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Molecular Targets of Phyto-bioactive Compounds in Female Reproductive System of Mammals: A Review

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ABSTRACT

Phytochemicals present in the plants are divided into primary (Alcohol Amino acids, nucleotides. *etc*) and secondary metabolites (Alkaloids, Saponins *etc*.). Carotenoids (reduces reactive oxygen species formation, decreases apoptotic cells, restoration of actin capping expression proteins *etc*.), Phenolics (inhibits extracellular signal-regulated kinase signalling pathway), Isoflavones (inhibits tyrosine kinase pathway) and alkaloids (downregulation of vascular endothelial growth factor, tumor necrosis factor-alpha and hypoxia-inducible factor 1-alpha messengers) are the major phytochemicals, having the potential effects towards ovarian function. Likewise, bioactive compounds are the chemicals that can interact with certain components of live tissue to exert their various effects (antioxidant, antineoplastic, receptor inhibition, gene expression *etc*.) respective to female fertility. Similarly, bioactive compounds: Kaempferol [phosphatidylinositol -3- kinase (PI3K)/protein kinase B (Akt) pathway], Quercetin (controlling the release of 17β-estradiol *etc*.), Myricetin (PI3K/Akt and MAPK signalling pathway), Galngin (inhibition of angiogenesis via decreasing the VEGF and p-Akt) and Resveratrol (regulation of Foxo3a and SIRT1 genes *etc*.) shows its effects by targeting different molecules and/or pathways at the ovarian microenvironment. However, Genistein (binding to estrogen receptors: ESRα and ESRβ *etc*.) and Diadzein (disrupting the endocrines *etc*.) emphatically interfere with the ovarian functions. Besides this, molecular effects exerted by these phyto-bioactive compounds on the *in vivo* and/or *in vitro* ovarian culture systems entirely depend on their dosage: Kaempferol @10 µM increased the primordial follicle activation, Quercetin @4 µM improved the quality of oocytes whereas @8 µM reduced the quality), Resveratrol @ 2 µM increased the blastocyst formation, Myricetin @ 100 mg/kg/day feeding in rats induced estrogenic activity, Genistein, feeding in female mice @ 500 and 1000ppm increased the gestation time and Diazdein causes the inhibition of 3-hydroxysteroid dehydrogenase at 40 µM doses. The assessment was done via the systemic collection of literature from sources such as newspapers, conference papers, journals, theory and dissertation articles, electronic databases, manuals, encyclopedia and annual reviews, as well as e-books and reporting. As a result, the preceding discussion focuses on the key phyto-bioactive compounds and their molecular targets in female fertility. This will aid in the successful and secure application of plant bioactive compounds in the field of female reproductive health.

Key words: Female reproduction, Molecular targets, Mammals, Phytochemicals.

Phytochemicals are the chemical compounds present in the fruits, vegetable, grains and other parts of the plant, produed by the primary/secondary metabolism (Oz and Kafkas 2017). They are the non-nutritive compounds, that plays a key role either in protection and/or prevention of disease in the mammals (antibacterial, antifungal, antiviral, cholesterol-lowering, antithrombotic and antiinflammatory properties: Monica and Susanne 2006 Ex: Lycopene in tomatoes, Isoflavones in soy acts as an anti oxidative, anti proliferative as well as anti-inflammatory compounds with a prevention of coronary diseases *etc*. (Naeem *et al*., 2011). Primary metabolites are compounds that directly participates in growth and development of a plant (Ex: Alcohol Amino acids, nucleotides, antioxidants, organic acids, vitamins and polyols) whereas, secondary metabolites are derived from the primary metabolites (Phenolics, Alkaloids, Saponins, Terpenes, Lipids and Carbohydrates) (Jamwal *et al*., 2018). Further, plant secondary metabolites are rich sources of manyactive compounds such as Yohimbine, Kaempferol, Quercetin *etc*. (Bellik *et al*., 2012), which plays a significant role in the modulation of ovarian functions.

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Bioactive compounds from the plants have been used as medicines for decades to treat various reproductive disorders in mammals (Atanasov*et al*., 2015).According to World Health Organization (WHO) report, more than 7500 plant species are being used as traditional medicines globally (Chen *et al*., 2016). WHO therefore recommend the promotion of ethno-veterinary practices, the conservation

as well as cultivation of the medicinal plants (Dalal, 1992). However, in order to use the plant and/or plant extracts (infusion, decoction, beverages, crude extracts) as medicines, scientific validation of their safety and efficacy is required.

Bioactive compounds can provide health benefits beyond the basic nutritional value although it is present in low concentration in plants (fruits, vegetables and whole grains) (Gokmen, 2015). Guaadaoui *et al*. (2014) suggested thatthese compounds interacts with certain components of live tissue to exert its various effects (antioxidant, receptor inhibition, gene expression *etc*) and can modulate their metabolic processes (Carbonell-Capella *et al.,* 2014). Besides, bioactive compounds have significant role in the regulation of ovarian folliculogenesis and/or steroidogenesis (both *in vivo* and *in vitro*) (Rice *et al*., 2006; Guaadaoui *et al*., 2014). Above all, the effects of thebioactive compounds are executed either by targeting the hormones, enzymes (Jha *et al*., 2010) and/or the elimination of the reactive oxygen species in the ovarian cells (Kang *et al*., 2016). Hence, the foregoing general review on some important plant bioactive compounds and their effects (both *in vivo* and *in vitro*) on female reproductive organs (mainly ovary).

Molecular targets of phytochemicals

Phytochemicals exert biphasic dose-dependent actions on the ovary (Jadwiga and Kujawska, 2020). Generally, there is a stimulatory effect at low doses and inhibitory effect at high doses (Calabrese and baldwin 1997). This as evidenced by the action of resveratrol, a stilbenoid, a type of natural phenolon rat ovarian granulosa cells, where it could increase the DNA synthesis at 10 µM. However, at 15, 30 and 50 µM doses there is a reduction in DNA synthesis (Ortega *et al*., 2012). Stimulatory effects of phytochemicals at low dosesare not always beneficial (Kendig *et al*., 2010). This evidenced by increased proliferation of tumor cells when exposed to the phytochemicals at lower doses (Thayer *et al*., 2005).

Phytochemicals regulate cellular activities such as growth, proliferation, survival and apoptosis by targeting one or more cascades. PKC (through Keap1), MAPK/ERK1/2 and PI3K/AKT pathways activate the common transcription factor (Nrf2), whereas AMPK pathway activate quite a different factor (FOXO3). However, PI3K/AKT pathway further activates the Bcl-2 molecule (pro-survival, anti-apoptotic and cytoprotective). The activated transcription factors further bind to the element ARE after translocating to the nucleus. This eventually stimulates the cytoprotective proteins (antioxidant enzymes, phase-2 proteins *etc*) which mediates the cell survival and apoptosis against the various stressors (Jadwiga and Kujawska, 2020). Presented in Fig 1 is the schematic diagram of molecular targets of phytochemicals.

Classification of phytochemicals

Phytochemicals are classified into carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulphur compounds (Liu 2004). Carotenoids can be further divided into α-carotene, β-carotene, β-cryptoxanthine, lutein, zeaxanthin, astaxanthin and lycopene. Phenolics are the largest group of phytochemical which isfurther divided into five groups namely: phenolic acid, flavonoids, stilbenes, courmarins and tannins. Phenolic acid is further divided into two groups:hydrooxy-bezonoic acid (*e.g*. gallic, vannilic, syringic and protocatechic) and hydroxy-cinnamic acids (*e.g*.

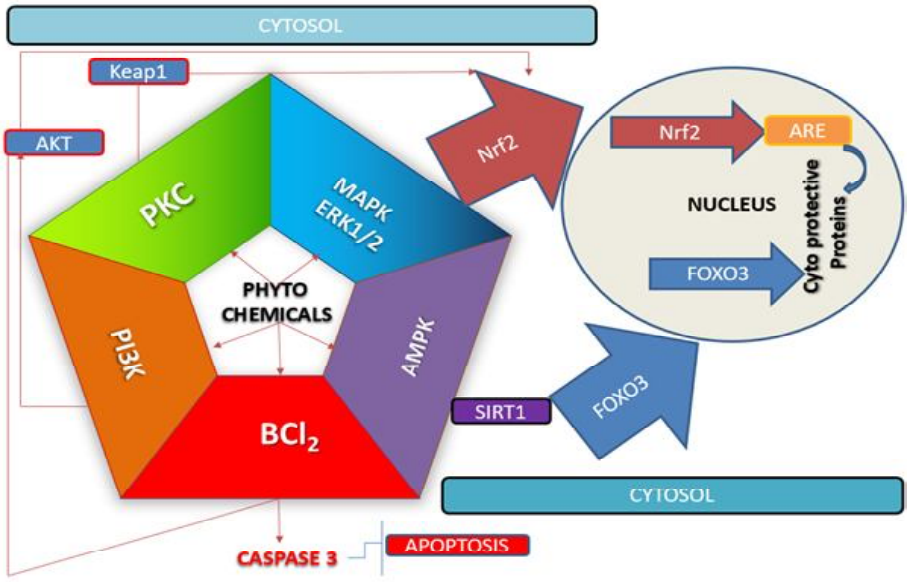

Fig 1: Molecular targets of phytochemicals

[**AKT**-serine/threonine-protein kinase, **AMPK**-AMP-activated protein kinase, **ARE**-antioxidant response elements, **Bcl_2**-B-cell lymphoma 2, **ERK**-extracellular signal-regulated kinase, **FOXO3**-forkhead box O3, **Keap1**-Kelch-like ECH-associated protein1, **Nrf2**-nuclear factor erythroid 2-related factor 2, **PI3K**-phosphatidylinositol 3-kinase, **PKC**-protein kinase C].

p-coumarin, caffeic, ferulic, sinapic). Likewise, flavonoids can be further divided into various groups based on their similarity in the chemical structure, such as flavonols (quercetin, kaempherol, myricetein, galangin andfisetin), flavones (apigenin, chrysin and luteolin), flavanols (catechin, epicatechin, epigallocatchingallate), flavanones (eriodictyol, hesperitin, naringenin), anthracyanidins (cyanidin, peonidin, malvidin, delphinidin and pelargonidin) and isoflavonoids (genistein, daidzein, glycitein, formonetin). The oragnosulfur compounds are:indoles, isthiocynates and allyatic sulfur compounds.

