GENISTEIN AS RADIOPROTECTIVE AGAINST PREMATURE OVARIAN FAILURE

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Abstract

Radiotherapy is one of the most important strategies in cancer treatment. Seriously, radiotherapy resulted in premature ovarian failure (POF) and infertility. Radiotherapy depends on the generation of reactive oxygen species (ROS) in cancer cells as a result of water radiolysis leading to induction of oxidative stress and diminution of antioxidant defense mechanisms and within this process, healthy tissues are also damaged. Moreover, germ cells seem to be much more susceptible to oxidative stress induced by radiotherapy than somatic cells. Seriously, ROS generated by ionizing radiation are capable of inducing tissue apoptosis by direct and indirect pathways leading to oxidative damage of cellular macromolecules (mainly DNA, proteins and lipids). Curiously, apoptosis was identified as the mechanism responsible for oocyte loss caused by radiotherapy. Soybeans products contain high amounts of isoflavones known as soy phytoestrogens which act as natural selective estrogen receptor modulators (SERMs). The most prominent phytoestrogen in soybean is genistein (GEN), which shows estrogenic properties through estrogen receptor beta (ER-β) binding. GEN has different pharmacological properties through its chemoprotective activity against cancers and cardiovascular diseases. GEN was also reported to protect against acute myelotoxicity, intestinal, lung, and testicular injuries-induced by radiation. The radioprotective effects of GEN was attributed to its antioxidant, anti-apoptotic, anti-inflammatory and anti-fibrotic activities. Concerning its effects on the ovaries, previous report confirmed the protective effect of GEN against ovarian carcinogenesis. Also, GEN slowed down follicular development, considerably improving the ovarian follicular stock and extend the ovarian lifespan. In this context, GEN was documented to delay ovarian ageing and prolong ovarian reproductive life, besides its protective effect against chemotherapy and radiotherapy induced ovarian toxicity.

Keywords: Ovarian failure, radiation, apoptosis, genistein, isoflavones, antioxidant.
The Female Reproductive System
Ovarian anatomy & physiology

Ovaries are two nut sized organs located within the female pelvis. They are attached on either side of the uterus near the opening of the fallopian tube. Ovaries have two main functions; to store and release oocytes (eggs) and to produce hormones. The regularity of the menstrual cycle is controlled by the balance of four hormones; estrogen, progesterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH). How much or how little of each hormone is made at any one time relies on a complicated feedback system between the brain: specifically the hypothalamus and the pituitary gland, which release LH and FSH, the ovaries, and the adrenal glands (Carrell and Peterson, 2010). In order to begin the ovulation process the ovaries begin to produce less estrogen. The drop in estrogen signals the brain to release a hormone called gonadatropin releasing hormone (GnRH). The release of this hormone triggers the production of FSH which helps the eggs to mature in the ovaries. The size of the ovaries declines with age, as does their function (Lebovic et al., 2005). The quality and number of eggs inside the ovaries diminishes with age and they become older and more difficult to be fertilized. Also, with age, the ovaries start to produce less of the female sex hormones estrogen and progesterone. Eventually ovulation and hormone production will stop and this is generally referred to as menopause (Carrell and Peterson, 2010).

Folliculogenesis
During the maturation process the follicle grows and goes through the primordial, primary, secondary and preantral stage before it acquires an antral cavity (Figure 1). At the antral stage most follicles go through atresia, but a few of them reach the pre-ovulatory phase under the influence of gonadotrophins. Following the preovulatory gonadotrophin surge, one dominant follicle will then release a mature oocyte ready for fertilization. While the follicle is still resting it is considered to be in the primordial stage and one layer of flat granulosa cells and a thin basal lamina surrounds the oocyte. Once it gets recruited into the growing phase, it transforms to a primary follicle and the granulosa cells change shape and become cuboidal. Production of proliferating cell nuclear antigen (PCNA) indicates that proliferation of the granulosa cells has started. The secondary follicle is surrounded by two or more layers of granulosa cells. Consequently, the follicle enters the preantral stage and a fluid filled antrum starts to develop. Under the influence of gonadotrophins and growth factors, the follicle grows and the granulosa cells proliferate and finally the pre-ovulatory follicle is formed. The communication between the oocyte and its surrounding granulosa cells results in maturation of a fertilizable oocyte (Gougeon, 1996; McGee and Hsueh, 2000).
Figure 1
Light micrographs of the different follicular stages A: Primordial follicles B: A transitional follicle from the primordial to the primary stage. C: Primary follicle (upper). D: Secondary follicle E: Antral follicle.

