogenic protein (Psahoulia et al., 2006). Some studies demonstrated that QUR may block apoptosis by inhibiting the phosphorylation of p38 and Bcl2 and also suppressing the activation of c-Jun NH2-terminal kinase (JNK) and other extracellular signal-related kinase (ERKs) pathways (Ishikawa & Kitamura, 2000; Marone et al., 2001). Furthermore, QUR activates Sirtuins. Sirtuins (SIRT1 to SIRT7) are critical proteins involved in different cellular and molecular processes. SIRT1 can protect cells from apoptosis by the elimination of Bax and the suppression of different pro-apoptotic transcription factors (Leyton et al., 2015). Moreover, QUR can control apoptosis in the mitochondria by the activation of p53, up-regulation of Bax, and down-regulation of Bcl-2 in tumor cells (Khan et al., 2016). The activation of caspase 3 and caspase 9 by QUR induces the cell death process in tumor cells (Duraj, Zazrivcova, Bodo, Sulikova, & Sedlak, 2005). The p53 mutation is common in most patients with cancer and QUR down-regulates the expression of mutant p53 leading to arresting cells in the G2-M phase of the cell cycle. P53 gene has a key role in the control of cell proliferation in G1 checkpoint (Avila, Cansado, Harter, Velasco, & Notario, 1996; Scambia et al., 1990). Heat shock proteins are found in various cancers, such as breast cancer. They help cancer cells in different ways, including allowing them to escape the normal mechanisms of cell cycle arresting, increasing their survival in stressful conditions, and increasing their resistance to chemotherapy drugs (Oesterreich et al., 1993). It is shown that QUR can inhibit the expression of tyrosine kinase with a possible involvement in the ontogenesis (Baghel et al., 2012; Boutin, 1994).

3.3 | Anti-inflammation

Inflammation is a self-protection process for healing and it does not always indicate the infection (5). QUR is known as an anti-inflammatory substance (Li et al., 2016). QUR prevents inflammation directly and indirectly. The direct way is the prevention of inflammatory factors gene expression and protein secretion including TNF-α, ERK, JNK, c-Jun, and nuclear factor-κB (NF-κB). The ndirect way is increasing the activity of peroxisome proliferator-activated receptor c (PPARγ), NF-κB, and activator protein-1 (AP-1) (Khan et al., 2016). QUR has the key role in the modulation of inflammation by declining the inflammatory mediators such as prostaglandins and leukotrienes through the inhibition of inflammatory enzymes cyclooxygenase (COX) and lipooxygenase (Warren et al., 2008; Xiao et al., 2011).

Studies have shown the effects of certain flavonoids intake including QUR for decreasing the levels of inflammatory risk factor C-reactive proteins (CRP) (Chun, Chung, Claycombe, & Song, 2008) and other inflammatory mediators such as NO and COX-2

(García-Mediavilla et al., 2007). Furthermore, QUR has an immunosuppressive effect (Huang et al., 2010).

4 | *IN VITRO* AND *IN VIVO* STUDIES

4.1 | QUR and ovary

The ovary is a part of the female reproductive system and is responsible for the production of mature gametes and steroid hormones. It is sensitive to cytotoxic agents and its function can be negatively affected by these factors. Some cytotoxic agents such as cadmium can be accumulated in the body organs, including ovaries and then, disrupt their functions. QUR as a natural antioxidant was used against the gonadotoxic effects of cadmium on the ovaries of rats and mice through scavenging free radicals and improving the activities of other antioxidants such as catalase, SOD, and GPx. Therefore, it improved the ovaries' health by increasing the secretion of estradiol, FSH, and LH (Izaguirry et al., 2017; Nna, Usman, Ofutet, & Owu, 2017). Since QUR is one of the main components of hydrolyzed and crude extracts of chia seeds (Reyes-Caudillo, Tecante, & Valdivia-López, 2008), Tarko et al. used xylene, as an environmental contaminant, and different doses of chia seed extract (1, 10 and 100 ng ml^{-1}) separately or together to investigate their effects on bovine ovarian cells activity (Tarko et al., 2017). Xylene when given alone induced the proliferation of bovine ovarian cells and inhibited the release of testosterone and progesterone. Moreover, chia seed extract when given alone inhibited proliferation and apoptosis of bovine ovarian cells. Furthermore, chia seed extract inhibited the release of IGF-1, progesterone, as well as testosterone from bovine ovarian cells. When ovarian cells were cultured with xylene and high doses of chia seed extract, chia seed extract inhibited the stimulatory effect of xylene on the ovarian cell proliferation. Xylene and lower doses of chia seed extract stimulated the apoptosis of cells. Additionally, xylene and high doses of chia seed extract increased the release of IGF-1 from bovine ovarian cells. The simultaneous addition of xylene and chia seed extract suppressed the release of progesterone. Furthermore, both xylene and chia seed extract when given together inhibited the release of testosterone from bovine ovarian cells. Since it is reported that antipsychotics induce the reproductive toxicity through oxidative stress, QUR can reduce the cytotoxic effects of antipsychotics on theca interstitial cells viability in female rats (Elmorsy, Al-Ghafari, Aggour, Khan, & Amer, 2017). Wang et al. evaluated the effects of QUR on the antioxidant capacity of menopause mice ovaries and showed no significant change in the serum levels of T-AOC, SOD, GSH, GSH-PX, and GST but an increase in the mRNA and protein expression of the oxidative stress-related genes, including SOD-1, CAT, and glutathione synthetase (GSS) (Wang et al., 2018). Ovarian ischemia-reperfusion injury (IR injury) can induce oxidative stress and histopathological changes in the ovaries in which was reported to be prevented by QUR (Gencer et al., 2014). It is indicated that QUR can decrease caspase 3 and TUNEL positive cells in the ovaries as well as the ischemia modified albumin (IMA) levels in the serum of IR-injured rats. In addition to the antioxidant activity of QUR, there is evidence demonstrating the estrogen-like effects of QUR in ovary development. Shu et al. showed that oral administration of QUR can pose estrogen-like effects on weight, follicle development, and hormone secretion of mice ovaries (Shu et al., 2011). It is reported that QUR can also act as a phytoestrogen and improve the productive performance by increasing the population of healthy follicles and the secretion of hormones in laying hens (Yang et al., 2018). In aging rats, polyphenols such as QUR can improve the lifespan of rat ovaries through affecting the ovarian follicular reserve (Chen et al., 2010). We should also mention that there is a systematic review summarizing the protective effects of QUR on ovarian cancer cells via various mechanisms (Parvaresh et al., 2016). A drug delivery system containing QUR can improve the anticancer activities of QUR through increasing the apoptosis of tumor cells and inhibiting the proliferation and angiogenesis which can potentially improve the ovarian cancer chemotherapy protocols (Xu et al., 2018).

On the other hand, QUR has also pro-oxidant effects leading to genotoxicity and anti-proliferative activity (Carver, Carrano, & MacGregor, 1983; Engen et al., 2015; Gliszczyńska-Świgło et al., 2003). Beazley et al. demonstrated that dietary QUR reduced the reproductive potential in female mice (Beazley & Nurminskaya, 2016). In Chinese hamster ovarian cells, QUR negatively affected the genetic stability of the cells, including chromosomal aberration and micronuclei (Carver et al., 1983; Engen et al., 2015). Using computational transcriptomics, the ovarian gene transcription, physiological endpoints, and endocrine disruptors (EDs) can be associated and QUR as an ED can perturb the development of largemouth bass ovary (Basili et al., 2018). Hence, it seems that QUR may have some negative effects on the special conditions and species.

4.2 | QUR and oocyte

Despite intensive efforts to improve the results of *in vitro* maturation (IVM), this technique still provides low quality and low yield of oocytes and embryos. Several studies have been conducted to improve the culture conditions of IVM such as increasing the external oxygen levels. However, this method can lead to the production of ROS and the subsequent disruption of embryonic development (Guerin et al., 2001; Kang et al., 2013). Therefore, supplementing IVM media with antioxidants may help to prevent the adverse effects of ROS production.

Kang et al. studied the effects of IVM medium supplementation with different concentrations of QUR on the maturation and blastocyst development of porcine oocyte. Although QUR did not improve the nuclear maturation of oocyte, a low concentration of QUR resulted in lower levels of ROS production and higher rates of oocyte development into blastocysts. However, QUR in low concentrations did not increase the cleavage rates and the number of blastocysts. According to this study, QUR in high concentrations had detrimental effects on the nuclear maturation of oocyte and blastocyst development (Kang et al., 2013; Kang et al., 2016). Moreover, the findings of other studies also showed that QUR had similar effects on the bovine

oocyte IVM (Sovernigo et al., 2017; Zootec, 2013). Although a study indicated that different doses of QUR can improve the cumulus cell expansion and the development of embryos, it is not clear what dose of QUR is optimal for porcine oocyte IVM (Orlovschi, Miclea, Zahan, Miclea, & Pernes, 2014). Furthermore, Karimian et al. reported that QUR had positive effects on the blastocyst production rate of oocyte IVM in sheep (Karimian, Zandi, Sanjabi, Masoumian, & Ofoghi, 2018). A recent study indicated that QUR supplementation improved the quality of oocyte and the development of follicles. Moreover, it reduced the apoptosis of granulosa cells (GCs) during heat stress (Naseer et al., 2017).

Even though antioxidants can improve the results of IVM, using them raises the cost of IVM medium. Therefore, the replacement of antioxidants by other substances with antioxidative activity can be considered to reduce the expenses of IVM. In a study by Silva et al., QUR was used as a substitute for cysteamine in IVM of goat oocytes. IVM medium supplementation with QUR had a significant effect on the expansion of cumulus cells, nuclear maturation rate, mitochondrial activity, and reducing the apoptosis rate. Therefore, it is suggested that QUR can be considered as a substitute for cysteamine in IVM of goat oocytes (Silva et al., 2018).

Postovulatory aging is a time-dependent deterioration in the oocyte quality when it is not fertilized for a long time (Miao, Kikuchi, Sun, & Schatten, 2009). Postovulatory aging is associated with structural and molecular alterations in the oocyte that can affect the development of embryo. It is well known that oxidative stress plays a key role in cellular aging (Lord & Aitken, 2013). Wang et al. investigated the protective effects of QUR against postovulatory aging induced by oxidative stress in the mouse oocytes. QUR treatment decreased aging-induced morphological alterations and also reduced defects in spindle organization and mitochondrial distribution (Wang, Jo, Oh, & Kim, 2017). Recently, it is reported that SIRT1, 2, and 3 have a protective role against postovulatory aging. Moreover, SIRT1 can regulate the trimethylation of histone H3 at lysine 9 (H3K9me3) (Vaquero et al., 2007; Zhang et al., 2016). Remarkably, Wang et al. showed that QUR can prevent the down-regulation of SIRT1, 2, and 3 and the modifications of histones during postovulatory aging. It is reported that the activity of maturation promoting factor (MPF) is decreased during the oocyte aging. QUR treatment can prevent a decrease in the activity of MPF and postovulatory aging. Furthermore, QUR can inhibit apoptosis through a decrease in the activity of Bcl-2 and caspases during postovulatory aging (Wang, Jo, et al., 2017).

Maintenance of the ovarian follicular reserve is very important to prolong the reproductive lifespan since the germ cells do not have the proliferative capacity and follicular depletion occurs during the folliculogenesis process. Chen et al. evaluated the effects of QUR on the ovarian functions and the ovarian follicular reserve in the early aged rats (12–15 months). Their findings showed that although QUR had no significant effect on the ovarian follicular reserve, the greater number of healthy follicles was seen in rats treated with QUR. Indeed, QUR increased the percentage of secondary and antral follicles which may be due to the positive effects of QUR on the prevention of follicular atresia (Chen et al., 2010).

4.3 | QUR and theca interstitial cells

Since life-long treatment with antipsychotics is usually important to cure psychotic disorders, there is a concern about the adverse effects of antipsychotics on the function of the female reproductive system (Peuskens, 1998; Santoni & Saubadu, 1995). There is evidence suggesting that these adverse effects may be related to the oxidative stress induced by antipsychotics. To examine this hypothesis, Elmorsy et al. evaluated the antioxidative effects of QUR on the rat ovarian theca interstitial cells treated with antipsychotics. Their findings showed that QUR can affect the oxidative stress induced by antipsychotics and inhibit the adverse effects of antipsychotics on the viability of theca interstitial cells (Elmorsy et al., 2017).