Carotenoids

Carotenoids (β-carotene, lycopene, lutein and zeaxanthin) from plant plays a major role in the reproduction of mammals (Lopez-flores *et al*., 2018). β-carotene is one of the major dietary carotenoids (Nishino *et al*., 2017) which has a role in oocyte as well as embryonic development because it is a precursor of vitamin A according to Johnson, 2002. Additionally, β-carotene has been proven to reduce oxidative stress in the microenvironment of oocytes as it is a lipid-soluble antioxidant (Pysz *et al*., 2016). Furthermore, research revealed that β-carotene, reduced oxidative stress *in-vivo* in cow: 1.2 g/cow/day (oral: Oliveira *et al*., 2015), Goat; 50 mg goat/day (for 35 days: oral: Arellano-Rodriguez *et al*., 2009), Rabbit: 2 mg/kg/day (for 7 day oral: Merhan *et al*., 2016), Rats: 50 and 100 mg/kg b. wt. (oral: Aksak *et al*., 2015) and sow (injection 70 mg/ sow: Szczubiał 2015) as well as *in vitro* (10 µM β carotene to the oocyte culture medium in the Kunming mice: Yu *et al*., 2019). in the Kunming mice, diets rich in β-carotene can improve ovarian steroidogenesis (both corpus luteum and follicular tissue) which will further help progesterone synthesis (Arellano-Rodriguez *et al*., 2009). Similarly, Meza-Herrera *et al*., 2013 revealed a positive influence ofshort-term supplementation of β-carotene on ovarian activity in goats. Likewise, De-Bie *et al*., 2016, reported an improvement in the follicular as well as oocyte development with the supplementation of β-carotene although there was oxidative stress in the cellular environment.

The mechanism by which β-carotene exerts its action isbyeither reducing the ROS formation (Haila *et al*., 1997), decreasing the apoptotic cells, restoring the actin capping (expression) proteins, forming the cortical granule-free domains, homogenizing the mitochondrial distribution and/ or improving the nuclear maturation rates (Aksak *et al*., 2015; Yu *et al*., 2019). Furthermore, β-carotene can also act as an HPG (hypothalamus-pitutary-gonadal) modulating molecule by down regulating the estrogen receptors) in the hormone dependent cancers (Hirch *et al*., 2007).

Phenolics

Phenolics are abundantly available phytochemicals in nature. Generally, phenolic compounds are synthesized from a common precursor molecule,phenylalanine or tyrosine (Harborne 1999). Phenolics are the vast group of compounds and further classified into phenolic acids, flavonoids, stilbenes, coumarins and tannins (Liu *et al*., 2004).

Flavonoids

Flavonoids are polyphenolic plant pigments and synthesized from phenylalanine molecule (polypropanoid pathway). Structurally, flavonoids have the basic C6-C3-C6 structural skeleton, consisting of two aromatic C6 rings (A and B) and one heterocyclic ring (C) that contain a single oxygen atom (Ghasemzadeh and Ghasemzadeh, 2011). Flavonoids are furtherclassified into flavonols, flavones, flavanols, anthocyanidins and isoflavonoids (Liu *et al*., 2004). Among them that arebioactive compounds belong to the group of flavonols, flavanols and isoflavonoidsthat exert the most potent action on the ovary both *in-vitro* and *in-vivo*.

Flavonols

Flavonols (3-hydroxyflavones and flavones) are the widespread group of secondary metabolites among all flavonoids (Kaurinovic and vastag 2019). Themajor bioactive compounds belonging to this group are kaempferol, quercetin, myricetin, galangin and fisetin.

Flavanols

Flavanols mainly contain catechins, epi-catechins and its derivatives. Catechins agentswere proven to be beneficial in the improvement of oocyte as well as embryo quality. For instance, injection of 0.4 ml of epi-gallocatechin gallate (EGCG100 mg/kg body weight) into the female mice increased the embryo quality (Roth *et al*., 2008). Catechins exert its action either as an antioxidant with lower concentration at 10 mg/ml and/or pro-oxidant with higher concentration at 25 mg/ml (Wang *et al*., 2007). Likewise, ECGC acts as an inhibitor of cellular proliferation and angiogenesis (Ricci *et al*., 2013). It can further, inhibits cellular proliferation by inhibiting the ERK signal cascade (Humans: Manohar *et al*., 2013, Animals: Ricci *et al*., 2013; Xu *et al*., 2011). The addition of ECGC into *in-vitro* culture medium also has a dose-dependent action. This is evidenced by improvement in the oocyte fertilization rates after addition of ECGC at lower doses (10 mg/ml) to the porcine IVF culture medium. However, there was a reduction in the fertilization rates of oocytes after adding higher concentrations (25 mg/ml) of the agent to the same medium (Spinaci *et al*., 2008). Similarly, the addition of lower doses (10µg/ml) of ECGC to embryo culture medium have also resulted in its improvement, whereas at higher doses (10 and 50 µM) it reduced the embryo quality (Yavari *et al*., 2010). Likewise, Roychoudahary *et al*., 2016 reported an improvement in the bovine *in-vitro* culture systems after the additionof 15 µM of ECGC.

Isoflavonoids

Isoflavones also exert a dose-dependent action during *in vitro* and *in vivo* conditions. In normal doses, they act as estrogen modulators (Carbonel *et al*., 2018) whereas at high doses it reduces cell proliferation (Talsness *et al*., 2015). Furthermore, in low doses, they act as stimulator and were

able to modify genes responsible for cell cycle control (Touny and Benerjee, 2006), cell survival (Moiseeva *et al*., 2007) and apoptosis (Touny and Benerjee, 2006).

Isoflavones acts invarious ways: by inhibiting tyrosine kinase (PTK: to prevent cell proliferation and angiogenesis) (Tepper *et al*., 2007), inhibiting the aromatase enzyme (Pelissero *et al*., 1996), decreasing the cyclin B1rr protein expression (Choi *et al*., 2000) levels, increasing p53 (Choi *et al*., 2000) levels and/or by stimulating the liver globulins (Adlercreutz *et al*., 1987). Additionally, isoflavones protect the ovary from oxidative stress by up-regulating the antioxidant enzymes (De-Bruin *et al*., 2002) and/or by sequestering the free radicals (Bertoncini *et al*., 2010).

Alkaloids

Plant alkaloids are nitrogenous and heterocyclic alkaline compounds (Mbemyaa *et al*., 2017). Alkaloids have been used in the prevention as well as treatment of ovarian angiogenic disorders (Sagar *et al*., 2006) as they have anti-proliferative and anti-angiogenic properties (Tang *et al*., 2009). Anti-angiogenic property of the alkaloids was achieved through the down-regulation (VEGF, TNF-α and HIF-1α messengers) and/or up-regulation (apoptotic genes) of certain factors (Tang *et al*., 2009). Alkaloids exert its actions either directly by blocking the angiogenic cascade: berberine, noscapine, brucine, evodiamine, homoharringtonine, matrine and tetrandrine (Alasvand *et al*., 2019) or indirectly by blocking the STAT3 signaling pathway: matrine and tetrandrine (Zhao *et al*., 2018). Furthermore,other actions of the plant alkaloidsinclude:inhibiting the β-catenin pathway such as evodiamine (Shi *et al*., 2016), regulating the Akt phosphorylation which includesanguinarine, capsaicin, taspine, harmine and pterogynidine (Min *et al*., 2004) and CDK expression (Zhang *et al*., 2011) and/or NF-κB translocation (Hamsa and Kuttan, 2010).

Bioactive compounds

Kaempferol

Kaempferol (KAE) is a polyphenolicflavonol (Liu *et al*., 2004). This bioactive compound plays a major role in the development of viable ovarian follicles (primary and secondary) with the maintenance of active mitochondrial levels (Yao *et al*., 2019). Furthermore, it helps inthe reduction of DNA fragmentation in cultured follicles of ovine and porcine species (Santos *et al.,* 2019).

