Can Resveratrol Supplementation Reduce Adverse Effects of Metabolic Syndrome on Ovaries?

Resveratrol Desteği, Metabolik Sendromun Overler Üzerindeki Olumsuz Etkilerini Azaltabilir mi?

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ABSTRACT Objective: This study aims to identify the effects of resveratrol administration on ovarian histology and biochemistry in an animal model of metabolic syndrome so that it can be clarified whether this agent with anti-inflammatory, anti-proliferative and anti-oxidant properties can be used to overcome the adverse effects of metabolic syndrome on ovaries. **Material and Methods:** Twenty six female Wistar albino rats were randomly divided into four groups. Group 1 (n=7) served as the control group. Group II (n=7) was fed with pellet chow enriched with resveratrol while group II-I (n=5) received 10% fructose as the drinking water of rats for six months. Group IV (n=7) was treated with pellet chow enriched with resveratrol and tap water fortified with fructose simultaneously for six months. **Results:** Group II rats had significantly lower body weight, omentum weight and standardized ovarian weight (p=0.004, p=0.002, and p=0.001, respectively). Group II rats had significantly lower levels of serum glucose, triglycerides and estradiol (p=0.003, p=0.004 and p=0.003, respectively). Although the number of ovarian follicles tended to be higher in group III rats, this difference was statistically insignificant (p=0.339). Mean follicle diameter was significantly wider while granulosa and theca cell layers were significantly thinner in group II rats (p=0.045, p=0.038 and p=0.044, respectively). **Conclusion:** Resveratrol supplementation improves the anatomical, biochemical, morphological and histomorphometric characteristics of rat ovaries which are affected by metabolic syndrome. Since metabolic syndrome is closely associated with PCOS, resveratrol can be used to reduce insulin resistance and induce weight loss in women with PCOS.

Key Words: Metabolic syndrome X; ovary; polycystic ovary syndrome; resveratrol

ÖZET Amaç: Sunulan çalışma, bir hayvan modelinde oluşturulan metabolik sendromda uygulanan resveratrolün over histolojisini ve biyokimyasını nasıl etkilediğini tespit etmeyi ve anti-inflamatuar, anti-proliferatif ve anti-oksidan özellikleri olan bu ajanın, metabolik sendromun overler üzerindeki olumsuz etkilerini gidermek amacıyla kullanılıp kullanılamayacağını belirlemeyi amaçlamaktadır. **Gereç ve Yöntemler:** Yirmi altı dişi Wistar albino rat, dört gruba ayrılmıştır. Grup 1 (n=7), kontrol grubu olarak kabul edilmiştir. Grup II (n=7), altı ay boyunca resveratrol ile zenginleştirilmiş pellet yemle beslenirken grup III (n=5), aynı süre zarfında içme suyuna karıştırılan %10 fruktoz çözeltisi almıştır. Grup IV (n=7) ise, altı ay boyunca, hem resveratrol ile zenginleştirilmiş pellet yem hem içme suyuna karıştırılmış %10 fruktoz çözeltisi ile beslenmiştir. **Bulgular:** Grup II ratların ortalama vücut, omentum ve standardize over ağırlıkları anlamlı olarak düşüktür (sırasıyla p=0,004, p=0,002 ve p=0,001). Grup II ratların serum glukoz, trigliserit ve östradiol seviyeleri anlamlı olarak düşüktür (sırasıyla p=0,003, p=0,004 ve p=0,003). Grup III ratlarda over folikülü sayısı daha yüksek seyretmeye eğilimli olsa da bu farklılık istatistiksel olarak anlamlı bulunamamıştır (p=0,339). Grup II ratlarda, ortalama over folikül çapı anlamlı olarak daha geniştir ve granulosa ile teka hücre tabakaları anlamlı olarak daha incedir (sırasıyla p=0,045, p=0,038 ve p=0,044). **Sonuç:** Resveratrol desteği, metabolik sendromun etkilediği rat overlerinin anatomik, biyokimyasal, morfolojik ve histomorfometrik özelliklerini olumlu yönde etkilemektedir. Metabolik sendrom, polikistik over sendromu (PKOS) ile yakından ilişkili olduğu için PKOS tanısı konulan kadınlarda insulin direncini azaltmak ve kilo kaybını hızlandırmak amacıyla resveratrol kullanılabilir.