4.4 | QUR and GCs

GCs are somatic cells that surround the oocyte and have important roles in the development of ovarian follicles (Charlier et al., 2012; Eppig, 2001). The main function of GCs is estradiol synthesis in response to the stimulation of FSH. Moreover, GCs produce various growth factors for oocyte maturity in the follicle. After the process of ovulation, GCs contribute to corpus luteum formation and progesterone synthesis which is necessary for the maintenance of a potential pregnancy (Brůčková et al., 2008). Several studies have investigated the effects of QUR on different cell lines (Ahn, Lee, Kim, Park, & Ha, 2008; Michaud-Levesque, Bousquet-Gagnon, & Béliveau, 2012; Min et al., 2007; Musonda & Chipman, 1998) and cancer cells. Importantly, QUR has been studied for its effects on GCs (E. J. Choi, Bae, & Ahn, 2008; Ma et al., 2006). T-2 toxin is a cytotoxic fungal metabolite that has a strong toxic effect on the reproductive potential and the development of embryo (Fang et al., 2012; Wu, Yuan, Yuan, & Wen, 2013). Capcarova, Zbynovska, Kolesarova, & Sirotkin, (2015) investigated the efficiency of QUR to eliminate the oxidative stress induced by T-2 toxin in porcine GCs. Despite QUR could not remove the ROS production induced by T-2, this antioxidant led to an increase in the activity of SOD and GPx as well as the total antioxidant status (TAS) in porcine GCs. The results of the *in vitro* culture of rat GCs in the presence of QUR and H_2O_2 showed that QUR improved the H_2O_2-induced reduction in the cell viability. Moreover, SOD-1, catalase, and GSS expression levels were increased in the presence of QUR. It seems that the protective effect of QUR on the *in vitro* culture of GCs was linked to the enhancement of the cellular antioxidant capacity (Wang et al., 2018). Jia et al. investigated the protective effects of QUR against cytotoxicity induced by cadmium in chicken GCs. Their results demonstrated that QUR can inhibit the cytotoxicity effects of cadmium in GCs via decreasing the lipid peroxidation and improving the antioxidant capacity (Jia et al., 2011). Furthermore, we recently indicated the protective effects of QUR against oxidative

stress on GCs by increasing Nrf2 and thioredoxin gene expression and activity (Rashidi et al., 2019). Several studies indicated that QUR can affect the proliferation and the apoptosis of GCs. For instance, it was reported that QUR decreased Bax, p53, and caspase 3 levels and increased Bcl-2 levels in GCs (Jia et al., 2011; Kolesarova et al., 2019; Sirotkin et al., 2019; Yang et al., 2018). However, Stochmalova et al. reported that QUR increased the expression of Bax in cultured GCs (Stochmalova, Kadasi, Alexa, & Sirotkin, 2014). Interestingly, QUR reduced the percentage of cells containing proliferating cell nuclear antigen (PCNA) in cultured GCs of pig and cattle (Sirotkin et al., 2019; Stochmalova et al., 2014). Nevertheless, it is reported that QUR can increase cyclin B1 as a marker of cell proliferation (Kolesarova et al., 2019). Contrary to prior reports, Santini, Basini, Bussolati, and Grasselli (2009) reported that QUR did not affect the proliferation of swine GCs. Furthermore, QUR had a dose-dependent effect on the release of Insulin-like growth factor 1 (IGF-1) in cattle GCs. Indeed, a high dose of QUR (100 ng/mL) inhibited the release of IGF-1, while lower doses (1 or 10 ng/mL) promoted the release of IGF-1 (Sirotkin et al., 2019).

GCs secrete steroid hormones that provide a receptive environment for embryo implantation and development (Albertini & Barrett, 2003). A study by Sirotkin et al. demonstrated that QUR had an inhibitory effect on the release of progesterone and testosterone in cultured pig GCs. Although QUR treatment inhibited the release of progesterone in cattle GCs, the secretion of testosterone was stimulated in these cells (Sirotkin et al., 2019). In line with this study, Kolesarova et al. (2019) showed that QUR had a dose-dependent effect on the secretion of progesterone. Although a study by Santini et al. (2009) confirmed that QUR had inhibitory effects on the production of progesterone in GCs. Another study showed that the activity of aromatase and 17 β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) enzymes was evaluated in the presence of QUR in human granulosa-luteal cells. They demonstrated that QUR had no acute effects on the activity of steroidogenic enzymes. In the chronic experiments, QUR inhibited FSH-induced 17b-HSD type 1 activity and progesterone synthesis. Furthermore, 10 μM QUR had no significant effect on the aromatase activity (Whitehead & Lacey, 2003). However, Rice et al. showed that a higher dose of QUR (10 μM) can inhibit the aromatase activity in human granulosa-luteal cells (Rice et al., 2006). Moreover, Lu et al. compared the inhibitory effect of several dietary flavonoids such as QUR on the aromatase activity in human ovarian granulosa-like KGN cells. According to the results of this study, high concentrations of QUR had inhibitory effects on the biosynthesis of 17β-estradiol while low concentrations of QUR increased the biosynthesis of 17β-estradiol (Lu, Yang, Wang, & Zhang, 2012). A study by Santini et al. confirmed these results and also reported that QUR can prevent the angiogenic process through the inhibition of VEGF production. Since steroidogenesis and angiogenesis play critical roles in the development of ovarian follicles, it can be concluded that QUR can negatively affect the physiology of ovary (Santini et al., 2009). Another investigation described the inhibitory effects of QUR on the 3β-hydroxysteroid dehydrogenase activity and the conversion of androstenedione to estradiol (Lacey, Bohday, Fonseka, Ullah, & Whitehead, 2005). These results indicated that QUR has a species-dependent effect on the secretion of hormones which may be due to the different numbers of estrogen receptors in the ovarian cells of each species (Sirotkin & Harrath, 2014). Table 1 summarized the effects of QUR on oocyte, GCs and theca interstitial cells.

4.5 | QUR and ovarian cancer

Ovarian cancer is one of the lethal types of cancer in the reproductive system and is a notable danger in women's health. Despite advanced therapeutic strategies such as surgery and chemotherapy, the 5-year survival rate of patients is 45%, and these therapeutic approaches are not sufficient, especially for patients in the advanced stages. Hence, it should be noted that developing a novel therapeutic approach with minimal side effects is required for ovarian cancer treatment (Roomi, Kalinovsky, Rath, & Niedzwiecki, 2017). Therefore, natural products such as flavonoids, especially QUR, can be used as a supplement therapy in ovarian cancer (Gao et al., 2012; Li et al., 2014). It is demonstrated that QUR exerts its anticancer effects on ovarian cancer by controlling the cell cycle, inhibition of tumor growth, angiogenesis, and induction of apoptosis (Parvaresh et al., 2016). The role of QUR in inhibiting the proliferation and inducing the apoptosis in ovarian cancer cells has been revealed by several studies (Hashemzaei et al., 2017; Ren, Deng, Ai, Yuan, & Song, 2015). It is reported that QUR can inhibit the proliferation of human ovarian cancer cells in a dose-dependent manner (Luo, Jiang, King, & Chen, 2008; Scambia, Ranelletti, Panici, et al., 1990). Wang et al. showed that QUR had cytotoxic/anti-proliferative properties against ovarian cancer cells (Wang et al., 2015). QUR regulates cell growth through blocking the GO/GI phase to G2/M and competing for binding to type II estrogen binding site (type II EBS) in the ovarian cancer cell line OVCA 433 (Scambia et al., 1990; Scambia, Ranelletti, Panici, et al., 1990). Furthermore, it seems that QUR can modulate the production of transforming growth factor β1 (TGFβ1) resulting in the inhibition of human ovarian cancer cells growth (Scambia et al., 1994). However, another study reported that 3,4′,7-O-trimethylquercetin, a derivative of QUR, suppressed the migration and invasion of ovarian cancer cells without affecting cell proliferation (Ashraf et al., 2018).

It is indicated that QUR induced the apoptosis in ovarian cancer cells (Teekaraman, Elayapillai, Viswanathan, & Jagadeesan, 2019; Yi et al., 2014). Gao et al. showed that QUR induced the apoptosis in ovarian cancer cells via the mitochondrial pathway of apoptosis (Gao et al., 2012). Zhou et al. suggested that QUR activated the death receptor-mediated extrinsic and intrinsic mitochondrial apoptotic pathways in human ovarian cancer cells (Zhou, Gong, Ding, & Chen, 2015).

Phytoestrogens like QUR may modulate ovarian estrogen synthesis. Aromatase CYP19A1 gene expression, which catalyzes the end step of estrogen synthesis, was increased by QUR in KGN human granulosa-like tumor cells. Indeed, QUR induced aromatase activity and reduced the migration of cells up to 30% (Sandra & van den Berg, 2014).

TABLE 1 Summary of the effects of QUR on oocyte, GCs and theca cells

Type of cell	Type of animal	Dose and duration of QUR	Function	References
Oocyte	Pig	1, 10, and 50 μg/mL for 44 hr	In low concentrations: Decreasing the ROS production and improving the blastocyst rates. In highest concentration: Detrimental effect on nuclear maturation of oocyte and formation of blastocyst.	Kang et al. (2013)
	Pig	5, 15, 25, 35 μg/ml QUR for 44 hr	Increasing the cumulus cell expansion rate. Increasing the embryo development in the morula cell stage.	Orlovschi et al. (2014)
	Pig	1, 10, and 50 μg/mL QUR or taxifolin for 44 hr	Improving the oocyte development into blastocysts with low concentration of QUR. Decreasing the ROS production with QUR. Increasing the intracellular GSH.	Kang et al. (2016)
	Cattle	2 μM QUR for 22 hr	Decreasing the oxidative stress. Increasing the GSH levels in oocytes. No positive effect on the total cell number of embryo. Improving the blastocyst development with similar efficacy.	Sovernigo et al. (2017)
	Mouse	1, 5, or 10 μM QUR for 12 hr and 24 hr	Reduction of aging-induced morphological changes, defects in spindle organization, and mitochondrial distribution. Prevention of decreased SIRT expression, histone methylation, MPF activity, and apoptosis initiation. Improving the oocyte quality and embryo development.	Wang et al. (2017)
	Goat	4 μM or 8 μM QUR for 24 hr	Improving the expansion of cumulus cells, nuclear maturation rate, and mitochondrial activity. Decreasing the apoptosis rate.	Silva et al. (2018)
	Rabbit	30 mg/kg QUR for 18–20 days	Increasing the retrieved oocytes, A-grade oocytes and follicle number. Improving the primordial and antral stage follicles. Decreasing the apoptosis of GCs.	Naseer et al. (2017)
	Bovine,	0.4, 2, 10, and 50 μM QUR for 22 hr	Increasing the GSH levels in cysteamine treatment. Improving the blastocyst development. Increasing the embryo production in QUR treatment. Similar results for rate of hatched embryos and the number of embryo cells.	Zootec (2013)
	Sheep	5 or 15 μg/mL QUR	The best rate of blastocyst production.	Karimian et al. (2018)
GCs	Pig	1, 10, and 100 ng/mL QUR and T-2 toxin separately or in combination.	No effect of QUR on the ROS production induced by T-2 toxin. Increasing the SOD and GPx activities in the higher doses of T-2 toxin and QUR.	Capcarova et al. (2015)
	Pig	0.01, 0.1, 1, 10, and 100 μmol L^{-1} QUR	Stimulation of progesterone release. Increasing the cyclin B1 in all concentrations. Inhibition of p53.	Kolesarova et al. (2019)
	Pig	1, 10, and 100 ng/mL QUR for 2 days	Decreasing the percentage of cells containing PCNA and Bax. Inhibition of progesterone, testosterone, and IGF-I release.	Sirotkin et al. (2019)
	cattle,	1, 10, and 100 ng/mL QUR for 2 days	Decreasing the percentage of cells containing PCNA and Bax. Inhibition of progesterone release. Stimulation of testosterone secretion. Stimulation of IGF-I release, and inhibition of IGF-I release.	Sirotkin et al. (2019)
	Chicken,	0.01–10 μg/ml QUR for 24 hr	Decreasing the viability and cell number, Improving the SOD and GSH-Px activities, Decreasing the caspase 3 activity and Bax expression, Increasing the BCL2 and XIAP expression.	Jia et al. (2011)
	Rat	400 μM H_2O_2 plus 20 μM QUR for 6 hr	Decreasing the H_2O_2-induced cell damage. No significant effect on the H_2O_2-induced estrogen reduction. Up-regulation of the protein expression of SOD-1, CAT and GSS.	Wang et al. (2018)
	Swine	5 or 50 μg/mL QUR for 48 hr	No significant effect on GCs proliferation by both doses. Inhibition of 17β estradiol production at the concentration of 50 μg/mL and increasing the 17β estradiol levels at the concentration of 5 μg/mL. Inhibition of progesterone production with a dose-dependent effect.	Santini et al. (2009)