The addition of KAE to the culture media of follicle, oocyte, embryohas a dose-dependent action. For instance, at a concentration of 10 µM, it could enhance the primordial follicle activation, cell proliferation and oocyte meiotic resumption in the ovine cultured follicles (Santos *et al.,* 2019). Similarly, at 0.1µM concentration, KAE was effective in increasing the blastocyst number as well as its formation rate in porcine cultured follicles (Zhao *et al.,* 2019). Likewise, at 1µM concentration KAE was proven to be an effective agent by increasing the follicle diameter and oocyte growth in mammals (Zhou *et al.,* 2015). The above specific effect was obtained by increasing the antioxidant enzyme expression levels such as the catalase, heme-oxygenase and glutathione which decreased lipid peroxidation (Zhou *et al.,* 2015).

Themolecular action of KAE acts in multiple ways. One of the major mechanisms is phosphatidylinositol-3- kinase (PI3K)/protein kinase B (Akt) pathway. Through this pathway, KAE exerts its effects on the culture of ovine preantral follicles *in-vitro* (Santos *et al.,* 2019). Besides this, another mechanism of KAE is to increase the mRNA expression levels of COX2 and SOX2 genes which have a role in embryonic developmentwith a significant reduction in the Caspase-3 levels (Zhao *et al*., 2019). This further, helps in the improvement of zygote development in porcine cultures (White *et al*., 2016).

Furthermore, by reducing the oxidative stress, KAE protects the oocytes during *in-vitro* maturation. KAE executes this action through various mechanisms. One among them is by up-regulating the mitochondrial ofhuman silent information regulator type 1 (SIRT1) gene expression (Guo *et al*., 2015). Likewise, theupregulation ofnuclear erythroid 2-related factor-Antioxidant related element (Nrf2-ARE) (Saw *et al.,* 2014) is obtained by increasing the levels of p p38, Nrf2, SOD and catalase (Kim *et al*., 2008). Nevertheless, it is an undeniable fact that the continuous production of ROS and /or calcium overload can target the mitochondria and can create oxidative stress (Ott *et al*., 2007). KAE was effective in ameliorating the above deleterious effect either by enhancing the mitochondrial membrane potential (MMP) (porcine embryos) (Guo *et al*. 2015) and /or reducing the MC3T3 E1 intracellular Ca2+ concentrations (Choi, 2011).

Despite all the above effective mechanisms, an indelible action of KAE was also seen on aging oocytes. KAE could delay the oocyte aging and thereby improve the subsequent embryonic development cascade (Yao *et al*., 2019). The delay in the aging of oocytes is further executedeither by reducing the apoptosis (decreasing ROS levels) and/or maintaining a sufficiency in thematrix metalloproteinase or matrixins (MMP) levels (Yao *et al*., 2019). Another reason attributed to the improvement of KAE treated aged oocytes could be an increase in the mRNA expression levels of transcriptional factors such as *SIRT1, NANOG, ITGA5 and Oct4* genes which has a role in embryonic pluripotency in the porcine (Zhang *et al*., 2015).

Quercetin

Quercetin (QUE) is an ovarian modulatory bio-flavonoid. Mostly used for the regulation of ovarian functions (ovarian folliculogenesis, oocyte maturation and ovulation) (Santini *et al*., 2009). QUE acts on ovarian follicular cells and oocytes either by enhancing the mucification process, mitochondrial activity and/or by controlling the DNA fragmentation (Tarazona *et al*., 2006).

Dietary QUE has a stimulatory effect on thefollicle stimulating hormone, leuteinizing hormone and prolactin levels at a concentration of 10, 100 and 1000 µg/kg body weight in female rabbits (Tusimova *et al*., 2017). Similarly,

feeding QUE to female mice improved folliculogenesis by increasingcell proliferation, ovarian weight, oocyte quality and litter sizewith a reduction in cell apoptosis (Beazley and Nurminskaja, 2016; Naseer *et al*., 2017). However, there is a suppression in the ovarian folliculogenesis and ovulation also ovarian follicular atresia in old mice fed with QUE (Shu *et al*., 2011).

QUE is effective at concentrations of 0.3 and 30 µg/mL in *in-vitro* assay (Ader *et al*., 2000). However, the addition of QUE to the culture medium of goat oocyte shows a dose-dependent activity. At a concentration of 4 µM of QUE, there was an improvement in the quality of oocytes (Silva *et al*., 2018) whereas 8 µM of QUE deteriorates the quality (Orlovschi *et al*., 2014). Similarly, the addition of QUE at 25µg/ml to theculture medium of porcine oocyte showed an improvement in the oocyte maturation rates, blastocyst development with a cumulus cell expansion (Orlovschi *et al.,* 2014). However, the addition of QUE at 10 and 100 ng/ml concentrations to granulosa cell cultureof the porcine show a reduction in the accumulation of proliferative (PCNA, cyclin B1) markers with the promotion of apoptotic markers (BAX) (Sirotkin *et al*., 2019).

Knowing the molecular targets of QUE is of prime importance besides its dosage if it is to be used safely and effectively as a bioactive compound. QUE acts in multiple ways and it has a dose-dependent bi-phasic action on the ovarian functions (Hung 2007). In swine granulosa cell cultures, QUE binds with estrogen receptors (ER β) and controls the release of 17 β-estradiol (Krazeisen *et al*., 2001) in a dose-dependent manner. At high concentrations, QUE had an inhibitory effect on 17 β-estradiol whereas at low concentrations a stimulatory effect (Lu *et al*., 2012). Furthermore, studies conducted by Hung (2007) and Santini *et al*. (2009) revealed that QUE can prevent the angiogenic process through the inhibition of VEGF production. Similarly, it can inhibit steroidogenesis by suppressing the cytochrome P450 enzyme in the granulosa cell cultures (Rice *et al*., 2006). Likewise, it could inhibit the process of aromatization in the ovarian microsomes either by modulating the cell signaling pathways and/or by interfering with the NO/NOS system in the granulosa cells (Santini *et al*., 2009). The above effects exerted by QUE indicates a negative effect of QUE on the ovarian physiology as it is inhibiting the process of angiogenesis, steroidogenesis as well as aromatization. Hence this distinctive property of QUE has being used extensively in ovarian cancer therapy (Hashemzaei *et al*., 2017). QUE exerts an anticancer property in a dose-dependent manner. It does this bycontrolling the cell cycle, modulating the TGFβ1 factor (Scambia *et al*., 1990); inhibition of tumor growth, angiogenesis and induction of apoptosis (Parvaresh *et al*., 2016). Besides, QUE mainly regulates the cell cycle by blocking the GO/GI to G2/M phase of meiosis (Scambia *et al*., 1990). Furthermore, the effect of QUE was also seen on aged oocytes, where it delays the postovulatory aging in the oocytes by regulating the expression of SIRT and MPF (maturation promoting factor) activities (Wang *et al*., 2017).

Besides, another major action of QUE is the antioxidant property (Wang *et al*., 2018). QUE is a strong antioxidant bio-flavonoid. QUE exerts its antioxidant action either by increasing the 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 (Wiegand *et al*., 2009; Xu *et al*., 2019) and/or by upregulating the Nrf2-ARE (Nuclear erythroid 2-related factor-Antioxidant related element) pathway which is similar to kaempferol (Belen *et al*., 2012; Saw *et al.,* 2014).

Furthermore, QUE has its influence on hormones also. It regulates the gonadotropins (Shu *et al*., 2011), steroid and peptide hormones (Sirotkin *et al*., 2019). It mainly decreases the release of progesterone (P4) and leptin resulting in an increase in testosterone levels in cultured granulosa cells of the porcine (Sirotkin *et al*., 2019). However, QUE reduces progesterone concentrations in granulosa cellsof human, which could be due to the inhibition of the 3β-hydroxysteroid enzyme (Lacey *et al*., 2005). Besides, QUE also has its effect on insulin-like growth factor 1 (IGF-1). Indeed, it shows a dose-dependent action on IGF-1 release in the granulosa cells of the cattle.Higher dose (100 ng/mL of QUE) has an inhibitory effect and lower doses (1 or 10 ng/mL) has a stimulatory effect (Sirotkin *et al*., 2019).

Myricetin

Myricetin (MYR) is a polyphenolic bio-flavonoid. MYR is a beneficial compound because it has an antioxidant, antiangiogenic, anti-inflammatory as well as antineoplastic properties. Furthermore, MYR can also exert an estrogenic activity. This is evident by the oral administration of MYR at 100 mg/kg/day in Wistar albino rats. This resulted into an increase in the height and weight of the uterus (Barlas *et al*., 2014).

It is an undeniable fact that an imbalance between reactive oxygen species (ROS) and antioxidant enzymes production can lead to disturbance in the ovarian functions. Such disturbance can be noticed duringoocyte maturation, ovulation, fertilization, implantation and embryo development (Wang *et al*., 2017). To counter this, MYR has the ability to protect the cells by restoring the activities of the antioxidant defense enzymes such as SOD, catalase and glutathione peroxidase by increasing its protein expression (Wang *et al*., 2010). Besides, MYR can also prevent the cells from oxidative stress-induced apoptosis by regulation of PI3K/Akt and MAPK signaling pathways (Kang *et al*., 2010).

