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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 (down regulation 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 1000 ppm 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, produced 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 that these 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 the bioactive 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 doses are 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 is further 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*.

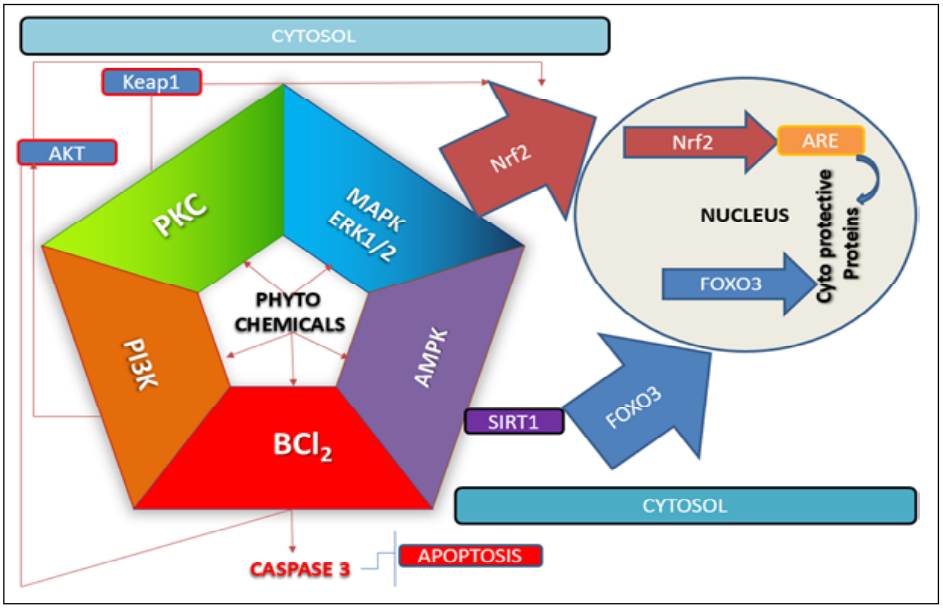

Fig 1: Molecular targets of phytochemicals.

[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 protein 1, 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 is by either 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 further classified into flavonols, flavones, flavanols, anthocyanidins and isoflavonoids (Liu *et al*., 2004). Among them that are bioactive compounds belong to the group of flavonols, flavanols and is oflavonoids that 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). The major bioactive compounds belonging to this group are kaempferol, quercetin, myricetin, galangin and fisetin.

Flavanols

Flavanols mainly contain catechins, epi-catechins and its derivatives. Catechins agents were 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 (10 µg/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 addition of 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 in the 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 0.1 µM 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 1 µM 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).

The molecular 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 development with 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 of human silent information regulator type 1 (SIRT1) gene expression (Guo *et al*., 2015). Likewise, the up regulation of nuclear 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 executed either by reducing the apoptosis (decreasing ROS levels) and/or maintaining a sufficiency in the matrix 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 the follicle 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 increasing cell proliferation, ovarian weight, oocyte quality and litter size with 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 25 µg/ml to the culture 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 culture of 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 by controlling 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-1α 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 1000 ppm 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 to poor 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-dependent kinase 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 80 µg/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 expansion might also 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 to poisomerase 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 by Yoshida 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 25 µM.

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 inhibition while for complete inhibition the concentration of DZN is 20 µg/ml (80 µM) (Galeati *et al*., 2009). Likewise, DZN hampers progesterone production in the 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 androstenedione in 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 µM into the culture mediums of 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 reserve of germ 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-α, 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.

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