What is premature ovarian failure? Definition and causes

Premature ovarian failure (POF) refers to the medical condition where a woman’s ovarian function slows or stops the production of mature eggs and reproductive hormones before the age of 40 (Goswami and Conway, 2005) with FSH levels exceeding 40 IU/L (Conway, 2000). It is characterised by irregular menstrual cycles and eventual cessation of menstruation (amenorrhea) and leaves women with the possibility of infertility and a range of complicated menopausal symptoms due to lowered estrogen levels (hypoestrogenism) (Graziottin and Basson, 2004). Approximately 1% of women younger than 40 years will experience spontaneous POF (Woad et al., 2006). This figure has been suggested as rising up to 8-10% where premature menopause results from surgery, chemotherapy and/or radiotherapy. With improved survival rates of cancer patients treated with chemotherapy and radiotherapy, the incidence of POF is increasing (Abdallah and Muasher, 2006). Some common causes of POF include genetic abnormalities, enzymatic defects, autoimmune diseases, hormone or receptor defects, and various environmental as well as physical causes (Hoek et al., 1997; Rebar, 2005). Women with POF have an increased risk of early morbidity, which is due to several factors. These risk factors include osteoporosis, impaired endothelial function, and cardiovascular disease (Chang et al., 2007). Hormone therapy is the primary treatment offered to patients with POF. This treatment, which replaces some of the estrogen that would normally be produced by the ovaries, helps to alleviate the risks to the cardiovascular system and keeps bone density from dropping too low (Arora and Polson, 2011).

Oxidative stress and female reproduction

Free radical species are unstable and highly reactive. They become stable by acquiring electrons from nucleic acids, lipids, proteins, carbohydrates or any nearby molecule causing a cascade of chain reactions resulting in cellular damage and disease.
There are two major types of free radical species: reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Attaran et al., 2000; Pierce et al., 2004).

**Antioxidants**

Under normal conditions, scavenging molecules known as antioxidants convert ROS to H2O and prevent overproduction of ROS. There are two types of antioxidants in the human body: enzymatic antioxidants and non-enzymatic antioxidants. Enzymatic antioxidants are also known as natural antioxidants, they are composed of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase while non-enzymatic antioxidants are known as synthetic antioxidants or dietary supplements, they include antioxidant vitamins and minerals such as vitamin C, vitamin E, selenium, zinc, taurine, hypotaurine, glutathione, beta carotene and carotene (Van Langendonckt et al., 2002; Agarwal et al., 2003; Pierce et al., 2004).

**Oxidative stress in female reproduction**

Oxidative stress (OS) influences the entire reproductive span of women’s life and even thereafter (i.e. menopause). ROS are a double-edged sword – they serve as key signal molecules in physiological processes but also have a role in pathological processes involving the female reproductive tract. ROS affect a variety of physiologic functions (i.e. oocyte maturation, ovarian steroidogenesis, ovulation, implantation, formation of blastocyst, luteolysis and luteal maintenance in pregnancy) (Vega et al., 1998; Suzuki et al., 1999; Sugino et al., 2000). It plays a role during pregnancy (Myatt and Cui, 2004) and normal parturition (Fainaru et al., 2002; Mocatta et al., 2004) and in initiation of preterm labor (Wall et al., 2002; Pressman et al., 2003). It has been suggested that the age-related decline in fertility is modulated by OS (de Bruin et al., 2002). There is growing literature on the effects of OS in the female reproduction with involvement in the pathophysiology of pre-eclampsia (Van Voorhis et al., 1994; Tsafriri and Reich, 2009), hydatidiform mole (Harma et al., 2003) free radical-induced birth defects (Loeken, 2004) and other situations such as abortions (Lagód et al., 2001). The pathological effects of OS are exerted by various mechanisms including lipid damage, inhibition of protein synthesis, and depletion of ATP (Ray et al., 2004).