Additionally, MYR acts as a chemo-protective agent against cancer cells by modifying several distinctive pathways such as the aberrant cell proliferation, signaling pathways, apoptosis, angiogenesis and tumor metastasis. Accordingly, MYR attenuates the neoplastic transformation of cancer cells by interacting with the oncoproteins, for example, protein kinase B (PKB)/(Akt), Fyn, MEK1 and JAK1– STAT3 (Janus kinase–signal transducer and activator

of transcription 3) (Devi *et al*., 2015). Furthermore, MYR, inhibits angiogenesis in the cancer cells *via* p21 (Cyclin kinase inhibitor-1)/HIF-1α (Hypoxia-induced factor)/VEGF pathway (Huang *et al*., 2015). Similarly, in the A2780/CP70 and OVCAR-3 cancer cells, MYR suppressed the angiogenesis by inhibiting the VEGF and/or decreasing the levels of p-Akt, pp70S6K and HIF-1α factors (Huang *et al*., 2015).

Galangin

Galangin is a bio-flavonoid which exhibits an antioxidant as well as antiproliferative properties in the ovarian (cancer) cells (Huang *et al*., 2015). This is evident in human umbilical vein endothelial cells by the findings of Kim *et al*., 2006 where Galangin exerts its action mainly through the inhibition of angiogenesis via decreasing the VEGF, p-Akt, p-p70S6k and HIF-1 α proteins in the cancer cells (OVCAR-3) (Huang *et al*., 2015).

Genistein

Genistein (GEN) is an isoflavonicphyto-estrogen and endocrine-disrupting chemical (Kuiper *et al*., 1997). GEN exerts a negative effect on ovarian function. For instance, dietary consumption of GEN at a rate of 500 and 1000ppm for 30 days in female mice at preconception stage led to a decrease in gestation time, 500 ppm for 60 days increased pup mortality, 300 ppm for 150 days prolonged the parturition, 300 ppm for 240 days decreased fertility rate and at 500 ppm for 240 daysled topoor maternal behavior (Patel 2017). In another instance, exposure to GEN at neonatal stage in rodents led to premature reproductive system (Medigovic *et al*., 2012) with atretic follicles and multi-oocyte follicle development (Bush *et al*., 1987).

GEN has a negative effect on *in-vitro* culture systems also. One of such effect is the inhibition of steroidogenic enzymes in the culture systems of preantral (Myllymaki *et al*., 2005), antral (Patel *et al*., 2016) and granulosa cells (Whitehead and Lacey 2000) of rat and porcine after their exposure to GEN. This inhibition can be obtained by increasing the expression levels of cell cycle inhibitors such as the cyclin-dependentkinase inhibitor 1A (Cdkn1a). Eventually, this leads to a cell cycle arrest (Patel 2017). Another effect of GEN is inhibition of the level of cytochrome P450 17A1 (Cyp17a1) enzyme expression in culture systems (Patel 2017). This inhibition also results into an alteration in the hormone levels such as increase in progesterone and DHEA levels with a reduction in estrone and estradiol levels (Patel 2017). Likewise, addition of GEN at 80µg/ml to porcine maturation medium *in vitro* completely inhibits the oocyte maturation.

At the molecular level GEN, mainly exerts its action by binding with the estrogen receptors (ESRα and ESRβ) (Yoon *et al.,* 2014). This binding is possible due to the chemical similarity between GEN and 17β-estradiol thereby mimicking estrogens (Burton and wells 2002). The consequence of this binding is the formation of abnormal chromatin by GEN. The reason attributed to this was that there is an induction of microtubules depolymerization in somatic cells by GEN. This disturbance occurs in somatic cells either by binding to a specific position on tubulin (Mukherjee *et al*., 2010) and/or inhibiting the expression of polo-like kinase 1, amammalian oocytes meiotic regulator (Seo *et al*., 2011). Furthermore, after binding with the receptors (ESRα and ESR β), GEN also causes alterations in the expression levels of key enzyme such as STAR in the steroidogenic process. Eventually, this binding alters the estradiol and/or steroidogenic pathways (Patel 2017). This also, results into adverse effects on ovarian functions in various species (Cheetah: Cabaton *et al*., 2011; Rodents: Setchell *et al*., 1987; Ewes: Mustonen *et al*., 2014).

Another molecular action of GEN is by inhibiting the tyrosine-protein kinase (Makarevich *et al*., 1997) receptors. The consequence of this inhibition again results into a dose-dependent blockade of the *in vitro* maturation of oocytes at the germinal vesicle stage (Mouse: Makarevich *et al*., 1997; Porcine: Jung *et al*., 1993; Cattle: Borzym *et al*., 2008), somatic cell inhibition at G2/M stage of the cell cycle (Mukherjee *et al*., 2010) and inhibition of the cumulus cell expansion in the oocytes (Mouse: Tirone *et al*., 1997; Porcine: Ježová *et al*., 2001). The reason attributed to the inhibition of cumulus cell expansionmightalso be due to blocking the functions of epidermal growth factor (EGF) receptors as well as the hormone, FSH (Procházka *et al*., 2003).

In addition to the above molecular mechanisms of GEN, it also inhibits DNA topoisomerase II (Markovits *et al*., 1989), S6 kinase (Linassier *et al*., 1990) protein kinase (A and C) (Van and Alexandre, 2000) and aromatase (Bolego *et al*., 2003).

Daidzein (DZN)

Similarto Genistein, DZN is another phyto-estrogenic bioactive compound. DZN is also a potential endocrine-disrupting chemical that causes severe developmental and reproductive disturbances in many species (Setchell *et al*., 1987). For instance, in rats, DZN exerts an anti-implantation effect. DZN executes this effect by causing a disturbance in the hypothalamic-pituitary-ovarian axis (Wu *et al*., 2005). Yet another instance, DZN shows its negative effect on mouse oocytes transition state. Where, DZN, stops the transition of the oocyte from germinal vesicle (GV) stage to metaphase I (MI) (Van and Alexandre, 2000). Indeed, this negative effect was exerted at a concentration of 50, 100 and 200 µM of DZN. Similarly, in a report byYoshida and Mizuno (2012) also revealed a DZN triggered inhibition on mouse oocytes at a concentration of 100 µM. However, the protective effect from DZN was observed at the concentrations of 5 and 25µM.

Furthermore, in porcine, DZN causes reproductive disorders (Wu *et al*., 2005). These effects are observed in the porcine either by inhibiting the granulosa cell functions there by hampering 3-hydroxysteroid dehydrogenase enzyme (3-HSD) and/or the steroidogenic activity (Tiemann *et al*., 2007). The above perturbance further affects the nuclear and cytoplasmic maturation rates of oocytes

during *in-vitro* maturation (IVM). These effects were observed at a concentration of 10 µg/ml (40 µM) for partial inhibitionwhile forcomplete inhibition the concentrationof DZN is 20 µg/ml (80µM) (Galeati *et al*., 2009). Likewise, DZN hampers progesterone production inthe cumulus cells of the oocyte cultures (48 hrs) as well as primary cultures of porcine granulosa cells at a concentration of 1 and 10 µM (Tiemann *et al.,* 2007; Nynca *et al.,* 2009).

At the molecular level DZN exerts its action either by interfering in the estrogen signaling mechanism and/or disrupting the endocrines (Yoon *et al*., 2014). This ultimately limits the free as well as the biologically active form of estrogen (Talsness *et al*., 2015). This perturbance is mainly due to binding of DZN to the estrogen receptors (ERα and ERβ) (Casanova *et al*., 1999). Furthermore, research reports revealed that DZN also carry-out its action through the induction of steroid-binding globulin *in vivo* (Adlercreutz *et al*., 1987) and/or inhibition of aromatase enzyme for the conversion of estradiol from androstenedionein the cultures of human granulosa cells (Lacey *et al*., 2005; Rice *et al*., 2006).

Resveratrol (REV)

REV is a naturally available polyphenolic and stilbene bioactive compound (Ortega and Duleba 2015). REV exerts a dose-dependent molecular events in the ovaries (Liu *et al*., 2013). Supplementation of REV at a concentration of 2 µMinto the culture mediumsof follicle, oocyte and granulosa cells increases the blastocyst formation with a decrease in the pro-apoptotic genes such as Bax, Bak and caspase 3 (swine: Kwak *et al*., 2012; bovine: Wang *et al*., 2014; caprine: Mukherjee *et al*., 2014, Ovine: Wang *et al*., 2012).

The administration of REV shows a protective effect on the ovarian reserveofgerm cell and follicular pool reserve (Liu *et al*., 2013). Moreover, it can keep the primordial follicles in a quiescent state possibly through the regulation of FOXO3a (Forkhead box class O 3a) and SIRT1 (NAD-dependent deacetylase sirtuin1) genes. However, it may delay the oocyte nest breakdown (Luo *et al*., 2012). Furthermore, activation of SIRT1 by REV results in a significant increase in the LH receptors in the granulosa cells (Morita *et al*., 2012).

Aside from this, REV also have its effect on key enzymes involving the ovarian functions. It is an effective stimulator for StAR, LH receptor, SIRT1 and P450 aromatase genes which are involved in the process of steroidogenesis (Su *et al*., 2012). However, it is an inhibitor for the enzyme aromatase which could results in impaired folliculogenesis due to a decrease in estrogen synthesis (Ortega *et al*., 2012). Further, REV can enhance the ovulation rate by binding with the estrogen receptors because of the high affinity for estrogen receptor (ERβ) (Singh *et al*., 2011),

Besides, REV decreases the expression of vascular endothelial growth factor (VEGF) in the granulosa cells of rat and swine (Ortega *et al*., 2012). It should be noted that VEGF is involved in the process of ovarian folliculogenesis (Araujo *et al*., 2013). Similarly, REV decreases the pro-inflammatory cytokines (TNF-a, IL-6) and DNA fragmentation. This further helps in the cessation of apoptosis in the granulosa cells and oocytes of rat *in vitro* cultures (Zhao *et al*., 2013).