Anahtar Kelimeler: Metabolik sendrom X; over; polikistik over sendromu; resveratrol

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Metabolic syndrome is a combination of medical disorders that, when occur together, increase the risk of developing cardiovascular disease and diabetes mellitus. The prevalence of metabolic syndrome has been estimated as high as 25% in the United States of America. The pathophysiology of metabolic syndrome is extremely complex and has been only partially elucidated. The most important underlying factors are weight, genetics, endocrine disorders, aging and sedentary life style (e.g. low physical activity, excess caloric intake).[1,2]

Polycystic ovary syndrome (PCOS) is amongst the endocrine disorders that are associated with metabolic syndrome. PCOS is the most frequently encountered endocrine and metabolic disease affecting approximately 5% of women at reproductive age. Although different hypotheses have been proposed to explain the pathophysiology of PCOS, the ongoing disagreement about the underlying mechanism indicates that its etiology is multifactorial.[3] In PCOS, the typically enlarged ovaries are characterized by thecal and stromal hyperplasia. This ovarian enlargement is associated with excessive ovarian androgen production and disruption of menstrual cycles. Improvement of ovarian functions, with restoration of ovulation and fertility was observed with surgical reduction of ovarian size and/or partial destruction of ovarian tissues by procedures such as wedge resection and ovarian drilling.[4]

Resveratrol (3,5,4'-trans-trihydroxystilbene) is a natural phytoalexin which is commonly found in grapes, peanuts, mulberries and red wine. This compound has various pharmacological effects including anti-inflammatory, anti-proliferative, anti-oxidant, anti-platelet, anti-atherogenic, and anti-carcinogenic activities.[5]

The present study aims to identify the effects of resveratrol on ovarian morphology, histology and biochemistry in an animal model of metabolic syndrome. Therefore, it would be clarified whether this agent with anti-inflammatory, anti-proliferative and anti-oxidant properties can be used to overcome the negative effects of metabolic syndrome on ovaries.

MATERIAL AND METHODS

ANIMALS

A total of 26 female Wistar albino rats (4 weeks old) weighing between 120 and 150 grams were housed in a room at a mean constant temperature (22±2°C) with a 12 hour light-dark cycle, 50-60% relative humidity and free access to water and standard pellet chow which was composed of 21% protein, 4% fat, 50% carbohydrate and 4.5% cellulose. All rats were maintained in these facilities for at least one week before the experiment. The present study was approved by the Gazi University School of Medicine Animal Care and Use Committee.

EXPERIMENTAL PROCEDURE

After a habituation period, rats were randomly divided into four groups. Group 1 (n=7) served as the control group and, thus, received the standard pellet chow diet and tap water during six months. Group II (n=7) was the resveratrol group and received the pellet chow enriched with resveratrol for six months. This enriched diet was prepared by adding 500 grams of resveratrol in one ton of standard pellet chow. Group III (n=5) was the fructose group and received the standard pellet chow diet and tap water fortified with fructose. That is, 10% fructose solution (prepared every two days) was given as the drinking water of rats for six months. Group IV (n=7) was the fructose plus resveratrol group and simultaneously received the pellet chow enriched with resveratrol and tap water fortified with fructose for six months.

Body weights of the animals were recorded at the beginning and end of the experiment. After six months of breeding, rats were fasted overnight, anesthetized by ketamine (80-100 mg/kg) and xylazine (5-10 mg/kg), and then sacrificed by exsanguination. In order to eliminate complications arising from the diurnal effects, all rats were sacrificed at the same time of the day. The blood acquired by exsanguination was collected in routine biochemical test tubes and centrifuged. Obtained sera were frozen at -70°C in aliquots until biochemical analyses and hormone assays were performed.

BIOCHEMICAL ANALYSES AND HORMONE ASSAYS

Serum concentrations of glucose and triglycerides were determined by enzymatic assay on an auto analyzer (Olympus AU 600, Hamburg, Germany). Serum estradiol was estimated by radioimmunoassay (Amersham Products, GE Healthcare Life Sciences, UK). Assay sensitivity for estradiol was 1.7 pg and intra-assay and interassay coefficients of variation were 9.3% and 11.4% respectively.

HISTOLOGICAL PREPARATION AND ANALYSIS

Two ovaries from each rat were isolated and trimmed free of fat and adhering tissues. Reproductive organ weights were standardized by dividing the organ weight (in mg), by the body weight of the female, and multiplying this factor by a standard female body weight of 300 mg. Adjusted uterine and ovarian weights were reported in mg/300 g body weight.