**Effect of radiation on ovarian function**

Radiotherapy is one of the most common known causes of POF (Nippita and Baber, 2007). Radiation is more toxic to the ovaries than chemotherapy (Sklar, 2005). Ionizing radiation can cause direct DNA damage to ovarian follicles, leading to follicular atrophy and decreased ovarian follicular reserve. This can hasten the natural decline of follicle numbers, leading to impaired ovarian hormone production, uterine dysfunction due to inadequate estrogen exposure, and early menopause. Although the radiosensitivity of the oocyte is thought to vary during the growth phase, primordial follicles are thought to be more radioresistant than maturing follicles (Ogilvy-Stuart and Shalet, 1993). Several factors have been identified as significant determinants of ovarian failure, including radiation dose, age at the time of radiation exposure, and extent of radiation treatment field (Lushbaugh and Casarett, 1976; Wallace et al., 1989; Bath et al., 1999). The ovaries are very sensitive to radiation with a median lethal dose (LED50) of 2 Gy. Older age at the time of irradiation involves a greater dose related risk.
Mechanism of radiation-induced ovarian damage

1. Oxidative Stress

Generally, the major mechanisms of ovarian injuries include follicle cell apoptosis, oxidative stress, ovarian atrophy, cortical fibrosis and blood-vessel damage (Zhang et al., 2016; Hamzeh et al., 2018). However, radiation causes damage mostly via two pathways; direct and indirect. The direct one is through the ionization of DNA which initiates physiological changes or cell death (Spitz et al., 2004) while the indirect way takes place by the production of ROS (Shirazi et al., 2007), that may damage DNA, proteins, and lipids by acting through radiolysis of water (Hall and Giaccia, 2006). Consequently, many anti-oxidant enzymes compete with the radiation-induced oxidative stress (Navarro et al., 1997), to reduce the transient free radicals and counteract these damaging effects (Borek, 2004). Increased ROS level and decreased antioxidant enzymes activity (such as GPx) combine together to impair the progesterone secretion (Noda et al., 2012) and lead to endometrial epithelium degeneration, and follicle regression (Beltran-Garcia et al., 2000; Devine et al., 2012). As a result, the balance between ROS and the anti-oxidants which is required for ovarian function get disrupted. Moreover, the increased ROS induces rapid primordial follicle loss in the ovaries (Spitz et al., 2004; Devine et al., 2012) and On the other hand, supresses cell proliferation (Dhillon et al., 2014).

2. Radiation induced apoptosis

Accumulating evidence show that excessive ROS generated by irradiation triggers antral follicular atresia by causing granulosa cell apoptosis (Devine et al., 2012). ROS generated by ionizing radiation are capable of inducing tissue apoptosis by direct and indirect pathways leading to oxidative damage of cellular macromolecules (mainly DNA, proteins and lipids). ROS activate the intrinsic mitochondrial pathway of apoptosis via activating tumor suppressor protein (p53) The p53 has been shown to regulate the expression of proapoptotic and antiapoptotic members of the Bcl-2 family such as the anti-apoptotic factor Bcl-2 and the pro-apoptotic factor Bax (Franco et al., 2009) which in turn contribute to disrupting the mitochondrial membrane integrity and the release of cytochrome c into the cytosol, which further activates caspase-9 (Acehan et al., 2002). In the same context, activated caspase-9, in turn, activates the effector caspases-3, 6, and 7 (Nemec and Khaled, 2008). On the other hand, the anti-apoptotic Bcl-2 proteins inhibit the oligomerization of the effector proteins Bax (Ola et al., 2011).

Fertility Preservation Techniques

Pelvic irradiation which is used for the treatment of many cancers has significant consequences for female fecundity. Complete ovarian failure occurs with a dose of 20 Gy in women under 40 years of age and with a dose of only 6 Gy in older women. The mean lethal dose for the human oocyte has been estimated at 2 Gy (Wallace et al., 2003). A typical course of neoadjuvant radiotherapy for rectal cancer would involve a total dose of 45 Gy over 5 weeks to the pelvis, which would result in complete ovarian failure unless other measures are taken.

The resultant decrease in sex steroid and inhibin secretion will decrease their plasma concentrations and subsequently the negative feedback on the hypothalamus and pituitary, resulting in an increase in FSH secretion. The increased FSH secretion may bring about an increased recruitment of preantral follicles to enter the one-way differentiational path of maturation, being further exposed to the gonadotoxic effects of the alkylating agents, ending in an increased, exponential rate of follicular apoptosis and degeneration. GnRH agonist (GnRH-a) acts to suppress ovarian function, creating a quiescent or 'prepubertal' state, and thus could theoretically protect ovarian function during cytotoxic therapy (Blumenfeld et al., 2008).