CONCLUSION

Plants are used to treat reproductive disorders from ancient times both in the animals and humans. Phytochemicals (bioactive compounds) present in the plants is an alternate and cheap source of drug against many infertility disorders. Though, plants and/or phytochemicals having a medicinal value, need scientific validation in terms of dosage if it is to be used. Hence, phyto-bioactive compound study is needed in terms of its effective dosage (positive and negative), molecular targets (*in vitro* and *in vivo*) in various species. Thus, this present review summarizes the importance and potential phytochemicals as well as bioactive compounds and its effects on ovarian functions. This further, help in designing plant-based drugs in terms of safety, efficacy and availability against many infertility disorders.

REFERENCES

Ader, P., Wessmann, A. and Wolffram, S. (2000). Bioavailability and metabolism of the flavonol quercetin in the pig, Free Radical Biology and Medicine. 28(7): 1056-1067.

Adlercreutz, H., Hockerstedt, K., Bannwart, C., Bloigu, S., Hamalainen, E., Fotsis, T. and Ollus, A. (1987). Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). Journal of Steroid Biochemistry. 27: 1135-1144.

Aksak, K.S., Toktay, E., Unal, D., Selli, J., Karamese, M., Malkoc, I. (2015). The protecttive effect of beta-carotene against ischemia/ reperfusion injuryin rat ovarian tissue. Acta Histochemistry 117(8): 790-797.

Alasvand, M., Assadollahi, V., Ambra, R., Hedayati, E., Kooti, W. and Peluso, I. (2019). Antiangiogenic effect of Alkaloids. Oxidative Medicine and cellular Longevity. 1-16.

Araujo, V.R., Duarte, A.B., Bruno J.B, Pinholopes, C.A. and Defigueiredo, J.R. (2013). Importance of vascular endothelial growth factor (VEGF) in ovarian physiology of mammals. Zygote. 21: 295-304.

Arellano-Rodriguez, G., Meza-Herrera, C.A., Rodriguez-Martinez, R., Dionisio-Tapia R., Hallford, D.M., Mellado, M. and Gonzalez-Bulnes, A. (2009). Short-term intake of β-carotene-supplemented diets enhances ovarian function and progesterone synthesis in goats. Journal of Animal Physiology and Animal Nutrition (Berl). 93: 710-715.

Atanasov, A.G., Waltenberger, B., Pferschy-Wenzig, E.-M., Linder, T., Wawrosch, C. and Uhrin, P. (2015). Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnology Advances. 33: 1582-1614.

Barlas, N., Ozer, S. and Karabulut, G. (2014). The estrogenic effects of apigenin, phloretin and myricetin based on uterotrophic assay in immature wistar albino rats. Toxicology letters. 226: 35-42.

Beazley, K.E. and Nurminskaya, M. (2016). Effects of dietary quercetin on female fertility in mice: Implication of transglutaminase 2. Reproduction, Fertility and Development. 28(7): 974-981.

Belen, G.S.A., Angeles Martin M., Bravo L., Goya L., Ramos S. (2012). Quercetin modulates Nrf2 and glutathione-related defenses in HepG2 cells: Involvement of p38. Chemico-Biological Interactions. 195(2): 154-164.

Bellik, Y., Boukraa, L., Alzahrani, H.A., Bakhotmah, B.A., Abdellah, F., Hammoudi, S.M., Iguer. Ouada, M. (2012). Molecular mechanism underlying anti-inflammatory and anti-allergic activities of phytochemicals: an update, Molecules. 18(1). 322- 353.

Bertoncini, C.R., Meneghini, R. and Tolentino, H. (2010). Nearest-neighbor nitrogen and oxygen distances in the iron (II)-DNA complex studied by extended X-ray absorption fine structure. Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy. 77(4): 908-10.

Bolego C., Poli A., Cignarella A., Paoletti R. (2003). Phytoestrogens: pharmacological and therapeutic perspectives. Current Drug Targets. 4: 77-87.

Borzym, E., Bobowiec, B., Kosior-Korzecka, U., Martelli, F., Burmaczuk, A. (2008). Disturbance of cow oocyte maturation by phytoestrogens. Medycyna Weterynaryjna. 64: 1107-1111.

Burton, J.L. and Wells, M. (2002). The effect of phytoestrogens on the female genital tract. Journal of Clinical Pathology. 55: 401-407.

Bush, T.L, Barrett-Connor E., Cowan, L.D., Criqui, M.H., Wallace R.B., Suchindran, C.M., Tyroler, H.A., Rifkind, B.M. (1987). Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation. 75(6): 1102-1109.

Cabaton, N.J., Wadia, P.R., Rubin, B.S., Zalko, D., Schaeberle, C.M., Askenase, M.H., Gadbois, J.L., Tharp, A.P., Whitt, G.S., Sonnenschein, C., Soto, A.M. (2011). Perinatal exposure to environmentally relevant levels of bisphenol A decreases fertility and fecundity in CD-1 mice. Environmental Health Perspectives.119: 547-552.

Calabrese, E.J., Baldwin, L.A. (1997). A quantitatively-based methodology for the evaluation of chemical hormesis. Human and Ecological Risk Assessment. 3: 545-554.

Carbonel, A.A.F., Simões, R.S,, Girão, J.H.C., Sasso, G.R.S., Bertoncini, C.R.A., Sorpreso, I.C.E.S., Junior, J.M., Simões, M.J. and Baracat, E.C. (2018). Isoflavones in gynecology. Revista da Associação Médica Brasileira. 64(6): 560-564.

Carbonell-Capella, J.M., Buniowska, M., Barba, F.J., Esteve, M.J. and Frígola, A. (2014). Analytical methods for determining bioavailability and bio-accessibility of bioactive compounds from fruits and vegetables: a review. Comprehensive Reviews in Food Science and Food Safety. 13(2): 155-171.

Casanova, M., You, L., Gaido, K.W., Archibeque-Engle, S., Janszen, D.B. and Heck, H.A. (1999). Developmental effects of dietary phytoestrogens in SpragueDawley rats and interactions of genistein and daidzein with rat estrogen receptors alpha and beta *in-vitro*. Toxicological Sciences. 51: 236-244.

Chen, S.L., Yu, H., Luo, H.M., Wu, Q., Li, C.F., and Steinmetz, A. (2016). Conservation and sustainable use of medicinal plants: problems, progress and prospects. Chinese Medicine. 11: 37.

Choi, E.M. (2011). Kaempferol protects MC3T3 E1 cells through anti oxidant effect and regulation of mitochondrial function. Food and Chemical Toxicology. 49(8): 1800-1805.

Choi, Y.H., Lee, W.H., Park, K-Y and Zhang, L. (2000). P^{53}-independent induction of P^{21} (WAf1/C1P1), reduction of cyclin B1 and G2/arrest by the isoflavone in human prostate carcinoma cells. 2000. Japanese Journal of Cancer Research. 91: 164-173.

Dalal, K.C. (1992). Presents status and perspectives of medicinal plants. Journal of Resear'ch and Education in Indian Medicine. 9: 15-20.

De Bie, J., Langbeen, A., Verlaet, A.A.J., Florizoone, F., Immig, I., Hermans, N., Fransen, E., Bols, P.E.J., Leroy, J.L.M.R. (2016). The effect of a negative energy balance status on β-carotene availability in serum and follicular fluid of nonlactating dairy cows. Journal of Dairy Science 99: 5808-5819.

De-Bruin, J.P., Dorland, M., Spek, E.R., Posthuma, G., Van Haaften, M., Looman, C.W. and te Velde, E.R. (2002). Ultrastructure of the resting ovarian follicle pool in healthy young women. Biology of Reproduction. 66: 1151-60.

Devi, K.P., Rajavel, T., Habtemariam, S., Nabavi, S.F., Nabavi, S.M. (2015). Molecular mechanisms underlying anticancer effects of myricetin. Life Sciences. 142: 19-25.

Galeati, G., Vallorani, C., Bucci, D., Bernardini, C., Tamanini, C., Parmeggiani, A., Spinaci, M. (2014). Daidzein does affect progesterone secretion by pig culumus cells but it does not impair oocytes IVM. Theriogenology. 74: 451-457.

Ghasemzadeh, A. and Ghasemzadeh, N. (2011). Flavonoids and phenolic acids: Role and biochemical activity in plants and human. Journal of Medicinal Plants Research. 5: 6697-6703.

Gökmen, V. (2015). Acrylamide in Food: Analysis, Content and Potential Health Effects. Elsevier. (1st Ed.). Academic press. pp.532.

Guaadaoui, A., Benaicha, S., Elmajdoub, N., Bellaoui, M. and Hamal, A. (2014). What is a bioactive compound? A combined definition for a preliminary consensus. International Journal of Food Science and Nutrition. 3(3): 174-179.

Guo, Z., Liao, Z., Huang, L., Liu, D., Yin, D., and He, M. (2015). Kaempferol protects cardiomyocytes against anoxia/reoxygenation injury via mitochondrial pathway mediated by SIRT1. European Journal of Pharmacology. 761: 245-253.