(Continues)

TABLE 1 (Continued)

Type of cell	Type of animal	Dose and duration of QUR	Function	References
			Inhibition of NO production at the concentration of 5 μg/mL and increase of NO levels at the concentration of 50 μg/mL. Inhibition of $O2^-$ production at the concentration of 50 μg/mL. No significant effect on H_2O_2 production. No significant effect on activity of SOD and peroxidase. Increasing the nonenzymatic antioxidant power at the concentration of 50 μg/mL. Inhibition of VEGF production by both doses.	
	Pig	QUR and resveratrol separately or in combination.	Decreasing the PCNA expression and increasing the Bax expression.	Stochmalova et al. (2014)
	Human	Apigenin, QUR, genistein, biochanin A, and daidzein at the concentrations of 10 μM and 100 nM, either individually or in combination for 48 or 72 hr	Decreasing the aromatase expression, at either concentration of all phytoestrogens except biochanin A. Down-regulation of aromatase expression only at the concentration of 100 nM apigenin. No significant effect on the aromatase expression in combination with various phytoestrogens at the concentration of 100 nM, except for the combination of biochanin A, genistein, and daidzein. A time-dependent decrease in aromatase activity.	Rice et al. (2006)
	Human	10 μM QUR for 4 hr (acute effects) or 24 hr (chronic effects) with or without steroid substrates	No significant effect on the estradiol production. Inhibition of progesterone synthesis.	Whitehead and Lacey (2003)
	Human	20 μM QUR for 24 hr	Decreasing the ROS production and apoptosis induced by H2O2. Increasing the Nrf2 gene and protein expression, as well as its nuclear translocation. Protecting GCs from oxidative stress by increasing Trx gene expression and activity.	Rashidi et al., 2019
Theca cells	Rat	50 mM QUR	Inhibition of adverse effects of antipsychotics on cell viability.	Elmorsy et al. (2017)

Abbreviations: Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; GCs, granulosa cells; GPx, Glutathione Peroxidase; GSH, glutathione; IGF-I, Insulin-like growth factor; MPF, mitosis-promoting facto; NO, nitric oxide; Nrf2, Nuclear factor erythroid 2-related factor 2; PCNA, Proliferating cell nuclear antigen; QUR, quercetin; ROS, Reactive Oxygen Species; SOD, Superoxide dismutase; Trx, Thioredoxin; VEGF, Vascular endothelial growth factor.

QUR in combination with tiazofurin as an anticancer drug eliminated human ovarian epithelial carcinoma cells through inhibiting PI kinase and decreasing the IP3 concentration (Weber et al., 1996). Moreover, 3,4′,7-O-trimethyl QUR (34′7TMQ), a QUR derivative, increased the levels of caspase 9 expression in CRL-1978, SK-OV-3, and CRL-11731 cancer cell lines. It also raised the Bax/Bcl-2 ratio in SK-OV-3 and CRL-1978 cell lines but inhibited it in CRL-11731 cell line. Therefore, 34′7TMQ induced cell death through different pathways in ovarian cancer cell lines (Ashraf et al., 2018). Angiogenesis is one of the important factors in the proliferation of cancer cells. It is reported that QUR inhibited the angiogenesis in OVCAR-3 cells by reducing the expression of VEGF (Luo et al., 2008). Genetic instability is another activity of QUR in the treatment of ovarian cancer. Inhibiting DNA topoisomerases I and II (topo I and topo II) and the consequent induction of endoreduplication by QUR may provide new therapy results in Chinese hamster ovarian cancer cells (Cantero, Campanella, Mateos, & Cortes, 2006). Furthermore, QUR regulates the production of TGFβ1 at posttranscriptional levels by inhibiting the growth of OVCA 433 cells and primary ovarian tumors (Giovanni Scambia et al., 1994).

It is reported that QUR increased the sensitivity of SKOV-3 cells to TNF-related apoptosis-inducing ligand (TRAIL) and enhanced their apoptosis through TRAIL-mediated the up-regulation of CCAAT-enhancer-binding protein homologous protein (CHOP) and the following cell death. Remarkably, it was observed that QUR increased endoplasmic reticulum stress (ER stress) (Yi et al., 2014). One of the new therapeutic approaches in ovarian cancer is the induction of ER stress. HSP70 is one of the essential proteins protecting cells in ER stress. Antitumor drugs such as farnesyltransferase inhibitors (FTIs) inhibit HSP70 and lead to the incidence of ER stress. QUR in combination with FTIs can inhibit HSP70 and increase the manumycin-induced cell death following ER stress through the caspase 3 dependent apoptosis pathway in ovarian cancer 2774 cells (Hu et al., 2003). Furthermore, it is also reported that QUR at the same time can affect ER stress and the

p-STAT3/Bcl-2 pathway and induce mitochondria apoptosis in CAOV3 human ovarian cancer cells. Moreover, it evokes autophagy and increases related markers and genes (Liu et al., 2017).

A major concern in the thermoradiotherapy for treating cancer is thermal resistance. It is reported that a high level of HSP is related to the expansion of thermotolerance. QUR inhibits the synthesis of HSPs especially HSP70 in ovarian cancer cells and it has high potency in the acidic environment. Moreover, the inhibition of HSP70 expression by QUR induces the cytotoxicity and apoptosis in acidified hamster ovarian carcinoma (OvCa) cells even at 428°C (Wachsberger et al., 2003).

Chemotherapy drugs, particularly Cisplatin, are critical agents for the treatment of ovarian cancer. However, resistance to chemotherapy drugs is one of the main obstacles in cancer treatment regardless of the advantages they may have. It is because of the prevention of interaction between drug and target cells or blocking the downstream apoptotic pathways (Blagosklonny, 2004). Therefore, it is important to investigate the adjuvant approaches to defeat this resistance in cancer treatment and to find anticancer drugs having fewer side effects for patients (Zhang et al., 2018). QUR has many anticancer features and is shown to amplify the efficacy of chemotherapeutic agents (Niedzwiecki, Roomi, Kalinovsky, & Rath, 2016). Cytotoxic effects of the polyphenols, especially QUR, include arresting the cancer cell cycle and promoting the apoptosis pathway in A431 cell line and cisplatin (CDDP)-resistant (C13 and A431Pt) cells. Moreover, ROS production was also increased in both cell lines (Catanzaro et al., 2014). The control of cell proliferation and the incidence of apoptosis by QUR during cell cycle phases have been confirmed in ovarian carcinoma (SKOV3; SKOV3/CDDP) cell lines. QUR significantly decreased the levels of cyclin D1 expression in SKOV3, but not in SKOV3/CDDP cells. This may be related to the G1/S phase alteration and blocking the cell cycle progression (Catanzaro, Ragazzi, Vianello, Caparrotta, & Montopoli, 2015). Moreover, QUR derivative (QUR 3-rhamnoside) available in Chinese bayberry leave flavonoids (BLF) arrested the G1 phase of cell cycle and induced the intrinsic apoptotic pathway in cisplatin-resistant cancer cell line A2780/CP70. This may be due to the low expression levels of cyclin D1, CDK4, and p-Erk and activating caspases 3, 7, and 9 (Zhang et al., 2018). Interestingly, low concentrations of QUR in combination with Cisplatin attenuated the ROS damage and the cytotoxicity of Cisplatin and increased the antioxidant activity in C13* and SKOV3 cancer cells both in *in vitro* and a xenograft tumor model (Li et al., 2014). The monofunctional platinum tris (imidazo (1,2-α) pyridine) chloroplatinum (II) chloride (coded as LH6), a chemotherapy drug for the treatment of ovarian cancer, is different from Cisplatin in the DNA binding. LH6 is more effective against A2780cisR cells and promotes more cell death. The presence of bulky hydrophobic imidazo (1,2-α) pyridine ligand in its structure facilitates its uptake through the cytoplasmic membrane. The effect of LH6 is enhanced in combination with QUR and has more capability of killing the ovarian cancer cells (Arzuman, Beale, Yu, & Huq, 2015). Synergic effects of QUR in combination with monofunctional platinum tris (benzimidazole) monochloroplatinum (II) chloride (coded as LH4) have been reported in drug-resistant tumor models (Arzuman, Beale, Chan, Yu, & Huq, 2014). In another study, QUR reduced the side effects of Cisplatin in drug-resistant cells. Indeed, QUR pretreatment enhanced the anticancer effect of cDDP in ovarian cancer (OV2008 and C13*) cell lines and in a xenograft mouse model of ovarian cancer. Hence, it may be related to the inhibition of STAT3 signaling and BCL-2 expression and the subsequent ERS activation (Yang et al., 2015). Moreover, the phosphorylation of JNK and AKT was induced by QUR from *Rubus coreanus* Miquel (RCM) extract which promoted apoptosis in doxorubicin-resistant NCI/ADR-RES cells (Kim, Choi, Cho, Shin, & Ko, 2016). Table 2 summarized the effects of QUR on chemotherapeutic drug-resistant ovarian cancer cells.

Suppressing the migration and metastasis of ovarian cancer cells is another activity of QUR. Malignant ovarian cancer cells migrate to the pelvis, abdomen, and other organs through cell adhesion and degradation of the extracellular matrix (ECM) or the circulatory or lymphatic system at the advanced stages of cancer (Duffy, 1992). Roomi et al. created a strong and metastatic ovarian tumor by the intraperitoneal injection of ovarian A-2780 cells into female mice. In this study, mice were fed with a particular nutrient mixture (0.5% EPQ) containing QUR for 4 weeks. Moreover, human A-2780 cells were treated with EPQ. The results indicated that nutrient components containing QUR inhibited the metastasis of ovarian cancer cells to the lung through the prevention of cell proliferation, matrix metalloproteinase (MMP)-9 secretion, and ECM degradation (Roomi et al., 2017). Furthermore, the invasion and growth of human metastatic ovarian PA-1 cancer cells are prevented by QUR through promoting the mitochondrial apoptotic pathway. It decreased the anti-apoptotic factors (Bcl-2 and Bcl-xL) while increased the pro-apoptotic factors (caspases 3, 9, Bid, Bad, Bax, and cytochrome c) for inducing apoptosis in cancer cells (Teekaraman et al., 2019). Other QUR derivatives such as 34'7TMQ inhibited the migration and invasion of CRL11731, SK-OV-3, and CRL1978 cells through reducing the expression of urokinase plasminogen activator (uPA) and MMP-2 which are important factors in the ovarian cancer cells metastasis. (Yamauchi et al., 2017).

Small interfering RNA (siRNA) is a noncoding RNA belonging to the class of double-stranded RNAs. These molecules have 20–25 base pairs and are similar to microRNAs (miRNAs or miRs). They silence the expression of specific genes through degrading mRNAs and preventing their translation. Today, suppressing genes by siRNA is a novel treatment approach for ovarian malignancies through various mechanisms (Mirzaei, Yazdi, & Salehi, 2016). Moreover, circular RNAs (circRNAs) are a class of long noncoding RNAs (lncRNAs) with a circular structure. CircRNAs can control cell proliferation and thus, they may be applied as a novel strategy for treating ovarian cancer (Shabaninejad et al., 2019). MiRNAs are noncoding RNAs regulating target gene expression by binding to the 3′ untranslated region (3′ UTR) site of the target mRNA (Jing & Chen, 2014). Some of them are suppressed in ovarian cancer such as miR-145. It is indicated that QUR increased the expression levels of miR-145 in A2780 and SKOV-3 cell lines. Moreover, QUR enhanced the expression of caspase 3 as an apoptotic marker and activated apoptosis via increasing the expression of miR-145 (Zhou et al., 2015).