2. Ovarian Transposition

Ovarian transposition (oophoropexy) is a technique that involves moving the ovaries out of the radiation field so that the direct effects of ionizing radiation are avoided (Sonmezer and Oktay, 2004). Nowadays, it is usually done laparoscopically avoiding a long abdominal incision and a prolonged hospital stay. Placing the ovaries above the pelvic brim and as lateral as possible will place them outside the radiation field. Transposition to this level can be achieved easily without separating the fallopian tubes from their uterine origin. This allows the possibility of spontaneous conception following successful cancer treatment (Ferrari et al., 2009). This ensures that the radiation dose given to the ovaries remains at a minimum. The dose to the transposed ovaries is reduced by approximately 90% to 95% compared to their normal pelvic position. (Spanos et al., 2008). The complications of ovarian transposition include benign ovarian cysts, chronic abdominal pain, adhesions formation, and, rarely, metastases in the transposed ovaries (Morice et al., 2000, 2001).

3. Embryo and Oocyte Cryopreservation.

Patients may elect to delay cancer treatment to undergo one cycle of hormone stimulation, followed by cryopreservation of either a mature oocyte or an embryo (Jeruss and Woodruff, 2009). Embryo cryopreservation is the most successful technique, affording a pregnancy rate of 20% to 30% per transfer of 2 to 3 embryos. (Centers for Disease Control and Prevention; American Society for Reproductive Medicine; Society for Assisted Reproductive Technology, 2006). However, it requires in vitro fertilization and it depends on the availability of a fertile male partner. This technique is associated with the risk of ovarian hyperstimulation syndrome and, for patients with cancer, a delay in their treatment and other potential risks in some cases because of the increased estrogen levels.

Genistein

Sources and health benefits

Certain phytochemicals, namely phytoestrogens, a group of molecules similar in structure to 17β-estradiol and, therefore, are called phytoestrogens (Dixon, 2004), have a non-steroidal structure, but possess a phenolic ring that enables them to bind to the estrogen receptor (ER) (Figure 2). Phytoestrogens elicit beneficial health effects in numerous animal and human studies including treatment and prevention of cardiovascular disease, cancer, hyperlipidemia, osteoporosis, and enhancement of immune function (Sakai and Kogiso, 2008). Isoflavones are the most abundant dietary source of phytoestrogens, the most common food sources of isoflavones are soybeans.
Genistein (4',5,7 trihydroxyisoflavone) is a small polyphenolic compound that belongs to flavonoids, specifically isoflavons. It represents the most abundant form of isoflavones found in soy. It has been studied extensively in the context of hormone-related disease including treatment and prevention of estrogen-responsive cancers, postmenopausal therapies, and cardiovascular pathogenesis (Cappelletti et al., 2006).

![Figure 2 Receptor binding domain similarity of genistein and 17β-estradiol, Taken from Wang et al., (1996).](image)

**Pharmacokinetics**

1. **Absorption and distribution**

   Isoflavones are found in soybeans mostly in their respective glycosylated forms (Xiao, 2008). The term, genistin, refers to the glucoside conjugate form (Figure 3). The term, genistein, refers to the aglycone form of the compound, without having a glycosyl group attached. Although it is genistin that is predominantly present in unprocessed soybeans, fermentation or cooking of soybeans leads to the release of the glucose moiety from genistin to produce genistein (Figure 3) (Dixon and Ferreira, 2002). Once consumed, genistin is converted into the aglycone form (genistein) by the action of β-glucosidases in gut flora before it can be absorbed from the intestinal tract by passive diffusion (Cederroth et al., 2012). An explanation mentioned that flavonoid glycosides show a greater hydrophilicity than their respective aglycones (Brown et al., 1998). glycosides were too polar to be absorbed by cells of the small intestine, so that absorption has to occur in the large intestine after bacterial deconjugation (Griffiths and Barrow, 1972).