Haila, K.M., Nielsen, B.R., Heinonen, M.I., Skibsted, L.H. (1997). Carotenoid reaction with free radicals in acetone and toluene at different oxygen partial pressures. European Food Research and Technology. 204: 81-87.

Hamsa, T.P. and Kuttan, G. (2010). Harmine inhibits tumour specific neo-vessel formation by regulating VEGF, MMP, TIMP and pro-inflammatory mediators both *in vivo* and *in vitro*, European Journal of Pharmacology. 649 (1-3): 64-73.

Harborne, J.B. (1999). Classes and Functions of Secondary Products. In: [Walton NJ, Brown DE, (editors.)] Chemicals from Plants, Perspectives on Secondary Plant products. Imperial College Press. 1-25.

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

Hirch, K., Atzmon, A., Danielenko, M., Sharoni, Y. (2007). Lycopene and other carotenoids inhibit estrogenic activity of 17beta-estradiol and genistein in cancer cells. Breast Cancer Research and Treatment. 104: 221-230.

Huang, H., Chen, A.Y., Rojanasakul, Y., Ye, X., Rankin, G.O., Chen, Y.C (2015). Dietary compounds galangin and myricetin suppress ovarian cancer cell angiogenesis. Journal of Functional Foods. 1(15): 464-475.

Hung, H. (2007). Dietary quercetin inhibits proliferation of lung carcinoma cells. In Nutrigenomics-Opportunities in Asia. Karger Publishers. 60: 146-157.

Jadwiga, J.L. and Kujawska, M. (2020). Bi-phasic dose response induced by phytochemicals: Experimental evidence. Journal of Clinical Medicine. 9(3): 718.

Jamwal, K., Bhattacharya, S. and Puri, S. (2018). Plant growth regulator mediated consequences of secondary metabolites in medicinal plants. Journal of Applied Research on Medicinal and Aromatic Plants: 9: 26-38.

Ježová, M., Scsuková, S., Nagyová, E., Vránová, J., Procházka, R., Kolena, J. (2001). Effect of intraovarian factors on porcine follicular cells: cumulus expansion, granulosa and cumulus cell progesterone production. Animal Reproduction Science. 65: 115-126.

Jha. M., Ganesh. N., Sharma. V. (2010). *In vitro* evaluation of free radical scavenging activity of Pistiastratiotes. Asian Pac. J. Trop. Dis. 2(1): 180-184.

Johnson, E.J. (2002). The role of carotenoids in human health. Nutrition in Clinical Care. 5: 56-65.

Jung T., Fulka, J. Jr., Lee, C., Moor, R.M. (1993): Effects of the protein phosphorylation inhibitor genistein on maturation of pig oocytes *in vitro*. Journal of Reproduction and Fertility. 98: 529-535.

Kang, K.A., Wang, Z.H., Zhang, R., Piao, M.J., Kim, K.C., Kang, S.S., Kim, Y.W., Lee, J., Park, D. and Hyun, J.W. (2010). Myricetin protects cells against oxidative stress-induced apoptosis via regulation of PI3K/Akt and MAPK signaling pathways. International journal of molecular sciences. 11(11): 4348-4360.

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-Australian Journal of Animal science. 29: 352-358.

Kaurinovic, B., Vastag, D. (2019). Flavonoids and Phenolic Acids as Potential Natural Antioxidants. In Antioxidants; Shalaby, E., Ed.; Intech Open: London, UK.

Kendig, E.L., Le, H.H., Belcher, S.M. (2010). Defining hormesis: Evaluation of a complex concentration response phenomenon. International Journal of Toxicology. 29: 235-246.

Kim, J.D., Liu, L., Guo, W., Meydani, M. (2006). Chemical structure of flavonols in relation to modulation of angiogenesis and immune-endothelial cell adhesion. The Journal of Nutritional Biochemistry. 17(3): 165-176.

Kim, B.W., Lee, E.R., Min, H.M., Jeong, H.S., Ahn, J.Y., Kim, J.H., Cho, S.G. (2008). Sustained ERK activation is involved in the kaempferol induced apoptosis of breast cancer cells and is more evident under 3 D culture condition. Cancer Biology and Therapy. 7(7): 1080-1089.

Kim, S.H. and Choi, K.C. (2013). Anti-cancer Effect and Underlying Mechanism(s) of Kaempferol, a Phytoestrogen, on the Regulation of Apoptosis in Diverse Cancer Cell Models. Toxicological Research. 29(4): 229-234.

Krazeisen, A., Breitling, R., Möller, G., Adamski, J. (2001). Phytoestrogens inhibit human 17β-hydroxysteroid dehydrogenase type 5. Molecular and Cellular Endocrinology. 171(1-2): 151-162.

Kuiper, G.G., Carlsson, B., Grandien, K., Enmark, E., Haggblad, J., Nilsson, S., Gustafsson, J.A. (1997). Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 138: 863-870.

Kwak, S.S., Cheong, S.A., Jeon, Y., Lee, E., Choi, K.C., Jeung, E.B., Hyun, S.H. (2012). The effects of resveratrol on porcine oocyte *in vitro* maturation and subsequent embryonic development after parthenogenetic activation and *in vitro* fertilization. Theriogenology. 78: 86-101.

Lacey, M., Bohday, J., Fonseka, S.M.R., Ullah, A.I. and 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.

Linassier, C., Pierre, M., Lepecq, J.B., Pierre, J. (1990). Mechanisms of action in Nih-3t3 cells of genistein, an inhibitor of EGF receptor tyrosine kinase-activity. Biochemical Phramacology. 39: 187-193.

Liu, R.H. (2004). Potential synergy of phytochemicals in cancer prevention: Mechanism of action. Journal of Nutrition. 134: 3479S-3485S

Liu, M., Yin, Y., Ye, X., Zeng, M., Zhao, Q., Keefe, D.L, (2013). Resveratrol protects against age-associated infertility in mice. Human Reproduction. 28: 707-17.

Lopez-flores, N.M., Meza-herrera, C.A., Galan-soldevilla, C., Bautista-rodriguez, D.A., Veliz-deras, F.G., Arellano-rodriguez, G., Garcia-de la Peña, C., Rosales-nieto, C.A., Macias-cruz, U. (2018). The key role of targeted beta-carotene supplementation on endocrine and reproductive outcomes in goats: Follicular development, ovulation rate and the GH-IGF-1 axis. Small Ruminant Research. 163: 29-33.

Lu, D.F., Yang, L.J., Wang, F. and 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, L.L., Chen, X.C., Fu, Y.C., Xu, J.J., Li, L., Lin, X.H., (2012). The effects of caloric restriction and a high-fat diet on ovarian lifespan and the expression of SIRT1 and SIRT6 proteins in rats. Aging Clinical and Experimental Research. 24: 125-33.

Manohar, M., Fatima, I., Saxena, R., Chandra, V., Sankhwar, P.L., and Dwivedi, A. (2013). (-)-Epigallocatechin-3-gallate induces apoptosis in human endometrial adenocarcinoma cells via ROS generation and p38 MAP kinase activation. Journal of Nutritional Biochemistry. 24(6): 940-947.

Makarevich A, Sirotkin A, Taradajnik T, Cherenek P. (1997). Effects of genistein and lavendustin on reproductive processes in domestic animals *in vitro*. J. Steroid Biochem Mol. Biol. 63: 329-37.

Markovits, J., Linassier, C., Fosse, P., Couprie, J., Pierre, J., Jacqueminsablon, A., Saucier, J.M., Lepecq, J.B., Larsen, A.K. (1989). Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase-Ii. Cancer Research. 49: 5111-5117.

Mbemyaa, G.T., Vieiraa, L., Canafistulaa, F.G., Pessoab, O.D.L., Rodrigues, A.P.R. (2017). Reports on *in vivo* and *in vitro* contribution of medicinal plants to improve the female reproductive function, Reprodução and Climatério. 32(2): 109-119.

Medigovic, I., Ristic, N., Trifunovic, S., Manojlovic-stojanoski, M., Milosevic, V., Zikic, D., Nestorovic, N. (2012). Genistein affects ovarian folliculogenesis: a stereological study. Microscopy Research and Technique. 75: 1691-1699.

Merhan, O., Özcan A., Atakİsİ, E., Öğün, M., Kükürt, A. (2016). The effect of β-carotene on acute phase response in di-ethylnitrosamine given rabbits. Kafkas Universitesi Veteriner Fakultesi Dergisi. 22: 533-537.

Meza-Herrera, C.A., Vargas-beltran, F., Tena-sempere, M., González-bulnes, A., Macias-cruz, U., Veliz-deras, F.G. (2013). Short-term beta-carotene-supplementation positively affects ovarian activity and serum insulin concentrations in a goat model. Journal of Endocrinological Investigation. 36: 185-189.

Min, J.K., Han, K.Y., Kim, E.C. (2004). Capsaicin inhibits *in vitro* and angiogenesis, Cancer Research. 64(2): 644-651.

Moiseeva, E.P., Almeida, G.M., Jones, G.D., Manson, M.M. (2007). Extended treatment with physiologic concentrations of dietary phytochemicals results in altered gene expression, reduced growth and apoptosis of cancer cells. Molecular Cancer Therapeutics. 6(11): 30713079.