TABLE 2 The effects of QUR on chemotherapeutic drugs-resistant ovarian cancer cells

Drug	Molecular structure	Cell line	Function	References
Cisplatin	$Pt(NH_3)_2Cl_2$	2008/C13	Inducing cell death. Arresting the cancer cell cycle. Increasing the ROS production.	Catanzaro et al. (2014)
Cisplatin	$Pt(NH_3)_2Cl_2$	SKOV3/CDDP	Decreasing the cyclin D1 expression in SKOV3, but not in SKOV3/CDDP cells.	Catanzaro et al. (2015)
Cisplatin	$Pt(NH_3)_2Cl_2$	A2780/CP70	Inducing apoptosis and G1 cell cycle arrest. Reducing the expression of p-Erk. Activating the caspase cascade. Up-regulating Bad and Bax. Down-regulating Bcl-xL and Bcl-2. Reducing the expression of cyclin D1, CDK4, and p-Erk.	Zhang et al. (2018)
Cisplatin	$Pt(NH_3)_2Cl_2$	C13*and SKOV3	At high concentration: pro-apoptotic effect. At low concentrations: reducing ROS damage and increasing the expression of endogenous antioxidant enzymes.	Li et al. (2014)
Cisplatin	$Pt(NH_3)_2Cl_2$	C13* and P-ris	Enhancing the cDDP cytotoxicity. Eliciting ERS. Suppressing the STAT3 phosphorylation. Down-regulating the BCL-2.	Yang et al. (2015)
Cisplatin	$Pt(NH_3)_2Cl_2$	Xenograft mouse model of ovarian cancer	Enhancing the antitumor effect of cDDP. Repressing the STAT3 phosphorylation. Down-regulating Bcl-2. Increasing apoptosis.	Yang et al. (2015)
LH6	$Pt(C_7H_6N2)_3Cl_2$-Cl	A2780, A2780cisR $A2780^{ZD0473R}$	Inducing the LH6 ability to induce cell death.	Arzuman et al. (2015)
LH4	$Pt(C_7H_5N2)_3Cl_2$-Cl	A2780/ A2780cisR/ $A2780^{ZD0473R}$	Inducing the LH4 ability to induce cell death.	Arzuman et al. (2014)
Doxorubicin	$C_{27}H_{29}NO_{11}$	NCI/ADR-RES	Inducing the phosphorylation of JNK and AKT. Increasing apoptosis.	Kim et al. (2016)

Abbreviations: 2008/C13; human ovarian carcinoma; A2780/CP70, human ovarian cancer cell line; AKT, Protein kinase B; Bcl-2, B-cell lymphoma 2; C13*, human epithelial ovarian cancer; C13, CDDP-resistant variant; Erk, Extracellular signal-regulated kinases; ERS, endoplasmic reticulum stress; G0, Gap0; G1, Gap1; LH4, the monofunctional platinum tris(benzimidazole)monochloroplatinum(II) chloride; LH6, the monofunctional platinum complex tris(imidazo(1,2-α)pyridine) chloroplatinum(II) chloride; M, Mitosis; P-ris, primary cancer cells; SKOV3/CDDP, ovarian carcinoma (SKOV3)/cisplatin (CDDP)-resistant counterparts (SKOV3/CDDP); STAT3, Signal transducer and activator of transcription 3.

Despite the significant function of QUR in cancer therapy in the laboratory, its application in the clinical research has been restricted because of its poor aqueous solubility and instability. These characteristics restrict the oral use of QUR in cancer therapy. Therefore, today, nanotechnology approaches, particularly nanocarriers, are applied to improve the bioavailability of QUR (da Silva et al., 2019; Gao et al., 2012).

Therefore, the encapsulation of QUR into polymer micelles, biodegradable monomethoxy poly (ethylene glycol)-poly (epsilon-caprolactone) (MPEG-PCL), can improve its solubility. QUR-encapsulated micelle is entirely soluble in water. It showed a high potential for the inhibition of proliferation and the incidence of apoptosis through increasing the expression of caspases 3, 9, and Bax and decreasing the expression of MCL-1, Bcl-2, phosphorylated p44/42 mitogen-activated protein kinase, and phosphorylated Akt in A2780S cells. Moreover, QU/MPEG-PCL micelles injection into the intravenous arrested ovarian tumors inhibited the angiogenesis and induced the apoptosis in xenograft model (Gao et al., 2012). Doxorubicin hydrochloride (ADR) is another chemotherapeutic drug in cancer therapy of which usage is restricted in certain concentrations due to the extensive cardiotoxic side effects and the ability to produce ROS and RNS. It is reported that using a polymeric micellar of QUR and resveratrol in combination with ADR has cardioprotective effects. Hence, using QUR + resveratrol + ADR (mRQA) at 10:10:1 molar ratio at the same time has synergic effects in human ovarian cancer cells (SKOV-3) and antagonistic effects in rat cardiomyocytes (H9C2) cells. Furthermore, although mRQA declines the activity of caspases 3 and 7 in H9C2 cells, it did not affect SKOV-3 cells (Cote, Carlson, Rao, & Alani, 2015). Another study reported that the use of a polymeric micellar of QUR alone improved the efficacy of QUR in ovarian cancer (SKOV-3 and multi-drug resistant NCI/ADR) cells (Patra et al., 2018).

In recent years, the natural products and extracts containing QUR are considered for ovarian cancer treatment. Studies showed that these extracts have anti-proliferative effects and activate the

TABLE 3 Summary of the effects of plant extracts containing QUR on ovarian cancer cells

Plant extracts	Components	Cell line	Function	References
Bayberry leaves flavonoids (BLF)	Myricitrin QUR	A2780/CP70	Increases the expression of cleaved caspases 3 and 7 Inducing apoptosis via a Erk-dependentcaspase 9 activation Up-regulating Bad and Bax Down-regulating Bcl-xL and Bcl-2 Reducing the expression of cyclin D1, CDK4 and p-Erk G1 cell cycle arrest	Zhang et al. (2018)
Ginkgo biloba	QUR Ginkgolide A Ginkgolide B	OVCA429	Anti-proliferative effects Cell cycle blockage at G0/G1 to S phase	Ye et al. (2007)
MeOH extract of *Loranthus. tanakae*	QUR 3-O Rhamnopyranosides	SK-OV-3	Inhibition of cell proliferation	Kim et al. (2004)
Mangifera zeylanica	QUR Catechin	SKOV-3	Cytotoxic effects increase caspases 3 and 7 activity	Ediriweera et al. (2016)
Rhus verniciflua Stokes (RVS)	Fisetin QUR Butein	SKOV-3/PAX	Inhibition of AKT activity reduce proliferation	Choi et al. (2016)
Rubus coreanus MiQURl (RCM)	QUR Ellagic Acid	NCI/ADR-RES	Induce the phosphorylation of JNK and AKT Induce JNK-mediated apoptosis	Kim et al. (2016)

Abbreviations: AKT, Protein kinase B; BAD, Bcl-2-associated death promoter; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra-large; BLF, bayberry leaves flavonoids; CDK4, Cyclin-dependent kinase 4; Erk, Extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinases; MeOH extract, Methanol extract A2780/CP70, human ovarian cancer cell line; NCI/ADR-RES, doxorubicin-resistant NCI/ADR-RES ovarian cancer cells; OVCA429, serous cancer cells; p-Erk, Phospho-Extracellular signal-regulated kinases; QUR, Quercetin; RCM, Rubus coreanus MiQURl; RVS, Rhus verniciflua Stokes; SKOV-3, a human ovarian cancer cell line with epithelial-like morphology; SKOV-3/PAX, paclitaxel-resistant SKOV-3/PAX.

apoptotic pathway in different types of ovarian cancer cells (Choi et al., 2016; Ediriweera et al., 2016; Kim et al., 2016; Kim, Kim, Choi, & Ryu, 2004; Ye et al., 2007; Zhang et al., 2018). Table 3 summarized the effects of different extracts containing QUR.

4.6 | QUR in PCOS

PCOS is a complex and common endocrine disorder in women and is characterized by hyperandrogenism, ovulatory dysfunction, and multiple ovarian cysts according to Rotterdam's criteria. There are several studies regarding the beneficial effects of QUR on the treatment of PCOS. In a systematic review, Tabrizi et al. reported that QUR reduced the levels of LH, testosterone, hyperandrogenaemia, and insulin resistance (IR). Moreover, it improved dyslipidemia and folliculogenesis. They suggested that these effects can be due to the antioxidative and anti-inflammatory properties of QUR (Tabrizi et al., 2020). Shah and Patel demonstrated that QUR can be used in the treatment of PCOS. They reported that the effects of QUR are mediated through inhibiting PI3K in ovarian theca cells leading to a decrease in the production of androgen and decreasing the expression of CYP17A1 gene in rats (Shah & Patel, 2016). QUR can also decrease IR among PCOS rats, inhibit the Toll-like receptor/NF-κB signaling pathway, and improve the inflammatory microenvironment of the ovarian tissue (Wang et al., 2017). A meta-analysis and systematic review of randomized controlled trials (RCTs) indicated that QUR supplementation reduced systolic blood pressure (SBP) in patients with metabolic syndrome. However, there was no significant effect on diastolic blood pressure (DBP), intercellular adhesion molecule 1 (ICAM-1) and, vascular cell adhesion molecule 1 (VCAM-1) levels (Tamtaji et al., 2019). Furthermore, a clinical trial study reported that QUR can be effective in the control of IR through increasing the levels of adiponectin and also, improving the hormonal profile among PCOS patients (Rezvan, Moini, Gorgani-Firuzjaee, & Hosseinzadeh-Attar, 2018). Another study showed that oral administration of QUR decreased IR and increased uterine ERα and GLUT4 gene expression in PCOS rats (Neisy, Zal, Seghatoleslam, & Alaee, 2019). Khorshidi et al. reported that 1,000 mg of QUR per day for 12 weeks might have beneficial effects on regulating some major contributors of PCOS. They indicated that QUR significantly improved fasting blood glucose (FBG) and IR. Furthermore, it considerably decreased the levels of resistin, LH, and testosterone in obese or overweight women with PCOS (Khorshidi et al., 2018).

Indeed, it is confirmed that QUR affects the treatment of hormonal and metabolic disturbances occurring in PCOS through the regulation of steroidogenesis, decreasing body weight and ovarian cysts, rescuing follicles, and maintaining lipid profile and redox state in rats with PCOS (Jahan et al., 2018).

4.7 | QUR and uterine smooth muscle contraction

Uterus, particularly the smooth muscle of the uterus means the myometrium, is very important for female reproduction. It acts during

the pregnancy, the birth, and the postpartum period. Preterm delivery and abortion due to untimed uterine contractions are some of the results of myometrial dysfunction and hypoxia (Pehlivanoğlu, Bayrak, & Doğan, 2013). One of the flavonoids activity is the control of contraction or relaxation that has been reported in different organs, including bladder (Dambros et al., 2005) and intestine (Amira, Rotondo, & Mulè, 2008).

Several *in vitro* and *in vivo* studies also examined the effects of flavonoids on uterine contractions. The cyclic adenosine monophosphate (cAMP) is known to promote the relaxation of smooth muscle (Price & Bernal, 2001). QUR enhances the intracellular cAMP levels (Ming-Ming, Zhi-Qi, ZHANG, & Hong, 2015). Revuelta et al. investigated the effect of QUR on tonic contraction in rat uterus. They indicated that QUR was capable of inhibiting the KCl (60 mM)-induced tonic contraction in rat smooth muscle trough suppressing the cAMP-dependent protein kinases (Revuelta, Cantabrana, & Hidalgo, 1997). In another study, they also reported that QUR promoted the relaxation of uterine smooth muscle by increasing the intracellular cAMP and β-adrenoceptors levels (Revuelta, Hidalgo, & Cantabrana, 1999).

Another study indicated that QUR as the main flavonoid in onion attenuated contraction in rat uterus. Indeed, they showed that the increasing levels of prostaglandins resulted in dysmenorrhea and abnormal uterine contractions. Moreover, Wu et al. indicated that QUR decreased PGF2α and oxytocin levels and suppressed the Ca^{2+}-dependent contractions in rats. The present findings suggest that QUR may be a potential adjuvant for treating uterine disorders (Wu, Shieh, Wang, Huang, & Hsia, 2015).