Both ovaries were fixed in 10% neutral formaldehyde at 4ºC overnight, followed by dehydration in a series of ethanol concentrations, clearing in xylene, and embedding in paraffin. After ovarian sections of 4 μm were prepared, five representative sections from each ovary were selected. The interval between sections was more than 100 μm so that follicles would not be counted twice. Ovarian sections were deparaffinized in xylene, hydrated through a series of ethanol concentrations, and stained with hematoxylin and eosin. These sections were examined under light microscopy with x20 objective lenses (Nikon Eclipse E600, Tokyo, Japan) by an experienced histologist who was unaware of the study groups. The histomorphometric measurements were made and recorded by means of BABS software.

STATISTICAL ANALYSIS

Collected data were analyzed by Statistical Package for Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA). Results were expressed as mean ± standard deviation. Shapiro-Wilks test was used to test normality. One-way ANOVA, Kruskal-Wallis and Spearman tests were also utilized. Values of $p<0.05$ were statistically significant.

RESULTS

The anatomical, biochemical and histomorphometric characteristics of 26 rats that were recruited for the present study were summarized (Table 1).

ANATOMY AND BIOCHEMISTRY

Group II rats had significantly lower body weight, omentum weight and standardized ovarian weight ($p=0.004$, $p=0.002$, and $p=0.001$, respectively). Moreover, group II rats had significantly lower levels of serum glucose, triglycerides and estradiol ($p=0.003$, $p=0.004$ and $p=0.003$, respectively) (Table 2).

MORPHOLOGY

Ovaries obtained from group I and group II rats exhibited primordial, primary, and atretic follicles, as well as interstitial glands. Preovulatory tertiary follicles and growing secondary follicles were observed in proestrous, whereas only secondary follicles and fresh corpora lutea were seen in diestrous cycles (Figure 1a, 1b). As for group III rats, small follicles in early development and atretic follicles were observed, in addition to small cystic follicles with thickened granulosa cell layers. Absence of corpus luteum and hyperplasia of interstitial glands was noted (Figure 1c). The ovaries of group IV rats showed follicular cysts besides primary and early secondary follicles. However, there was a conspicuous absence of large secondary and tertiary follicles as well as corpus luteum (Figure 1d).

TABLE 1: Anatomical, biochemical and histomorphometric characteristics of study populations.

	Mean±Standard deviation (Minimum-Maximum)
Body weight (grams)	243.0±20.7 (190.0-283.0)
Omentum weight (grams)	2.74±1.22 (1.41-5.43)
Standardized ovarian weight (mg)	135.8±3.4
Standardized uterine weight (mg)	432.7±25.6
Serum glucose level (mg/dl)	102.3±15.2 (71.0-141.0)
Serum triglyceride level (mg/dl)	139.4±76.8 (29.0-292.0)
Serum estradiol level (pg/ml)	22.7±22.3 (4.0-68.0)
Follicle number	10.2±5.3 (1.0-26.0)
Follicle diameter (μm)	28.674±14.444 (10.800-68.345)
Granulosa thickness (μm)	10.157±3.038 (5.140-17.028)
Theca layer thickness (μm)	1.879±0.359 (1.319-2.916)

TABLE 2: Anatomical and biochemical characteristics of study groups.

	Group I (n=7)	Group II (n=7)	Group III (n=5)	Group IV (n=7)	p
Body weight (grams)	249.4±20.5	220.2±18.1	263.4±3.3	241.2±4.9	0.004†*
Omentum weight (grams)	2.18±0.22	1.43±0.02	4.29±1.35	2.57±029	0.002†*
Standardized ovarian weight (mg)	131.1±3.1	127.0±5.2	146.2±4.3	142.2±4.8	0.001†*
Standardized uterine weight (mg)	419.2±56.1	361.1±21.2	475.5±47.4	488.0±67.4	0.277
Serum glucose level (mg/dl)	103.7±9.2	85.3±10.3	119.2±14.8	103.7±4.6	0.003†*
Serum triglyceride level (mg/dl)	102.3±53.5	78.3±55.6	235.8±59.8	157.0±36.5	0.004†*
Serum estradiol level (pg/ml)	6.00±1.16	10.71±6.58	57.20±8.17	26.71±22.05	0.003†*

*p<0.05 was accepted to be statistically significant.