Morita, Y., Wada-hiraike, O., Yano, T., Shirane, A., Hirano, M., Hiraike, H. (2012). Resveratrol promotes expression of SIRT1 and StAR in rat ovarian granulosa cells: an implicative role of SIRT1 in the ovary. Reproductive Biology and Endocrinology. 10: 14.

Monika, S. and Susanne. H. (2006) Phytochemicals in Fruit and Vegetables: Health Promotion and Postharvest Elicitors, Critical Reviews in Plant Sciences. 25(3): 267-278.

Mukherjee, S., Acharya, B.R., Bhattacharyya, B., Chakrabati, G. (2010). Genistein arrests cell cycle progression of A549 cells at the G2/M phase and depolymerizes interphase microtubules through binding to a unique site of tubulin. Biochemistry. 49: 1702-1712.

Mukherjee, A., Malik, H., Saha, A.P., Dubey, A., Singhal, D.K., *et al.* (2014). Resveratrol treatment during goat oocytes maturation enhances developmental competence of parthenogenetic and hand-made cloned blastocysts by modulating intracellular glutathione level and embryonic gene expression. Journal of Assisted Reproduction and genetics. 31: 229-239.

Mustonen, E., Taponen, S. andersson, M., Sukura, A., Katila, T., Taponen, J. (2014). Fertility and growth of nulliparous ewes after feeding red clover silage with high phyto-oestrogen concentrations. Animal. 8 (10): 1699-1705.

Myllymaki, S., Haavisto, T., Vainio, M., Toppari, J., Paranko, J. (2005). *In vitro* effects of diethylstilbestrol, genistein, 4-tert-butylphenol and 4-tert-octylphenol on steroidogenic activity of isolated immature rat ovarian follicles. Toxicology and applied pharmacology. 204(1): 69-80.

Naeem, M., Khan, M.M.A., Moinuddin. (2011). Triacontanol-mediated regulation of growth and other physiological attributes, active constituents and yield of Mentha arvensis L. Plant Growth Regulation 65: 195-206.

Naseer, Z, A.E., Epikmen, E.T., Uçan, U., Boyacioglu, M., Ipek, E., Akosy, M. (2017). Quercetin supplemented diet improves follicular development, oocyte quality and reduces ovarian apoptosis in Tarazona during summer heat stress. Theriogenology. 96: 136-141.

Nishino, A., Yasui, H., Maoka, T. (2017). Reaction and scavenging mechanism of β-carotene and zeaxanthin with reactive oxygen species. Journal of Oleo Sciences. 66: 77-84.

Nynca, A., Jablonska, O., Slomczynska, M., Petroff, B.K., Ciereszko, R.E. (2009). Effects of phytestrogen daidzein and estradiol on steroidogenesis and expression of estrogen receptors in porcine luteinized granulosa cells from large follicles. Journal of Physiology and pharmacology. 60(2): 95-105.

Oliveira, R.C., Guerreiro, B.M., Morais J.N.N., Araujo, R.L., Pereira, R.A., Pereira, M.N. (2015). Supplementation of prepartum dairy cows with β-carotene. Journal of Dairy Science. 98(9): 6304-6314.

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

Ortega, I., Wong, D.H., Villanueva, J.A., Cress, A.B., Sokalska, A., Stanley, S.D., Duleba, A.J. (2012). Effects of resveratrol on growth and function of rat ovarian granulosa cells, Fertility and Sterility. 98:1563-1573.

Ortega, Israel, Duleba, Antoni. (2015). Ovarian actions of resveratrol. Annals of the New York Academy of Sciences. 1348: 86-96.

Ott, M., Gogvadze, V., Orrenius, S. and Zhivotovsky, B. (2007). Mitochondria, oxidative stress and cell death. Apoptosis. 12(5): 913-922.

Oz, A.T., Kafkas, E. (2017). Phytochemicals in fruits and vegetables. In: Waisundara V. Superfood and functional food. London: Intech Open. 2017. p175-184.

Parvaresh, A., Razavi, R., Rafie, N., Ghiasvand, R., Pourmasoumi, M. and 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.

Patel, S., Peretz, J., Pan, Y.X., Helferich, W.G., Flaws, J.A. (2016). Genistein exposure inhibits growth and alters steroidogenesis in adult mouse antral follicles. Toxicology and Applied Pharmacology. 293: 53-62.

Patel, Shreya, A. (2017). The effects of adult exposure to genistein on female reproductive outcomes. Doctoral thesis. http://hdl.handle.net/2142/97673.

Pelissero, C., Lenczowski, M.J., Chinzi, D., Cuisset-Davail, B., Sumpter, P., Fostier, A. (1996). Effects of flavonoids on aromatase activity, an *in vitro* study. The Journal of Steroid Biochemistry and Molecular Biology. 57: 215-23.

Procházka, R., Kalab, P., Nagyová, E. (2003). Epidermal growth factor-receptor tyrosine kinase activity regulates expansion of porcine oocyte-cumulus cell complexes *in-vitro*. Biology of Reproduction. 68: 797-803.

Pysz, K., Leszczyñska, T., Kopeć, A. (2016). Intake of vitamin C, β-carotene and polyphenolic compounds by children and adolescents from orphanages. Journal of the American College of Nutrition. 35:75-85.

Ricci, A.G., Olivares, C.N., Bilotas, M.A., Bastón, J.I., Singla, J.J., Meresman, G.F., Barañao, R.I. (2013). Natural therapies assessment for the treatment of endometriosis, Human Reproduction. 28(1): 178-188.

Rice, S., Mason, H.D. and Whitehead, S.A. (2006). Phyto-estrogens and their low dose combinations inhibit mRNA expression and activity of aromatase in human granulosaluteal cells. Journal of Steroid Biochemistry and Molecular Biology. 101: 216-225.

Roth, Z., Aroyo, A., Yavin, S. and Arav, A. (2008). The antioxidant epi-gallocatechin gallate (EGCG) moderates the deleterious effects of maternal hyperthermia on follicle-enclosed oocytes in mice. Theriogenology. 70: 887-897.

Roychoudhary, S., Sharma, R., Sikka, S. (2016). Diagnostic application of total antioxidant capacity in seminal plasma to assess oxidative stress in male factor infertility. Journal of Assisted Reproduction and Genetics. 33: 627-635.

Sagar, S.M., Yance, D. and Wong, R.K. (2006). Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-part 1, Current Oncology. 13(1): pp. 14-26.

Santini, S.E., Basini, G., Bussolati, S. and Grasselli, F. (2009). The phytoestrogen quercetin impairs steroidogenesis and angiogenesis in swine granulosa cells *in vitro*. Bio Medical Research International. Article ID 419891.

Santos, J.M.S., Lins, T.L.B.G., Barberino, R.S., Menezes, V.G., Gouveia, B.B., Matos, M.H.T. (2019). Kaempferol promotes primordial follicle activation through the phosphatidylinositol 3-kinase/protein kinase B signaling pathway and reduces DNA fragmentation of sheep preantral follicles cultured *in vitro*.Molecular Reproduction and Development. 86(3): 319-329.

Saw, C.L.L., Guo, Y., Yang, A.Y., Paredes Gonzalez, X., Ramirez, C., Pung, D. and Kong, A. N. (2014). The berry constituents quercetin, kaempferol and pterostilbene synergistically attenuate reactive oxygen species: Involvement of the Nrf2 ARE signaling pathway. Food and Chemical Toxicology. 72: 303-311.

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.

Seo, Y.J., Kim, B.S., Chun, S.Y., Park, Y.K., Kang, K.S., Kwon, T.G. (2011). Apoptotic effects ofgenistein, biochanin-A and apigeninon LNCaP and PC-3 cells by p21 through transcriptional inhibition of polo-like kinase-1. Journal of Korean Medical Science. 26: 1489-1494.

Setchell, K.D., Gosselin, S.J., Welsh, M.B., Johnston, J.O., Balistreri, W.F., Kramer, L.W., Dresser, B.L., Tarr, M.J. (1987). Dietary estrogens-a probable cause of infertility and liver disease in captive cheetahs. Gastroenterology. 93: 225-233.

Shi, L., Yang, F., Luo, F. (2016). Evodiamine exerts anti-tumor effects against hepatocellular carcinoma through inhibiting β-catenin-mediated angiogenesis, Tumor Biology. 37(9): 12791-12803.

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 Bao. 46: 051-1057.

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.

Singh, M., Parent, S., Leblanc, V., Asselin, E. (2011). Resveratrol modulates the expression of PTGS2 and cellular proliferation in the normal rat endometrium in an AKT-dependent manner. Biology of Reproduction. 84: 1045-52.

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

Spinaci, M., Volpe, S., De, Ambrogi, M., Tamanini, C., Galeati, G. (2008). Effects of epigallocatechin-3-gallate (EGCG) on *in vitro* maturation and fertilization of porcine oocytes. Theriogenology. 69: 877-885.

Su, E.J., Xin, H., Monsivais, D. (2012). The emerging role of estrogen receptor-beta in human reproduction. Seminars in Reproductive Medicine. 30: 62-70.

Szczubiał, M. (2015). Effect of supplementation with vitamins E, C and βcarotene on antioxidative/oxidative status parameters in sows during the postpartum period. Polish Journal of Veterinary Sciences. 18: 299-305.