Similar to this study, Hsia et al. investigated the effects of adlay hull extract as a traditional Chinese medicine for treating dysmenorrhea. They showed that adlay hull extract containing QUR decreased the intracellular Ca^{+2} concentrations induced by PGF2 and thus, caused the inhibition of Ca^{2+}-dependent uterine contractions (Hsia, Kuo, Chiang, & Wang, 2008).

Another study in the field of traditional medicine reported that Opuntia ficus-indica (OFI) cladodes contain a notable amount of polyphenols such as QUR. OFI cladodes caused rabbit muscle uterine relaxation. Indeed, the contraction of the smooth muscle depends on the concentration of cytoplasmic free Ca^{+2}. Remarkably, the flavonoids may inhibit the contractility of smooth myocytes, by inhibiting the availability of Ca^{2+} for muscle contraction (Lanuzza et al., 2017).

As mentioned before, one of the results of myometrial dysfunction is an untimed contraction leading to abortion or preterm delivery. In this manner, QUR may exert immunological regulatory and antiabortive effects. IL-10 is one of the immunological agents playing a key role in controlling the inflammatory pathways during pregnancy. Zhao et al. used lipopolysaccharide (LPS) to induce abortion in 7-day-gestation mice after pretreatment with QUR and bornyl acetate at days 4 to 7 of gestation. They observed that the level of IL-10 was decreased significantly in uterus treated with LPS. However, QUR combined with bornyl acetate prevented the LPS-induced abortion, elevated the levels of IL-10, and prevented the embryo loss (Zhao, Wang, Shi, & Zhong, 2011).

Therefore, since inappropriate uterine contractions may lead to abortion and dysfunction of the uterine smooth muscle, the use of flavonoid compounds such as QUR may regulate the secretion and function of prostaglandins, interleukins, and macrophages which are involved in smooth muscle contraction in the uterine.

5 | CONCLUSION

QUR as a natural antioxidant has been traditionally used to prevent or treat a variety of diseases such as cancer, cardiovascular disease, PCOS, obesity, chronic inflammation, and reproductive system dysfunction. QUR also has bidirectional activities. Despite the significant activity of QUR in cancer therapy, its use in clinical research has been restricted because of its poor aqueous solubility and instability. Therefore, today, nanotechnology approaches, particularly nanocarriers, are applied to improve the bioavailability of QUR. Furthermore, the encapsulation of QUR into polymer micelles can improve its solubility. It should be noted that it further inhibited the proliferation rate and increased apoptosis in ovarian cancer cells. Moreover, QUR can be used as a complementary and alternative therapy in ovarian cancer with drug-resistance. QUR promotes the ovarian reserve, follicle development, and hormone secretion. QUR improves the quality of oocytes, the development of embryos, and the production of blastocysts. Moreover, it may help to prevent the adverse effects of oxidative stress. It affects the proliferation and apoptosis and decreases lipid peroxidation and ER stress in GCs. Furthermore, QUR may regulate the secretion and function of factors such as prostaglandins, interleukins, and macrophages that are involved in smooth muscle contraction in the uterine. It seems that QUR as a supplementary factor affects the treatment of hormonal and metabolic disturbances in PCOS. However, further investigations are needed for understanding the efficacy of QUR in the treatment of gynecological patients.

AUTHOR CONTRIBUTIONS

Zahra Rashidi and Fardin Amidi together initiated, designed the manuscript, Zahra Rashidi, Zahra Khosravizadeh, and Ali Talebi and Kajal Khodamoradi drafted the manuscript. Kajal Khodamoradi and Reyhane Ebrahimi contributed to the literature collection. All authors revised the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest in any form.

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REFERENCES

Ahn, J., Lee, H., Kim, S., Park, J., & Ha, T. (2008). The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochemical and Biophysical Research Communications*, *373*(4), 545–549.

Albertini, D. F., & Barrett, S. L. (2003). Oocyte-somatic cell communication. *Reproduction (Cambridge, England) Supplement*, *61*, 49–54.

Alrawaiq, N. S., & Abdullah, A. (2014). A review of flavonoid quercetin: Metabolism, bioactivity and antioxidant properties. *International Journal of PharmTech Research*, *6*(3), 933–941.

Amidi, F., Rashidi, Z., Khosravizadeh, Z., Khodamoradi, K., Talebi, A., Navid, S., & Abbasi, M. (2019). Antioxidant effects of quercetin in freeze-thawing process of mouse spermatogonial stem cells. *Asian Pacific Journal of Reproduction*, *8*(1), 7.

Amira, S., Rotondo, A., & Mulè, F. (2008). Relaxant effects of flavonoids on the mouse isolated stomach: Structure-activity relationships. *European Journal of Pharmacology*, *599*(1-3), 126–130.

Arzuman, L., Beale, P., Chan, C., Yu, J. Q., & Huq, F. (2014). Synergism from combinations of tris(benzimidazole) monochloroplatinum(II) chloride with capsaicin, quercetin, curcumin and cisplatin in human ovarian cancer cell lines. *Anticancer Research*, *34*(10), 5453–5464. Retrieved from http://ar.iiarjournals.org/content/34/10/5453.full.pdf

Arzuman, L., Beale, P., Yu, J. Q., & Huq, F. (2015). Monofunctional platinum-containing pyridine-based ligand acts synergistically in combination with the phytochemicals curcumin and quercetin in human ovarian tumour models. *Anticancer Research*, *35*(5), 2783–2794. Retrieved from. http://ar.iiarjournals.org/content/35/5/2783.full.pdf

Ashraf, A., Afroze, S. H., Yamauchi, K., Zawieja, D. C., Keuhl, T. J., Erlandson, L. W., & Uddin, M. N. (2018). Differential mechanism of action of 3,4′,7-O-trimethylquercetin in three types of ovarian cancer cells. *Anticancer Research*, *38*(9), 5131–5137. https://doi.org/10.21873/anticanres.12835

Avila, M. A., Cansado, J., Harter, K. W., Velasco, J. A., & Notario, V. (1996). Quercetin as a modulator of the cellular neoplastic phenotype. In *Dietary phytochemicals in cancer prevention and treatment*, Part of the Advances in Experimental Medicine and Biology book series (AEMB) (Vol. 401, pp. 101–110). New York: Edited under the auspices of the American Institute for Cancer Research, Plenum Press.

Baghel, S. S., Shrivastava, N., Baghel, R. S., Agrawal, P., & Rajput, S. (2012). A review of quercetin: Antioxidant and anticancer properties. *World Journal of Pharmaceutical Sciences*, *1*(1), 146–160.

Basili, D., Zhang, J.-L., Herbert, J., Kroll, K., Denslow, N. D., Martyniuk, C. J., … Antczak, P. (2018). In silico computational transcriptomics reveals novel endocrine disruptors in largemouth bass (Micropterus salmoides). *Environmental Science & Technology*, *52*(13), 7553–7565.

Beazley, K. E., & Nurminskaya, M. (2016). Effects of dietary quercetin on female fertility in mice: Implication of transglutaminase 2. *Reproduction, Fertility and Development*, *28*(7), 974–981. https://doi.org/10.1071/RD14155

Blagosklonny, M. V. (2004). Prospective strategies to enforce selectively cell death in cancer cells. *Oncogene*, *23*(16), 2967.

Boots, A. W., Haenen, G. R., & Bast, A. (2008). Health effects of quercetin: From antioxidant to nutraceutical. *European Journal of Pharmacology*, *585*(2), 325–337.

Boutin, J. A. (1994). Tyrosine protein kinase inhibition and cancer. *International Journal of Biochemistry*, *26*(10-11), 1203–1226.

Brůčková, L., Soukup, T., Moos, J., Moosová, M., Pavelková, J., Řežábek, K., … Mokrý, J. (2008). The cultivation of human granulosa cells. *Acta Medica (Hradec Králové)*, *51*(3), 165–172.

Cantero, G., Campanella, C., Mateos, S., & Cortes, F. (2006). Topoisomerase II inhibition and high yield of endoreduplication induced by the flavonoids luteolin and quercetin. *Mutagenesis*, *21*(5), 321–325.

Cao, Y., Zhuang, M.-F., Yang, Y., Xie, S.-W., Cui, J.-G., Cao, L., … Zhu, Y. (2014). Preliminary study of quercetin affecting the hypothalamic-pituitary-gonadal axis on rat endometriosis model. *Evidence-based Complementary and Alternative Medicine*, *2014*, 1–12.

Capcarova, M. P. P., Zbynovska, K., Kolesarova, A., & Sirotkin, A. V. (2015). Changes in antioxidant status of porcine ovarian granulosa cells after quercetin and T-2 toxin treatment. *Journal of Environmental Science and Health, Part B*, *50*(3), 201-206.

Carver, J., Carrano, A., & MacGregor, J. (1983). Genetic effects of the flavonols quercetin, kaempferol, and galangin on Chinese hamster ovary cells in vitro. *Mutation Research/Environmental Mutagenesis and Related Subjects*, *113*(1), 45–60.

Catanzaro, D., Ragazzi, E., Vianello, C., Caparrotta, L., & Montopoli, M. (2015). Effect of quercetin on cell cycle and cyclin expression in ovarian carcinoma and osteosarcoma cell lines. *Natural Product Communications*, *10*(8), 1365–1368.

Catanzaro, D., Vianello, C., Ragazzi, E., Caparrotta, L., & Montopoli, M. (2014). Cell cycle control by natural phenols in cisplatin-resistant cell lines. *Natural Product Communications*, *9*(10), 1465–1468.

Charlier, C., Montfort, J., Chabrol, O., Brisard, D., Nguyen, T., Le Cam, A., … Uzbekova, S. (2012). Oocyte-somatic cells interactions, lessons from evolution. *BMC Genomics*, *13*(1), 560.

Chen, Z. G., Luo, L. L., Xu, J. J., Zhuang, X. L., Kong, X. X., & Fu, Y. C. (2010). Effects of plant polyphenols on ovarian follicular reserve in aging rats. *Biochemistry and Cell Biology*, *88*(4), 737–745. https://doi.org/10.1139/o10-012

Choi, E. J., Bae, S. M., & Ahn, W. S. (2008). Antiproliferative effects of quercetin through cell cycle arrest and apoptosis in human breast cancer MDA-MB-453 cells. *Archives of Pharmacal Research*, *31*(10), 1281.

Choi, H. S., Kim, M. K., Choi, Y. K., Shin, Y. C., Cho, S.-G., & Ko, S.-G. (2016). Rhus verniciflua Stokes (RVS) and butein induce apoptosis of paclitaxel-resistant SKOV-3/PAX ovarian cancer cells through inhibition of AKT phosphorylation. *BMC Complementary and Alternative Medicine*, *16*(1), 122.

Chun, O. K., Chung, S.-J., Claycombe, K. J., & Song, W. O. (2008). Serum C-reactive protein concentrations are inversely associated with dietary flavonoid intake in US adults. *The Journal of Nutrition*, *138*(4), 753–760.

Cote, B., Carlson, L. J., Rao, D. A., & Alani, A. W. G. (2015). Combinatorial resveratrol and quercetin polymeric micelles mitigate doxorubicin induced cardiotoxicity in vitro and in vivo. *Journal of Controlled Release*, *213*, 128–133. https://doi.org/10.1016/j.jconrel.2015.06.040

da Silva, T. A., Gomes, J. H. R., de Bulhões, L. C. G., Neto, R., Junior, I. D. B., de Moura, M., … Grillo, L. (2019). Therapeutic potential of quercetin based on nanotechnology: A review. *Revista Virtual de Química*, *11*(4), 1–12.

Dambros, M., van Deutekom, M., de Jongh, R., van Koeveringe, G. A., De Mey, J. G., & van Kerrebroeck, P. (2005). The inhibitory effect of the flavonoid galangin on urinary bladder smooth muscle contractility is mediated in part by modulation of Ca2+ release from intracellular stores. *Planta Medica*, *71*(10), 962–964.

David, A. V. A., Arulmoli, R., & Parasuraman, S. (2016). Overviews of biological importance of quercetin: A bioactive flavonoid. *Pharmacognosy Reviews*, *10*(20), 84.

De, A., De, A., Papasian, C., Hentges, S., Banerjee, S., Haque, I., & Banerjee, S. K. (2013). Emblica officinalis extract induces autophagy and inhibits human ovarian cancer cell proliferation, angiogenesis, growth of mouse xenograft tumors. *PLoS One*, *8*(8), e72748.

de Boer, V. C., Dihal, A. A., van der Woude, H., Arts, I. C., Wolffram, S., Alink, G. M., … Hollman, P. C. (2005). Tissue distribution of quercetin in rats and pigs. *The Journal of Nutrition*, *135*(7), 1718–1725.