†Statistical significance refers to a difference between Group II and Group III.

HISTOMORPHOMETRY

Although the number of ovarian follicles tended to be higher in group III rats, this difference was statistically insignificant (p=0.339). Mean follicle diameter was significantly wider while granulosa and theca cell layers were significantly thinner in group II rats (p=0.045, p=0.038 and p=0.044, respectively) (Table 3). There was a statistically significant correlation between the thicknesses of granulosa and theca cell layers (r=0.551, p=0.004). Ovarian follicle diameter correlated with serum concentrations of estradiol (r=-0.516, p=0.007).

DISCUSSION

PCOS has been considered as a progressive multiglandular endocrinopathy where the delicate balance of the hypothalamic-pituitary-adrenal-ovarian axis is disturbed, resulting in a failure of the cyclic reproductive mechanism. In order to assess PCOS, numerous experimental models have been established in rats. These models have employed adrenocorticotropic hormone, dehydroepiand- rosterone, estradiol valerate, neonatal androgenization and continuous light exposure so that PCOS is induced. A period of irregular rhythmicity usually precedes total loss of cyclic reproductive alterations in the aforementioned models.[6,7]

Alternatively, the present study aims to identify the effects of resveratrol on ovarian morphology, histology and biochemistry by investigating an experimental model of metabolic syndrome which has been established in rats. However, it is not possible to reproduce human PCOS using a rat model. Thus, comparisons between the rat PCOS model and human PCOS should be considered very carefully because rat polycystic ovaries contain multiple follicular cysts and their structure does not mimic the follicular growth arrest found in human

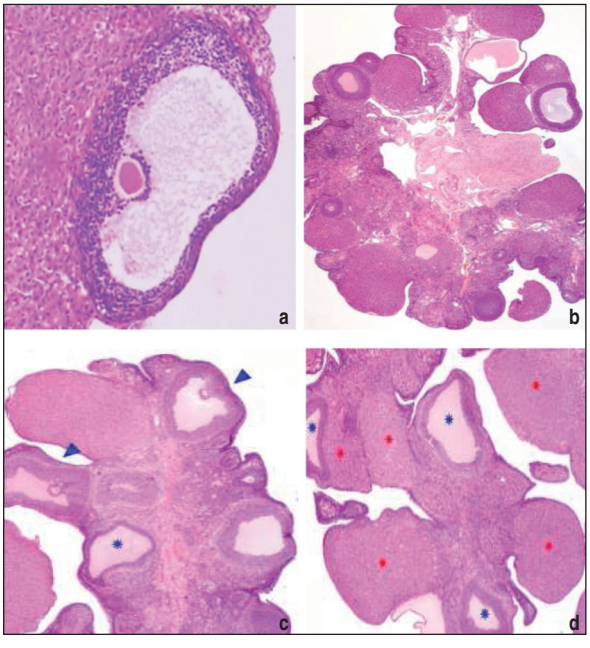

FIGURE 1: (a) Preovulatory tertiary follicles and growing secondary follicles were observed in proestrous cycles(hematoxylin and eosin, x100 magnification). **(b)** Secondary follicles and fresh corpora lutea were detected in diestrous cycles (hematoxylin and eosin, x40 magnification). **(c)** Large and multiple preovulatory follicles (arrowheads) with hyperplasic granulosa, with few large atretic follicles lined by a thinner granulosa cell layer (blue asterisk) (hematoxylin and eosin, x40 magnification). **(d)** Corpora lutea (red asterisks) were observed besides nonovulated abortive follicles (blue asterisks), that become cystic (arrowhead) or degenerate with pyknotic granulosa cells and abundant apoptotic bodies (hematoxylin and eosin, x40 magnification).
(See color figure at
http://www.turkiyeklinikleri.com/journal/jinekoloji-obstetrik-dergisi/1300-0306/)

TABLE 3: Histomorphometric characteristics of study groups.

	Group I (n=7)	Group II (n=7)	Group III (n=5)	Group IV (n=7)	p
Follicle number	9.3±2.1	9.3±4.2	14.2±8.4	9.3±5.6	0.339
Follicle diameter (μm)	36.960±11.245	37.185±23.303	21.269±9.230	21.679±5.780	0.045†*
Granulosa thickness (μm)	9.756±1.819	7.184±1.622	12.000±4.039	10.838±2.243	0.038†*
Theca layer thickness (μm)	1.764±0.135	1.681±0.231	2.187±0.439	1.825±0.357	0.044†*

*p<0.05 was accepted to be statistically significant.