![Figure 3 Genistin is hydrolyzed into genistein before absorption into the intestine.](image)
2. Bioavailability

Information concerning the bioavailability of genistein could give insight into the effective dose needed to exert its claimed beneficial health effects. The bioavailability of isoflavones is low, since a single dose of 50 mg of genistein aglycone, leads to a maximum concentration of approximately 2 μM of total genistein in plasma (Manach et al., 2005). In humans, the average time required to reach peak plasma concentration after ingestion of phytoestrogen-enriched food is 4-7 hours for genistein and 8-11 hours for genistin, indicating hydrolysis of the glucose moiety as the rate-limiting step in absorption (Cederroth et al., 2012). The half-life of genistein is 7.77 hours in humans and 2.97 hours in adult male rats (Chang et al., 2000; Setchell et al., 2003).

3. Metabolism and excretion

It is well established that intestinal cells are the major site of metabolism for genistein and not the liver (Setchell, 1998). Genistein is predominantly conjugated in the intestine with glucuronic acid and to a lesser extent with sulfate (Adlercreutz et al., 1995). The sulfate and glucuronide conjugates may also be important as carriers of aglycones to target tissues such as breast and prostate. In target tissues these conjugates may be biologically active or hydrolysed to generate the aglycon (Wong and Keung, 1997). Intestinal bacteria appear to contribute as well to the conversion of genistein to 4-ethylphenol. Oxidative metabolism of genistein catalyzed by cytochrome P450 enzymes in vivo and by liver microsomes in vitro showed the hydroxylated metabolite 3'-OH-genistein (Kulling et al., 2001; Heinonen et al., 2003). Phase II enzymes, such as uridine-5'-diphosphate-glucuronosyl transferase (UDPGT) and sulfotransferase catalyze the genistein conjugation to glucuronide and sulfate conjugates. In urine, genistein is mainly excreted, to a level of approximately 53-76%, as a monoglucuronide and to a much lesser extent as a diglucuronide (12-16%) and as a sulfoglucuronide (2-15%) (Adlercreutz et al., 1995).

Pharmacodynamics

1. Antioxidant activity of genistein

Genistein has been widely used as an antioxidant in a number of studies suggesting a potential property of genistein to scavenge ROS and RNS considerably. Earlier study demonstrated that genistein is able to strengthen the antioxidant defense system of a cell and prevents apoptosis by modulating the expression of various genes and proteins (Ganai et al., 2015). Antioxidant activity of phenolic compounds can be direct, through their activity as free radical scavengers, or indirect as modulators of intracellular pro- and anti-oxidant enzymes (Schewe et al., 2008). Genistein was also reported to increase the expression of antioxidant enzymes such as glutathione peroxidase in human prostate cancer cells and protects these cells against oxidative DNA damage in vitro (Suzuki et al. 2002; Raschke et al. 2006). These findings suggest that pretreatment with genistein prior to irradiation prepares the animals to sustain oxidative stress and thus inhibit radiation-induced cellular damage (Dixit et al., 2012).

2. Antiapoptotic activity of Genistein

Genistein was found to inhibit apoptotic cell death probably by using the same ER-kinase pathway as estrogen (Schreihofe and Redmond, 2009). It was reported that genistein inhibits the mitochondrial-dependent apoptotic pathway especially decreasing
cytochrome c release, thereby resulting in less caspase-3 activation and DNA fragmentation (Qian et al., 2012).

3. **Estrogenic properties of genistein**
   The diphenolic chemical structure of genistein has similarities to the structure of estrogen and so it competes with 17β-estradiol to bind to estrogen receptors (ERs) (Zava and Duwe, 1997). Genistein has a 21-fold greater binding affinity for ERβ over ERα (Kuiper et al., 1998). Estrogenic activity of genistein contributed to many of its biological effects, Genistein has been reported to have beneficial effects for health issues ranging from cancer, cardiovascular diseases, menopause, and osteoporosis.