Duffy, M. (1992). The role of proteolytic enzymes in cancer invasion and metastasis. *Clinical & Experimental Metastasis*, *10*(3), 145–155.

Duraj, J., Zazrivcova, K., Bodo, J., Sulikova, M., & Sedlak, J. (2005). Flavonoid quercetin, but not apigenin or luteolin, induced apoptosis in human myeloid leukemia cells and their resistant variants. *Neoplasma*, *52*(4), 273–279.

Ediriweera, M. K., Tennekoon, K. H., Adhikari, A., Samarakoon, S. R., Thabrew, I., & De Silva, E. D. (2016). New halogenated constituents from Mangifera zeylanica Hook. f. and their potential anti-cancer effects in breast and ovarian cancer cells. *Journal of Ethnopharmacology*, *189*, 165–174.

Elmorsy, E., Al-Ghafari, A., Aggour, A. M., Khan, R., & Amer, S. (2017). The role of oxidative stress in antipsychotics induced ovarian toxicity. *Toxicology In Vitro*, *44*, 190–195.

Engen, A., Maeda, J., Wozniak, D. E., Brents, C. A., Bell, J. J., Uesaka, M., … Kato, T. A. (2015). Induction of cytotoxic and genotoxic responses by natural and novel quercetin glycosides. *Mutation Research, Genetic Toxicology and Environmental Mutagenesis*, *784*, 15–22.

Eppig, J. J. (2001). Oocyte control of ovarian follicular development and function in mammals. *Reproduction*, *122*(6), 829–838.

Fang, H. W. Y., Guo, J., Rong, J., Ma, L., Zhao, Z., Zuo, D., & Peng, S. (2012). T-2 toxin induces apoptosis in differentiated murine embryonic stem cells through reactive oxygen species-mediated mitochondrial pathway. *Apoptosis*, *17*(8), 895-907.

Ferraresi, R., Troiano, L., Roat, E., Lugli, E., Nemes, E., Nasi, M., … Cossarizza, A. (2005). Essential requirement of reduced glutathione (GSH) for the anti-oxidant effect of the flavonoid quercetin. *Free Radical Research*, *39*(11), 1249–1258.

Filipa Brito, A., Ribeiro, M., Margarida Abrantes, A., Salome Pires, A., Jorge Teixo, R., Guilherme Tralhao, J., & Filomena Botelho, M. (2015). Quercetin in cancer treatment, alone or in combination with conventional therapeutics? *Current Medicinal Chemistry*, *22*(26), 3025–3039.

Fischer, C., Speth, V., Fleig-Eberenz, S., & Neuhaus, G. (1997). Induction of zygotic polyembryos in wheat: Influence of auxin polar transport. *The Plant Cell*, *9*(10), 1767–1780.

Formica, J., & Regelson, W. (1995). Review of the biology of quercetin and related bioflavonoids. *Food and Chemical Toxicology*, *33*(12), 1061–1080.

Gao, X., Wang, B., Wei, X., Men, K., Zheng, F., Zhou, Y., … Guo, G. (2012). Anticancer effect and mechanism of polymer micelle-encapsulated quercetin on ovarian cancer. *Nanoscale*, *4*(22), 7021–7030.

García-Mediavilla, V., Crespo, I., Collado, P. S., Esteller, A., Sánchez-Campos, S., Tuñón, M. J., & González-Gallego, J. (2007). The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. *European Journal of Pharmacology*, *557*(2-3), 221–229.

Gencer, M., Karaca, T., Güngör, A. N. C., Hacivelioğlu, S. Ö., Demirtaş, S., Turkon, H., … Hanci, V. (2014). The protective effect of quercetin on IMA levels and apoptosis in experimental ovarian ischemia-reperfusion injury. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *177*, 135–140. https://doi.org/10.1016/j.ejogrb.2014.03.036

Gliszczyńska-Świgło, A., van der Woude, H., de Haan, L., Tyrakowska, B., Aarts, J. M., & Rietjens, I. M. (2003). The role of quinone reductase (NQO1) and quinone chemistry in quercetin cytotoxicity. *Toxicology In Vitro*, *17*(4), 423–431.

Graf, B. A., Ameho, C., Dolnikowski, G. G., Milbury, P. E., Chen, C.-Y., & Blumberg, J. B. (2006). Rat gastrointestinal tissues metabolize quercetin. *The Journal of Nutrition*, *136*(1), 39–44.

Guerin, P., El Mouatassim, S., Menezo, Y., & Human reproduction update. (2001). Oxidative stress and protection against reactive oxygen species in the pre-implantation embryo and its surroundings. *Human Reproduction Update*, *7*(2), 175–189.

Guo, Y., & Bruno, R. S. (2015). Endogenous and exogenous mediators of quercetin bioavailability. *The Journal of Nutritional Biochemistry*, *26*(3), 201–210.

Hashemzaei, M., Delarami Far, A., Yari, A., Heravi, R. E., Tabrizian, K., Taghdisi, S. M., … Tzanakakis, G. (2017). Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo. *Oncology Reports*, *38*(2), 819–828.

Heijnen, C. G., Haenen, G. R., Vekemans, J. A., & Bast, A. (2001). Peroxynitrite scavenging of flavonoids: Structure activity relationship. *Environmental Toxicology and Pharmacology*, *10*(4), 199–206.

Hsia, S.-M., Kuo, Y.-H., Chiang, W., & Wang, P. S. (2008). Effects of adlay hull extracts on uterine contraction and Ca2+ mobilization in the rat. *American Journal of Physiology—Endocrinology and Metabolism*, *295*(3), E719–E726.

Hu, W., Wu, W., Verschraegen, C. F., Chen, L., Mao, L., Yeung, S. C., … Kavanagh, J. J. (2003). Proteomic identification of heat shock protein 70 as a candidate target for enhancing apoptosis induced by farnesyl transferase inhibitor. *Proteomics*, *3*(10), 1904–1911. https://doi.org/10.1002/pmic.200300547

Huang, R.-Y., Yu, Y.-L., Cheng, W.-C., OuYang, C.-N., Fu, E., & Chu, C.-L. (2010). Immunosuppressive effect of quercetin on dendritic cell activation and function. *The Journal of Immunology*, *184*(12), 6815–6821.

Ishikawa, Y., & Kitamura, M. (2000). Anti-apoptotic effect of quercetin: Intervention in the JNK-and ERK-mediated apoptotic pathways. *Kidney International*, *58*(3), 1078–1087.

Izaguirry, A. P., Soares, M. B., Vargas, L. M., Spiazzi, C. C., dos Santos Brum, D., Noremberg, S., … Santos, F. W. (2017). Blueberry (Vaccinium ashei Reade) extract ameliorates ovarian damage induced by subchronic cadmium exposure in mice: Potential δ-ALA-D involvement. *Environmental Toxicology*, *32*(1), 188–196. https://doi.org/10.1002/tox.22225

Jahan, S., Abid, A., Khalid, S., Afsar, T., Qurat Ul, A., Shaheen, G., … Razak, S. (2018). Therapeutic potentials of Quercetin in management of polycystic ovarian syndrome using Letrozole induced rat model: A histological and a biochemical study. *Journal of ovarian research*, *11*(26), 1–10. https://doi.org/10.1186/s13048-018-0400-5

Jia, Y., Lin, J., Mi, Y., & Zhang, C. (2011). Quercetin attenuates cadmium-induced oxidative damage and apoptosis in granulosa cells from chicken ovarian follicles. *Reproductive Toxicology*, *31*(4), 477–485. https://doi.org/10.1016/j.reprotox.2010.12.057

Jing, Z.-H. Y., & Chen, K. (2014). A genetic variant in MiR-146a modifies digestive system cancer risk: A meta-analysis. *Asian Pacific Journal of Cancer Prevention*, *15*(1), 145–150.

Kang, J. T., Kwon, D.-K., Park, S. J., Kim, S. J., Moon, J. H., Koo, O. J., … Lee, B. C. (2013). Quercetin improves the in vitro development of porcine oocytes by decreasing reactive oxygen species levels. *Journal of Veterinary Science*, *14*(1), 15–20.

Kang, J. T., Moon, J. H., Choi, J. Y., Park, S. J., Kim, S. J., Saadeldin, I. M., & Lee, B. C. (2016). Effect of antioxidant flavonoids (quercetin and taxifolin) on in vitro maturation of porcine oocytes. *Asian-Australasian Journal of Animal Sciences*, *29*(3), 352.

Karimian, M., Zandi, M., Sanjabi, M. R., Masoumian, M., & Ofoghi, H. (2018). Effects of grape seed extract, quercetin and vitamin C on ovine oocyte maturation and subsequent embryonic development. *Cellular and Molecular Biology*, *64*(4), 98–102.

Kawabata, K., Mukai, R., & Ishisaka, A. (2015). Quercetin and related polyphenols: New insights and implications for their bioactivity and bioavailability. *Food & Function*, *6*(5), 1399–1417.

Khan, F., Niaz, K., Maqbool, F., Ismail Hassan, F., Abdollahi, M., Nagulapalli Venkata, K., … Bishayee, A. (2016). Molecular targets underlying the anticancer effects of quercetin: An update. *Nutrients*, *8*(9), 529.

Khanduja, K., Verma, A., & Bhardwaj, A. (2001). Impairment of human sperm motility and viability by quercetin is independent of lipid peroxidation. *Andrologia*, *33*(5), 277–281.

Khorshidi, M., Moini, A., Alipoor, E., Rezvan, N., Gorgani-Firuzjaee, S., Yaseri, M., & Hosseinzadeh-Attar, M. J. (2018). The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. *Phytotherapy Research*, *32*(11), 2282–2289.

Kim, M. K., Choi, H. S., Cho, S. G., Shin, Y. C., & Ko, S. G. (2016). Rubus coreanus Miquel extract causes apoptosis of doxorubicin-resistant NCI/ADR-RES ovarian cancer cells via JNK phosphorylation. *Molecular Medicine Reports*, *13*(5), 4065–4072.

Kim, Y.-K., Kim, Y. S., Choi, S. U., & Ryu, S. Y. (2004). Isolation of flavonol rhamnosides fromloranthus tanakae and cytotoxic effect of them on human tumor cell lines. *Archives of Pharmacal Research*, *27*(1), 44–47.

Kolesarova, A., Roychoudhury, S., Klinerova, B., Packova, D., Michalcova, K., Halenar, M., … Galik, B. (2019). Dietary bioflavonoid quercetin modulates porcine ovarian granulosa cell functions in vitro. *Journal of Environmental Science and Health, Part B*, *54*(6), 533–537.

Lacey, M., Bohday, J., Fonseka, S. M., Ullah, A. I., & Whitehead, S. A. (2005). Dose-response effects of phytoestrogens on the activity and expression of 3β-hydroxysteroid dehydrogenase and aromatase in human granulosa-luteal cells. *The Journal of Steroid Biochemistry and Molecular Biology*, *96*(3-4), 279–286.

Lakhanpal, P., & Rai, D. K. (2007). Quercetin: A versatile flavonoid. *Internet Journal of Medical Update*, *2*(2), 22–37.

Lanuzza, F., Occhiuto, F., Monforte, M. T., Tripodo, M. M., D'Angelo, V., & Galati, E. M. (2017). Antioxidant phytochemicals of Opuntia ficus-indica (L.) Mill. Cladodes with potential anti-spasmodic activity. *Pharmacognosy Magazine*, *13*(Suppl 3), S424.

Leyton, L., Hott, M., Acuña, F., Caroca, J., Nuñez, M., Martin, C., … Otth, C. (2015). Nutraceutical activators of AMPK/Sirt1 axis inhibit viral production and protect neurons from neurodegenerative events triggered during HSV-1 infection. *Virus Research*, *205*, 63–72.

Li, N., Sun, C., Zhou, B., Xing, H., Ma, D., Chen, G., & Weng, D. (2014). Low concentration of quercetin antagonizes the cytotoxic effects of antineoplastic drugs in ovarian cancer. *PLoS One*, *9*(7), e100314. https://doi.org/10.1371/journal.pone.0100314

Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M., Wang, S., … Yin, Y. (2016). Quercetin, inflammation and immunity. *Nutrients*, *8*(3), 167.