†Statistical significance refers to a difference between Group II and Group III.

PCOS. Contrary to previously published evidence, the granulosa cells in the follicles accumulating in the human ovary are not atretic.[8] In order to accomplish these discrepancies, an experimental model for metabolic syndrome has been constituted for the present study. The reason is that PCOS is closely associated with metabolic syndrome so that women with PCOS have an increased risk of hypertension and type II diabetes.[9] Although the establishment of an experimental model for metabolic syndrome would inadequately reflect the histological and morphological characteristics of polycystic ovaries, the establishment of such a model might allow for the assessment of insulin resistance as an underlying mechanism for PCOS.

Why and how ovaries become polycystic have been the subject of considerable speculation as well as the object of meticulous studies with different approaches. Nevertheless, still much is unknown about the mechanisms that cause their development.[3,9]

Theca-interstitial cells play a crucial role in the regulation of ovarian functions. In case of PCOS, the ovaries are typically enlarged and ovarian functions are impaired. This evident increase in the ovarian size has been attributed to the thecal and stromal hyperplasia. The excessive growth of theca-interstitial compartment may be induced by stimuli such as oxidative stress and insulin. Moreover, insulin protects theca-interstitial cells from apoptosis and anti-oxidant agents inhibit the growth of theca-interstitial cells.[10,11] This ovarian enlargement is associated with excessive ovarian androgen production and the disruption of menstrual cycles. In accordance, ovarian functions are improved and fertility may be restored after ovarian size is reduced surgically and/or ovarian tissue is partially damaged by procedures such as wedge resection and laparoscopic ovarian drilling.[12]

Over the past decade, resveratrol has been introduced as a promising nutritional supplement with diverse therapeutic potential. Although it has been shown that resveratrol has anti-inflammatory, anti-proliferative and anti-oxidant properties, the studies focusing on the its effects on ovarian functions are limited. Due to the anti-proliferative and anti-oxidant activity of resveratrol, it can be hypothesized that resveratrol may be used to treat PCOS.[13,14]

In fact, resveratrol may act as a selective estrogen receptor modulator. That is, tissues with high amounts of α estrogen receptors (i.e. endometrium, breast cancer cells, ovarian stroma cells, and hypothalamus) are antagonized by resveratrol. On the other hand, tissues with high content of β estrogen receptors (i.e. kidney, brain, bone, heart, lungs, intestinal mucosa, and endothelial cells) are more sensitive to the estrogenic activity of resveratrol.[15]

Although the power of the present study is limited by the relatively small cohort size, its findings designate that resveratrol administration decreases body weight and omentum weight as well as serum concentrations of glucose and triglycerides. These results are compatible with the agonistic activity of resveratrol over the β estrogen receptors which are located in the endothelial, renal and gastrointestinal cells.[15]

Resveratrol may also possess prolonged anti-estrogenic effects in ovarian stromal cells, thereby decreasing plasma estradiol concentration and

reducing ovarian stromal volume.[13-15] Accordingly, the present study has pointed out a significant decrease in the thickness of granulosa and theca cell layers along with a significant increase in the follicle diameter. These effects of resveratrol may result from its anti-proliferative and anti-oxidant features.

As for its anti-proliferative activity, an *in vitro* study has demonstrated that resveratrol inhibits the cell proliferation and promotes the apoptosis of the ovarian theca-interstitial cells by limiting DNA synthesis and cell viability, increasing DNA fragmentation and inducing nuclear and cytoskeletal morphological changes.[16] What is more, resveratrol is a free radical scavenger which inhibits the peroxidation of membrane lipids and, thus, protects cells from peroxidative stress and cell death induced by oxidized lipoproteins. It has been shown that resveratrol (at a dose of 10 mg/kg) reduces ischemia/reperfusion injury of the cardiac and ovarian tissues by antioxidant and free-radical-scavenging mechanism.[17,18] This anti-oxidant activity of resveratrol may participate in the suppression of thecal-interstitial proliferation. Another benefit of resveratrol treatment is the reduction in body weight and the decrease in plasma glucose levels which, in turn, may help to break down insulin resistance and treat PCOS. Consequently, it may be concluded that resveratrol can be used to reduce insulin resistance, induce weight loss and adjust ovarian functions in women with PCOS.