Talsness, C., Grote, K., Kuriyama, S., Presibella, K., Sterner-Kock, A., Poça, K. and Chahoud, I. (2015). Prenatal exposure to the phytoestrogen daidzein resulted in persistent changes in ovarian surface epithelial cell height, folliculogenesis and estrus phase length in adult Sprague-Dawley Rat Offspring, Journal of Toxicology and Environmental Health, Part A. 78(10): 635-644.

Tang, J., Feng, Y., Tsao, S., Wang, N., Curtain, R. and Wang, Y. (2009). Berberine and Coptidisrhizoma as novel antineoplastic agents: a review of traditional use and biomedical investigations, Journal of Ethnopharmacology. 126(1): 5-17.

Tarazona, A.M., Rodriguez, J.I., Restrepo, L.F. and Olivera-Angel, M. (2006). Mitochondrial activity, distribution and segregation in bovine oocytes and in embryos produced *in vitro*. Reproduction in Domestic Animals. 41: 5-11.

Tepper, C.G., Vinall, R.L., Wee, C.B., Xue, L., and Xu, B., Burich, R., Mack, P.C., and White, R.W. (2007). GCP-mediated growth inhibition and apoptosis of prostate cancer cells *via* androgen receptor-dependent and -independent mechanisms. The Prostate. 67: 521-35.

Thayer, K.A., Melnick, R., Burns, K., Davis, D., Huff, J. (2005). Fundamental flaws of hormesis for public health decisions. Environmental Health Perspectives. 113: 1271-1276.

Tiemann, U., Schneider, F., Vanselow, J., Tomek, W. (2007). *In vitro* exposure of porcine granulosa cells to the phytestrogens genistein and daidzein: effects on the biosynthesis of reproductive steroid hormones. Reproductive Toxicology. 24(3- 4): 317-25.

Tirone, E., D'Alessandris, C., Hascall, V.C., Siracusa, G., Salustri, A. (1997). Hyaluronan synthesis by mouse cumulus cells is regulated by interactions between follicle-stimulating hormone (or epidermal growth factor) and a soluble oocyte factor (or transforming growth factor beta1). Journal of Biological Chemistry. 272: 4787-4794.

Touny, L.H., Banerjee, P.P. (2006). Identification of both Myt-1 and Wee-1 as necessary mediators of the p21-independent inactivation of the cdc-2/cyclin B1 complex and growth inhibition of TRAMP cancer cells by genistein. Prostate. 66: 1542-1555.

Tušimová, E., Packová, D., Kováèik, A., Ondruška, ľ., Jurèík, R. and Kolesárová, A. (2017). Possible stimulatory effect of quercetin on secretion of selected pituitary hormones. Scientific Papers Animal Science and Biotechnologies. 50(1): 135-139.

Van, C.A. and Alexandre, H. (2000). Effect of genistein alone and in combination with okadaic acid on the cell cycle resumption of mouse oocytes. The International Journal of Developmental Biology. 44: 409-420.

Wang, Z.G., Yu, S.D., Xu, Z.R. (2007). Improvement in bovine embryo production *in-vitro* by treatment with green tea polyphenols during *in-vitro* maturation of oocytes. Animal Reproduction Science. 100: 22-31.

Wang, Z.H., Kang K, Ah., Zhang, R., Piao, M.J., Jo, S.H., Kim, J.S., Kang, S.S., Lee J.S., Park, D.H., Hyun, J.W. (2010). Myricetin suppresses oxidative stress-induced cell damage *via* both direct and indirect antioxidant action. Environmental Toxicology and Pharmacology. 29: 12-18.

Wang, L., Lin, J., Huang, J., Wang, J., Zhao, Y., Chen, T. (2012). Selection of ovine oocytes by brilliant cresyl blue staining. Journal of Biomedicine and Biotechnology. 2012: 161372.

Wang, F., Tian, X., Zhang, L., He, C., Ji, P., Li, Y., Tan, D., Liu, G. (2014). Beneficial effect of resveratrol on bovine oocyte maturation and subsequent embryonic development after *in vitro* fertilization. Feritily and Sterility. 101: 577-586.

Wang, H., Jo, Y.J., Oh, J. S., and Kim, N. H. (2017). Quercetin delays postovulatory aging of mouse oocytes by regulating SIRT expression and MPF activity. Oncotarget. 8(24): 38631-38641.

Wang, J., Qian, X., Gao, Q., Lv, C., Xu, J., Jin, H. and 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.

Wiegand, H., Boesch-Saadatmandi, C., Regos, I., Treutter, D., Wolffram, S., Rimbach, G. (2009). Effects of quercetin and catechin on hepatic glutathione-S transferase (GST), NAD (P) H quinone oxidoreductase 1 (NQO1) and antioxidant enzyme activity levels in rats. Nutrional Cancer: 61(5): 717-22.

White, M.D., Angiolini, J.F., Alvarez, Y.D., Kaur, G., Zhao, Z.W., Mocskos, E., Bruno, L., Bissiere, S., Levi, V. and Plachta, N. (2016). Long-lived binding of Sox2 to DNA predicts cell fate in the four-cell mouse embryo. Cell. 165: 75-87.

Whitehead, S.A. and Lacey, M. (2000). Protein tyrosine kinase activity of lavendustin A and the phytoestrogen genistein on progesterone synthesis in cultured rat ovarian cells. Fertility and Sterility. 73: 613-619.

Wu, Z., Yang, Y., Chen, Y., Xia, G., Zhang, R. (2005). Effects of subcutaneous administration of daidzein on blastocyst implantation in rats. Food and Chemical Toxicology. 43: 167-72.

Xu, H., Becker, CM., Lui, W.T., Chu, C.Y., Davis, T.N., Kung, A.L., Birsner, A.E., Amato, R.J.D., Man, G.C.W., Wang, C.C. (2011). Green tea epigallocatechin-3-gallate inhibits angiogenesis and suppresses vascular endothelial growth factor C/vascular endothelial growth factor receptor 2 expression and signaling in experimental endometriosis *in vivo*. Fertility and Sterility. 96(4): 1021-1028.

Xu, D., Hu, M.J., Wang, Y.Q. and Cui, Y.L. (2019). Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. Molecules. 24(6): 1123.

Yao, X., Jiang, H., Li, Y.H., Gao, Q., Xu, Y.N., Kim, N.H. (2019). Kaempferol alleviates the reduction of developmental competence during aging of porcine oocytes. Animal Science Journal. 90(11): 1417-1425.

Yavari, M., Naoi, H., Kaedei, Y., Tanihara, F., Namula, Z., Viet, V.L. (2010). Effects of epigallocatechin-3-gallate on the developmental competence of parthenogenetic embryos in the pig. Italian Journal of Animal Science. 9: 386-9.

Yoon, K., Kwack, S.J., Kim, H.S., Lee, B.M. (2014). Estrogenic endocrine-disrupting chemicals: molecular mechanisms of actions on putative human diseases. Journal of Toxicology and Environmental Health, Part B, Critical Reviews. 17: 127-174.

Yoshida, N. and Mizuno, K. (2012). Effect of physiological levels of phytoestrogens on mouse oocyte maturation *in vitro*. Cytotechnology. 64: 241 247.

Yu, S., Zhao, Y., Feng, Y., Zhang, H., Li, L., Shen, W., Zhao, M., Min, L. (2019). β-carotene improves oocyte development and maturation under oxidative stress *in vitro*. *In vitro* Cellular and Developmental Biology. 55: 548-558.

Zhang, Y., Jiang, Q., Wang, N., Dai, B., Chen, Y. and He, L. (2011). Effects of taspine on proliferation and apoptosis by regulating caspase-3 expression and the ratio of Bax/ Bcl-2 in A431 cells, Phytotherapy Research. 25(3): 357-364.

Zhang, S., Guo, Y., Cui, Y., Liu, Y., Yu, T., Wang, H. (2015). Generation of intermediate porcine iPS cells under culture condition favorable for mesenchymal-to-epithelial transition. Stem Cell reviews and Reports. 11: 24-38.

Zhao, X., Ze, Y., Gao, G., Sang, X., Li, B., Gui, S., Lei, S., Sun, Q., Cheng, J., Cheng, Z., Hu, R., Wang, L., Hong, F. (2013). Nanosized TiO2-induced reproductive system dysfunction and its mechanism in female mice. PLoS One. 8(4): e59378.

Zhao, X.B., Qin, Y., Niu, Y.L. and Yang, J. (2018). Matrine inhibits hypoxia/reoxygenation-induced apoptosis of cardiac microvascular endothelial cells in rats via the JAK2/ STAT3 signaling pathway, Biomedicine and Pharmacotherapy. 106: 117-124.

Zhao, Y., Xu, Y., Li, Y., Jin, Q., Sun, J., Zhiqiang, E., Gao, Q. (2019). Supplementation of kaempferol to *in vitro* maturation medium regulates oxidative stress and enhances subsequent embryonic development in vitro. Zygote. 28: 1-6.

Zhou, M., Ren, H., Han, J., Wang, W., Zheng, Q., Wang, D. (2015). Protective effects of Kaempferol against myocardial ischemia/reperfusion injury in isolated rat heart via antioxidant activity and inhibition of glycogen synthase kinase-3. Oxidative Medicine and Cellular Longevity.1-8p.Article ID. 481405.