Liu, Y., Gong, W., Yang, Z. Y., Zhou, X. S., Gong, C., Zhang, T. R., … Gao, Q. L. (2017). Quercetin induces protective autophagy and apoptosis through ER stress via the p-STAT3/Bcl-2 axis in ovarian cancer. *Apoptosis*, *22*(4), 544–557. https://doi.org/10.1007/s10495-016-1334-2

Lord, T., & Aitken, R. J. (2013). Oxidative stress and ageing of the post-ovulatory oocyte. *Reproduction in Domestic Animals*, *146*(6), R217–R227.

Lu, D. F., Yang, L. J., Wang, F., & Zhang, G. L. (2012). Inhibitory effect of luteolin on estrogen biosynthesis in human ovarian granulosa cells by suppression of aromatase (CYP19). *Journal of Agricultural and Food Chemistry*, *60*(34), 8411–8418.

Luo, H., Jiang, B.-H., King, S. M., & Chen, Y. C. (2008). Inhibition of cell growth and VEGF expression in ovarian cancer cells by flavonoids. *Nutrition and Cancer*, *60*(6), 800–809.

Ma, L., Feugang, J. M., Konarski, P., Wang, J., Lu, J., Fu, S., … Wang, Z. (2006). Growth inhibitory effects of quercetin on bladder cancer cell. *Frontiers in Bioscience*, *11*(5), 2275–2285.

Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition*, *79*(5), 727–747.

Manach, C., Williamson, G., Morand, C., Scalbert, A., & Rémésy, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American Journal of Clinical Nutrition*, *81*(1), 230S–242S.

Marone, M., D'Andrilli, G., Das, N., Ferlini, C., Chatterjee, S., & Scambia, G. (2001). Quercetin abrogates taxol-mediated signaling by inhibiting multiple kinases. *Experimental Cell Research*, *270*(1), 1–12.

Mendoza, E., & Burd, R. (2011). Quercetin as a systemic chemopreventative agent: Structural and functional mechanisms. *Mini Reviews in Medicinal Chemistry*, *11*(14), 1216–1221.

Mendoza-Wilson, A. M. A., & Glossman-Mitnik, D. (2004). CHIH-DFT determination of the molecular structure, infrared and ultraviolet spectra of the flavonoid quercetin. *Journal of Molecular Structure: THEOCHEM*, *681*(1-3), 71–76.

Miao, Y. L., Kikuchi, K., Sun, Q. Y., & Schatten, H. (2009). Oocyte aging: Cellular and molecular changes, developmental potential and reversal possibility. *Human Reproduction Update*, *15*(5), 573–585.

Michaud-Levesque, J., Bousquet-Gagnon, N., & Béliveau, R. (2012). Quercetin abrogates IL-6/STAT3 signaling and inhibits glioblastoma cell line growth and migration. *Experimental Cell Research*, *318*(8), 925–935.

Min, Y.-D., Choi, C.-H., Bark, H., Son, H.-Y., Park, H.-H., Lee, S., … Kim, S.-H. (2007). Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-κB and p38 MAPK in HMC-1 human mast cell line. *Inflammation Research*, *56*(5), 210–215.

Ming-Ming, C., Zhi-Qi, Y., ZHANG, L.-Y., & Hong, L. (2015). Quercetin promotes neurite growth through enhancing intracellular cAMP level and GAP-43 expression. *Chinese Journal of Natural Medicines*, *13*(9), 667–672.

Mirzaei, H., Yazdi, F., & Salehi, R. (2016). SiRNA and epigenetic aberrations in ovarian cancer. *Journal of Cancer Research and Therapeutics*, *12*(2), 498–508.

Murakami, A., Ashida, H., & Terao, J. (2008). Multitargeted cancer prevention by quercetin. *Cancer Letters*, *269*(2), 315–325.

Musonda, C. A., & Chipman, J. K. (1998). Quercetin inhibits hydrogen peroxide (H2O2)-induced NF-kappaB DNA binding activity and DNA damage in HepG2 cells. *Carcinogenesis*, *19*(9), 1583–1589.

Naseer, Z, A. E., Epikmen, ET, Uçan, U, Boyacioğlu, M, İpek, E, Akosy, M. (2017). Quercetin supplemented diet improves follicular development, oocyte quality, and reduces ovarian apoptosis in rabbits during summer heat stress. *Theriogenology*, *96*, 136-141.

Neisy, A., Zal, F., Seghatoleslam, A., & Alaee, S. (2019). Amelioration by quercetin of insulin resistance and uterine GLUT4 and ERα gene expression in rats with polycystic ovary syndrome (PCOS). *Reproduction, Fertility and Development*, *31*(2), 315–323.

Niedzwiecki, A., Roomi, M. W., Kalinovsky, T., & Rath, M. (2016). Anticancer efficacy of polyphenols and their combinations. *Nutrients*, *8*(9), 552–569. https://doi.org/10.3390/nu8090552

Nna, V. U., Usman, U. Z., Ofutet, E. O., & Owu, D. U. (2017). Quercetin exerts preventive, ameliorative and prophylactic effects on cadmium chloride - induced oxidative stress in the uterus and ovaries of female Wistar rats. *Food and Chemical Toxicology*, *102*, 143–155. https://doi.org/10.1016/j.fct.2017.02.010

Oesterreich, S., Weng, C.-N., Qiu, M., Hilsenbeck, S. G., Osborne, C. K., & Fuqua, S. A. (1993). The small heat shock protein hsp27 is correlated with growth and drug resistance in human breast cancer cell lines. *Cancer Research*, *53*(19), 4443–4448.

Orlovschi, D., Miclea, I., Zahan, M., Miclea, V., & Pernes, A. J. (2014). Quercetin efficacy on in vitro maturation of porcine oocytes. *Scientific Papers Animal Science and Biotechnologies*, *47*(1), 113–115.

Park, S., Lim, W., Bazer, F. W., Whang, K.-Y., & Song, G. (2019). Quercetin inhibits proliferation of endometriosis regulating cyclin D1 and its target microRNAs in vitro and in vivo. *The Journal of Nutritional Biochemistry*, *63*, 87–100.

Parvaresh, A., Razavi, R., Rafie, N., Ghiasvand, R., Pourmasoumi, M., & Miraghajani, M. (2016). Quercetin and ovarian cancer: An evaluation based on a systematic review. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*, *9*(21), 34–40.

Patra, A., Satpathy, S., Shenoy, A. K., Bush, J. A., Kazi, M., & Hussain, M. D. (2018). Formulation and evaluation of mixed polymeric micelles of quercetin for treatment of breast, ovarian, and multidrug resistant cancers. *International Journal of Nanomedicine*, *13*, 2869.

Pehlivanoğlu, B., Bayrak, S., & Doğan, M. (2013). A close look at the contraction and relaxation of the myometrium; the role of calcium. *Journal of the Turkish German Gynecological Association*, *14*(4), 230.

Peuskens, J., Sienaert, P., De Hert, M., & European Psychiatry. (1998). Sexual dysfunction: The unspoken side effect of antipsychotics. *European Psychiatry*, *13*, 23s–30s.

Pietta, P.-G. (2000). Flavonoids as antioxidants. *Journal of Natural Products*, *63*(7), 1035–1042.

Price, S. A., & Bernal, A. L. (2001). Uterine quiescence: The role of cyclic AMP. *Experimental Physiology*, *86*(2), 265–272.

Psahoulia, F. H., Moumtzi, S., Roberts, M. L., Sasazuki, T., Shirasawa, S., & Pintzas, A. (2006). Quercetin mediates preferential degradation of oncogenic Ras and causes autophagy in Ha-RAS-transformed human colon cells. *Carcinogenesis*, *28*(5), 1021–1031.

Rafiq, R. A., Quadri, A., Nazir, L. A., Peerzada, K., Ganai, B. A., & Tasduq, S. A. (2015). A potent inhibitor of phosphoinositide 3-kinase (PI3K) and mitogen activated protein (MAP) kinase signalling, quercetin (3,3′,4′,5,7-pentahydroxyflavone) promotes cell death in ultraviolet (UV)-B-irradiated B16F10 melanoma cells. *PLoS One*, *10*(7), e0131253.

Rashidi, Z., Aleyasin, A., Eslami, M., Nekoonam, S., Zendedel, A., Bahramrezaie, M., & Amidi, F. (2019). Quercetin protects human granulosa cells against oxidative stress via thioredoxin system. *Reproductive Biology*, *19*(3), 245–254. https://doi.org/10.1016/j.repbio.2019.07.002

Ren, M. X., Deng, X. H., Ai, F., Yuan, G. Y., & Song, H. Y. (2015). Effect of quercetin on the proliferation of the human ovarian cancer cell line SKOV-3 in vitro. *Experimental and Therapeutic Medicine*, *10*(2), 579–583.

Revuelta, M., Cantabrana, B., & Hidalgo, A. (1997). Depolarization-dependent effect of flavonoids in rat uterine smooth muscle contraction elicited by CaCl2. *General Pharmacology: The Vascular System*, *29*(5), 847–857.

Revuelta, M., Hidalgo, A., & Cantabrana, B. (1999). Involvement of cAMP and β-adrenoceptors in the relaxing effect elicited by flavonoids on rat uterine smooth muscle. *Journal of Autonomic Pharmacology*, *19*(6), 353–358.

Reyes-Caudillo, E., Tecante, A., & Valdivia-López, M. (2008). Dietary fibre content and antioxidant activity of phenolic compounds present in Mexican chia (*Salvia hispanica* L.) seeds. *Food Chemistry*, *107*(2), 656–663.

Rezvan, N., Moini, A., Gorgani-Firuzjaee, S., & Hosseinzadeh-Attar, M. J. (2018). Oral quercetin supplementation enhances adiponectin receptor transcript expression in polycystic ovary syndrome patients: A randomized placebo-controlled double-blind clinical trial. *Cell Journal (Yakhteh)*, *19*(4), 627.

Rice, S., Mason, H. D., & Whitehead, S. A. (2006). Phytoestrogens and their low dose combinations inhibit mRNA expression and activity of aromatase in human granulosa-luteal cells. *The Journal of Steroid Biochemistry and Molecular Biology*, *101*(4-5), 216–225.

Richards, J. S., & Pangas, S. A. (2010). The ovary: Basic biology and clinical implications. *The Journal of Clinical Investigation*, *120*(4), 963–972.

Robaszkiewicz, A., Balcerczyk, A., & Bartosz, G. (2007). Antioxidative and prooxidative effects of quercetin on A549 cells. *Cell Biology International*, *31*(10), 1245–1250.

Roomi, M. W., Kalinovsky, T., Rath, M., & Niedzwiecki, A. (2017). A specific mixture of nutrients suppresses ovarian cancer A-2780 tumor incidence, growth, and metastasis to lungs. *Nutrients*, *9*(3), 303–314. https://doi.org/10.3390/nu9030303

Russo, G. L., Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S., Iannitti, R., & Palumbo, R. (2014). Quercetin: A pleiotropic kinase inhibitor against cancer. In *Advances in nutrition and cancer* (pp. 185–205). Avellino, Italy: Springer.

Sak, K. (2014). Site-specific anticancer effects of dietary flavonoid quercetin. *Nutrition and Cancer*, *66*(2), 177–193.

Sandra, K. A. S. F. W., & van den Berg, M. (2014). Excessive levels of diverse phytoestrogens can modulate steroidogenesis and cell migration of KGN human granulosa-derived tumor cells.

Santini, S. E., Basini, G., Bussolati, S., & Grasselli, F. (2009). The phytoestrogen quercetin impairs steroidogenesis and angiogenesis in swine granulosa cells in vitro. *BioMed Research International*, *2019*, 1–8

Santoni, J. P., & Saubadu, S. (1995). Adverse events associated with neuroleptic drugs: Focus on neuroendocrine reactions. *Acta Theriologica*, *21*(3-4), 193–204.

Scambia, G., Panici, P. B., Ranelletti, F., Ferrandina, G., De Vincenzo, R., Piantelli, M., … Mancuso, S. (1994). Quercetin enhances transforming growth factor β1, secretion by human ovarian cancer cells. *International Journal of Cancer*, *57*(2), 211–215.

Scambia, G., Ranelletti, F., Benedetti, P. P., Bonanno, G., De, R. V., Piantelli, M., & Mancuso, S. (1990). Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth. *Anti-Cancer Drugs*, *1*(1), 45–48.