4. **Radioprotective activity of genistein**
   Radioprotective agents are compounds that are administered before ionizing radiation exposure to reduce the damaging effects (Stone et al., 2004). Because of their potential low toxicity, naturally occurring phytochemicals offer opportunities for development as effective chemopreventive and radioprotective agents (Weiss and Landauer, 2003; Coleman et al., 2004; Sarkar and Li, 2004). Genistein has a number of biological properties that have been associated with radioprotection (Bump and Malaker, 1998). For example, genistein has been shown to have antioxidant, free radical scavenging (Kruk et al., 2005), estrogenic (Valachovicova et al., 2004), antimicrobial (Hong et al., 2006), anti-inflammatory (Verdrengh et al., 2003), and protein tyrosine kinase inhibitory properties (Akiyama et al., 1987) and also affects the production of a variety of cytokines (Dijssselbloem et al., 2004). Genistein has also been reported in clinical trials to reduce the adverse effects of chemotherapy and radiotherapy (Ahmad et al., 2010; Tacyildiz et al., 2010). The protective effects of genistein for radiation-induced injury to the bone marrow were observed in a murine model of acute radiation syndrome, where neutrophils and platelets were protected (Landauer et al., 2003; Davis et al., 2007). Genistein also protected bone marrow progenitor cell populations, thus preventing hematopoietic stem cell pool exhaustion (Davis et al., 2007, 2008). Genistein administration reduced radiation-induced injury in the lung and increased survival from thoracic irradiation in mice (Para et al., 2009). Genistein reduced micronuclei in bone marrow cells and primary lung fibroblasts suggesting a direct reduction of radiation-induced DNA damage (Day et al., 2008; Para et al., 2009; Mahmood et al., 2011). Landauer et al also found genistein to be protective against radiation-induced lethality when administered to normal mice (2003).

5. **Genistein and female fertility**
   A previous study (Zhuang et al., 2010) found that genistein reduced age-related follicular development decline which suggests that genistein inhibits the transition of primordial to primary follicles thus increasing the ovarian reserve. This study reported that rat ovaries exposed to genistein had more primordial follicles and total surviving follicles, and less atresia follicles. The age at which rats cease estrous was also delayed by genistein suggesting that genistein may be beneficial in delaying ovarian decline and increasing ovarian longevity. Chen et al. also revealed that genistein increased ovarian follicular reserve in early aged rats by stepping down the transition from primordial to primary follicle and by depressing follicular atresia (2010). Medigović et al. found that genistein led to ovarian volume increase in immature rats, owing to increased ovarian stroma volume (2012). A previous report confirmed the protective effect of GEN
against ovarian carcinogenesis (Kim et al., 2011) besides its protective effect against chemotherapy-induced ovarian toxicity (Saleh and Mansour, 2016).

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Genistein كواقي ضد الإشعاع في فشل المبيض المبكر

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العلاج الإشعاعي هو أحد أهم الانتباهات في علاج السرطان. يؤدي العلاج الإشعاعي إلى قتل المبيض المبكر (POF) والدم. عند استخدام العلاج الإشعاعي لعلاج الإصابة، يمكن أن تشكل آثار الإشعاع المضادة للاكسدة وتعتبر أن تكون أثر جزء من التفاعلات الناتجة عن الاضطرابات في السيرتولين والدهون مباشرة. بما يؤدي إلى تلف الخلايا الكبدية (الدم الغبلي والبروتينات والدهون) نتيجة للتأكد. يعتبر موت الخلايا المبرمج هو الأليئة المصدرة لفقدان الثدييات الناجح عن علاج السرطان وهو ما يحدث بواسطة الإشعاع. تحتوي منتجات أولويات الصيدلية على كميات عالية من كميات الأسيتامين وأيض المعرق المركبات الأكسدة بالخلايا الجسدية، وتعتبر أن الأكسجين السهلABLE más المركبات الأكسدة المبرمجة (SERMs). يعتبر جينيستين (Genistein) هو الاستروجين الذاتي الأكثر انتشار في كميات الصيدلية والذارين الذي يظهر خصائص استروجينية من الاستروجين (ER-β). يملك جينيستين خصائص كوية مختلفة مما هو من نشاط كيميائيات تخليص الطبيعة الدائمة والإصابات المزمنة والنسيجية وإصابات الخصائص النافية عن الإشعاع. وترعى تأثيرات جينيستين الوليدة في الإشعاع إلى شاشة المضادات الكبدية والمضادات المضادة للالتهاب والمضادات للتلف، وتفتح لتتأثر في الجهاز المبيض، كما يعد جينيستين إضافة للшейخة الجياجية في محزن المبيض. ويعتبر العمر الإنجابي للفشل، بالإضافة إلى تأثيرها الوقائي ضد سمية المبيض الناتجة عن العلاج الكيميائي.