Although resveratrol is largely absorbed by the human body, it has short half-life, extensive conjugation and low bioavailability. Resveratrol may be converted into compounds that sometimes, as for piceatannol, are effective but usually lack of its activities. It is difficult to achieve the concentrations required for the emergence of effects of resveratrol by merely drinking one or two glasses of red wine a day. Therefore, developing more potent analogues of resveratrol may provide a feasible means of achieving effective concentrations.[19,20] Large scale studies are warranted for the utilization of resveratrol in the treatment of PCOS.

REFERENCES

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287(3):356-9.
2. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al.; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112 (17):2735-52.
3. Hoo P, Shaw R. The patient with polycystic ovary syndrome. Practitioner 2005;249(1673): 552, 555-7, 559-10.
4. Xita N, Georgiou I, Tsatsoulis A. The genetic basis of polycystic ovary syndrome. Eur J Endocrinol 2002;147(6):717-25.
5. Frémont L. Biological effects of resveratrol. Life Sci 2000;66(8):663-73.
6. Salvetti NR, Gimeno EJ, Canal AM, Lorente JA, Ortega HH. Histochemical study of the extracellular matrix components in the follicular wall of induced polycystic ovaries. Braz J Morphol Sci 2003;20(2):93-100.
7. Salvetti NR, Canal AM, Gimeno EJ, Ortega HH. Polycystic ovarian syndrome: temporal characterization of the induction and reversion process in an experimental model. Braz J Vet Res Anim Sci 2004;41(6):389-95.
8. Stener-Victorin E, Lundeberg T, Waldenström U, Manni L, Aloe L, Gunnarsson S, et al. Effects of electro-acupuncture on nerve growth factor and ovarian morphology in rats with experimentally induced polycystic ovaries. Biol Reprod 2000;63(5):1497-503.
9. Raja A, Hashmi SN, Sultana N, Rashid H. Presentation of polycystic ovary syndrome and its management with clomiphene alone and in combination with metformin. J Ayub Med Coll Abbottabad 2005;17(2):50-3.
10. Duleba AJ, Foyouzi N, Karaca M, Pehlivan T, Kwintkiewicz J, Behrman HR. Proliferation of ovarian theca-interstitial cells is modulated by antioxidants and oxidative stress. Hum Reprod 2004;19(7):1519-24.
11. Spaczynski RZ, Tilly JL, Mansour A, Duleba AJ. Insulin and insulin-like growth factors inhibit and luteinizing hormone augments ovarian theca-interstitial cell apoptosis. Mol Hum Reprod 2005;11(5):319-24.
12. Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Success of laparoscopic ovarian wedge resection is related to obesity, lipid profile, and insulin levels. Fertil Steril 2003;79(4):1008-14.
13. Henry LA, Witt DM. Resveratrol: phytoestrogen effects on reproductive physiology and behavior in female rats. Horm Behav 2002;41(2):220-8.
14. Henry LA, Witt DM. Effects of neonatal resveratrol exposure on adult male and female reproductive physiology and behavior. Dev Neurosci 2006;28(3):186-95.
15. Bowers JL, Tyulmenkov VV, Jernigan SC, Klinge CM. Resveratrol acts as a mixed agonist/antagonist for estrogen receptors alpha and beta. Endocrinology 2000;141(10):3657-67.
16. Wong DH, Villanueva JA, Cress AB, Duleba AJ. Effects of resveratrol on proliferation and apoptosis in rat ovarian theca-interstitial cells. Mol Hum Reprod 2010;16(4):251-9.
17. de la Lastra CA, Villegas I. Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. Biochem Soc Trans 2007;35(Pt 5):1156-60.
18. Hascalik S, Celik O, Turkoz Y, Hascalik M, Cigremis Y, Mizrak B, et al. Resveratrol, a red wine constituent polyphenol, protects from ischemia-reperfusion damage of the ovaries. Gynecol Obstet Invest 2004;57(4):218-23.
19. Basini G, Tringali C, Baioni L, Bussolati S, Spatafora C, Grasselli F. Biological effects on granulosa cells of hydroxylated and methylated resveratrol analogues. Mol Nutr Food Res 2010;54(Suppl 2):S236-43.
20. Cardile V, Chillemi R, Lombardo L, Sciuto S, Spatafora C, Tringali C. Antiproliferative activity of methylated analogues of E- and Z-resveratrol. Z Naturforsch C 2007;62(3-4):189-95.