Scambia, G., Ranelletti, F., Panici, P. B., Piantelli, M., Bonanno, G., De Vincenzo, R., … Mancuso, S. (1990). Inhibitory effect of quercetin on OVCA 433 cells and presence of type II oestrogen binding sites in primary ovarian tumours and cultured cells. *British Journal of Cancer*, *62*(6), 942.

Shabaninejad, Z., Vafadar, A., Movahedpour, A., Ghasemi, Y., Namdar, A., Fathizadeh, H., … Mirzaei, H. (2019). Circular RNAs in cancer: New insights into functions and implications in ovarian cancer. *Journal of ovarian research*, *12*(1), 84.

Shah, K. N., & Patel, S. S. (2016). Phosphatidylinositide 3-kinase inhibition: A new potential target for the treatment of polycystic ovarian syndrome. *Pharmaceutical Biology*, *54*(6), 975–983. https://doi.org/10.3109/13880209.2015.1091482

Shu, X., Hu, X. J., Zhou, S. Y., Xu, C. L., Qiu, Q. Q., Nie, S. P., & Xie, M. Y. (2011). Effect of quercetin exposure during the prepubertal period on ovarian development and reproductive endocrinology of mice. *Yao Xue Xue Bao*, *46*(9), 1051–1057.

Silva, A. A., MNP, S., Figueiredo, L. B., Gonçalves, J. D., Silva, M. J., Loiola, M. L., … Gouveia, B. B. (2018). Quercetin influences in vitro maturation, apoptosis and metabolically active mitochondria of goat oocytes. *Zygote*, *26*(6), 465–470.

Sirotkin, A. V., & Harrath, A. (2014). Phytoestrogens and their effects. *European Journal of Pharmacology*, *741*, 230–236.

Sirotkin, A. V., Hrabovszká, S., Štochmaľová, A., Grossmann, R., Alwasel, S., & Harrath, A. H. (2019). Effect of quercetin on ovarian cells of pigs and cattle. *Animal Reproduction Science 205*(2019), 44–51.

Sovernigo, T., Adona, P., Monzani, P., Guemra, S., Barros, F., Lopes, F., & Leal, C. (2017). Effects of supplementation of medium with different antioxidants during in vitro maturation of bovine oocytes on subsequent embryo production. *Reproduction in Domestic Animals*, *52*(4), 561–569.

Stochmalova, A., Kadasi, A., Alexa, R., & Sirotkin, A. (2014). Plant molecules quercetin and resveratrol can affect ovarian cells and invert FSH action. *InSociety for Endocrinology BES*, *2014*, 34.

Stochmalová, A., Sirotkin, A., Kádasi, A., & Alexa, R. (2013). Physiological and medical effects of plant flavonoid quercetin. *The Journal of Microbiology, Biotechnology and Food Sciences*, *1915*(34), 318.

Tabrizi, F. P. F., Hajizadeh-Sharafabad, F., Vaezi, M., Jafari-Vayghan, H., Alizadeh, M., & Maleki, V. (2020). Quercetin and polycystic ovary syndrome, current evidence and future directions: A systematic review. *Journal of Ovarian Research*, *13*(1), 11.

Taepongsorat, L., Tangpraprutgul, P., Kitana, N., & Malaivijitnond, S. (2008). Stimulating effects of quercetin on sperm quality and reproductive organs in adult male rats. *Asian Journal of Andrology*, *10*(2), 249–258.

Tamtaji, O. R., Milajerdi, A., Dadgostar, E., Kolahdooz, F., Chamani, M., Amirani, E., … Asemi, Z. (2019). The effects of quercetin supplementation on blood pressures and endothelial function among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Current Pharmaceutical Design*, *25*(12), 1372–1384.

Tarko, A., Stochmalova, A., Hrabovszka, S., Vachanova, A., Harrath, A., Grossman, R., & Sirotkin, A. (2017). Can xylene and chia (*Salvia hispanica* L.) seed extract directly affect basic bovine ovarian cell functions? *Journal of Animal and Feed Sciences*, *26*(2), 109–115.

Teekaraman, D., Elayapillai, S. P., Viswanathan, M. P., & Jagadeesan, A. (2019). Quercetin inhibits human metastatic ovarian cancer cell growth and modulates components of the intrinsic apoptotic pathway in PA-1 cell line. *Chemico-Biological Interactions*, *300*, 91–100.

Vaquero, A., Scher, M., Erdjument-Bromage, H., Tempst, P., Serrano, L., & Reinberg, D. (2007). SIRT1 regulates the histone methyl-transferase SUV39H1 during heterochromatin formation. *Nature*, *450*(7168), 440.

Wachsberger, P. R., Burd, R., Bhala, A., Bobyock, S. B., Wahl, M. L., Owen, C. S., … Leeper, D. B. (2003). Quercetin sensitizes cells in a

tumour-like low pH environment to hyperthermia. *International Journal of Hyperthermia*, *19*(5), 507–519. https://doi.org/10.1080/02656730310000078697

Wang, H., Jo, Y.-J., Oh, J. S., & Kim, N. H. (2017). Quercetin delays postovulatory aging of mouse oocytes by regulating SIRT expression and MPF activity. *Oncotarget*, *8*(24), 38631.

Wang, J., Qian, X., Gao, Q., Lv, C., Xu, J., Jin, H., & Zhu, H. (2018). Quercetin increases the antioxidant capacity of the ovary in menopausal rats and in ovarian granulosa cell culture in vitro. *Journal of Ovarian Research*, *11*(1), 51.

Wang, W., Wang, C., Ding, X. Q., Pan, Y., Gu, T. T., Wang, M. X., … Kong, L. D. (2013). Quercetin and allopurinol reduce liver thioredoxin-interacting protein to alleviate inflammation and lipid accumulation in diabetic rats. *British Journal of Pharmacology*, *169*(6), 1352–1371.

Wang, Y., Han, A., Chen, E., Singh, R. K., Chichester, C. O., Moore, R. G., … Vorsa, N. (2015). The cranberry flavonoids PAC DP-9 and quercetin aglycone induce cytotoxicity and cell cycle arrest and increase cisplatin sensitivity in ovarian cancer cells. *International Journal of Oncology*, *46*(5), 1924–1934.

Wang, Z., Zhai, D., Zhang, D., Bai, L., Yao, R., Yu, J., … Yu, C. (2017). Quercetin decreases insulin resistance in a polycystic ovary syndrome rat model by improving inflammatory microenvironment. *Reproductive Sciences*, *24*(5), 682–690. https://doi.org/10.1177/1933719116667218

Warren, C. A., Paulhill, K. J., Davidson, L. A., Lupton, J. R., Taddeo, S. S., Hong, M. Y., … Turner, N. D. (2008). Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. *The Journal of Nutrition*, *139*(1), 101–105.

Weber, G., Shen, F., Prajda, N., Yeh, Y., Yang, H., Herenyiova, M., & Look, K. (1996). Increased signal transduction activity and down-regulation in human cancer cells. *Anticancer Research*, *16*(6A), 3271–3282.

Whitehead, S. A., & Lacey, M. (2003). Phytoestrogens inhibit aromatase but not 17β-hydroxysteroid dehydrogenase (HSD) type 1 in human granulosa-luteal cells: Evidence for FSH induction of 17β-HSD. *Human Reproduction Update*, *18*(3), 487–494.

Wiseman, H., & Halliwell, B. (1996). Damage to DNA by reactive oxygen and nitrogen species: Role in inflammatory disease and progression to cancer. *Biochemical Journal*, *313*(Pt 1), 17.

Wu, C.-H., Shieh, T.-M., Wang, K.-L., Huang, T.-C., & Hsia, S.-M. (2015). Quercetin, a main flavonoid in onion, inhibits the PGF2α-induced uterine contraction in vitro and in vivo. *Journal of Functional Foods*, *19*, 495–504.

Wu, J., Tu, D., Yuan, L. Y., Yuan, H., & Wen, L. X. (2013). T-2 toxin exposure induces apoptosis in rat ovarian granulosa cells through oxidative stress. *Environmental Toxicology and Pharmacology*, *36*(2), 493–500.

Xiao, X., Shi, D., Liu, L., Wang, J., Xie, X., Kang, T., & Deng, W. (2011). Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. *PLoS One*, *6*(8), e22934.

Xu, G., Li, B., Wang, T., Wan, J., Zhang, Y., Huang, J., & Shen, Y. (2018). Enhancing the anti-ovarian cancer activity of quercetin using a self-assembling micelle and thermosensitive hydrogel drug delivery system. *RSC Advances*, *8*(38), 21229–21242.

Yamauchi, K., Afroze, S. H., Mitsunaga, T., McCormick, T. C., Kuehl, T. J., Zawieja, D. C., & Uddin, M. N. (2017). 3, 4', 7-O-trimethylquercetin inhibits invasion and migration of ovarian cancer cells. *Anticancer Research*, *37*(6), 2823–2829.

Yang, J., Chaudhry, M., Yao, J., Wang, S., Zhou, B., Wang, M., … Li, Y. (2018). Effects of phyto-oestrogen quercetin on productive performance, hormones, reproductive organs and apoptotic genes in laying hens. *Journal of Animal Physiology and Animal Nutrition*, *102*(2), 505–513.

Yang, Z., Liu, Y., Liao, J., Gong, C., Sun, C., Zhou, X., … Ma, D. (2015). Quercetin induces endoplasmic reticulum stress to enhance cDDP cytotoxicity in ovarian cancer: Involvement of STAT3 signaling. *The FEBS Journal*, *282*(6), 1111–1125.

Ye, B., Aponte, M., Dai, Y., Li, L., Ho, M. C., Vitonis, A., … Cramer, D. W. (2007). Ginkgo biloba and ovarian cancer prevention: Epidemiological and biological evidence. *Cancer Letters*, *251*(1), 43–52. https://doi.org/10.1016/j.canlet.2006.10.025

Yi, L., Zongyuan, Y., Cheng, G., Lingyun, Z., Guilian, Y., & Wei, G. (2014). Quercetin enhances apoptotic effect of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in ovarian cancer cells through reactive oxygen species (ROS) mediated CCAAT enhancer-binding protein homologous protein (CHOP)-death receptor 5 pathway. *Cancer Science*, *105*(5), 520–527. https://doi.org/10.1111/cas.12395

Zhang, M., An, C., Gao, Y., Leak, R. K., Chen, J., & Zhang, F. (2013). Emerging roles of Nrf2 and phase II antioxidant enzymes in neuroprotection. *Progress in Neurobiology*, *100*, 30–47.

Zhang, T., Zhou, Y., Li, L., Wang, H. H., Ma, X. S., Qian, W. P., … Sun, Q. Y. (2016). SIRT1, 2, 3 protect mouse oocytes from postovulatory aging. *Aging (Albany NY)*, *8*(4), 685.

Zhang, X., Wang, X., Wang, H., Yang, Q., & Qie, M. (2009). Inhibition effect and mechanisms of quercetin on surgically induced endometriosis. *Sichuan da xue xue bao. Yi xue ban = Journal of Sichuan University, Medical science edition*, *40*(2), 228–231 244.

Zhang, Y., Chen, S., Wei, C., Rankin, G. O., Ye, X., & Chen, Y. C. (2018). Flavonoids from Chinese bayberry leaves induced apoptosis and G1 cell cycle arrest via Erk pathway in ovarian cancer cells. *European Journal of Medicinal Chemistry*, *147*, 218–226.

Zhao, Y.-T., Wang, X.-D., Shi, W.-Y., & Zhong, X.-H. (2011). Anti-abortive effect of quercetin and bornyl acetate on macrophages and IL-10 in uterus of mice. *African Journal of Biotechnology*, *10*(43), 8675–8682.

Zhou, J., Gong, J., Ding, C., & Chen, G. (2015). Quercetin induces the apoptosis of human ovarian carcinoma cells by upregulating the expression of microRNA-145. *Molecular Medicine Reports*, *12*(2), 3127–3131. https://doi.org/10.3892/mmr.2015.3679

Zootec, A. B. M. V. (2013). Maturação in vitro de oócitos bovinos em meios suplementados com quercetina e seu efeito sobre o desenvolvimento embrionário. *Arquivos Brasileiros de Medicina*, *65*(6), 1616–1624.

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