DERLEME REVIEW

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Alternative Pharmacological Approach to Male Infertility: Anti-Aromatase Compounds: A Systematic Review

Erkek İnfertilitesine Alternatif Farmakolojik Yaklaşım: Anti-Aromataz Bileşikler: Sistematik Derleme

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ABSTRACT Infertility is a reproductive system disease in which pregnancy does not occur despite long-term, regular and unprotected sexual intercourse. In the near future, it is estimated that approximately 15% of the world population will be affected by infertility and the majority of this will be male-induced infertility. In male infertility, 90% defective sperm production is effective and it is known that in infertile men, as a result of the increase in estrogen levels due to aromatase activity, the testosterone/estradiol ratio may decrease and spermatogenesis is impaired. Therefore, research on increasing intratesticular testosterone levels and improving impaired spermatogenesis has focused on aromatase inhibitors. However, since the efficacy and safety of aromatase inhibitors have not been clarified, it has been thought that anti-aromatase compounds with fewer side effects and stronger efficacy can be used as alternative therapeutic agents in the treatment of infertility. Phytoestrogens are estrogenic plant-derived compounds. Many have been shown to have aromatase inhibition, thereby increasing testosterone levels. In addition, it is known that there are different mechanisms that affect spermatogenesis apart from binding to estrogen receptors in their effects on the male reproductive system. Therefore, our aim is to review the latest developments and treatment approaches to natural polyphenolic compounds with anti-aromatase activity in male infertility. According to the literature, the most commonly used anti-aromatase compounds include resveratrol, quercetin, apigenin, and naringenin. All the compounds in this review were found to have positive effects on male infertility.

Keywords: Aromatase inhibitors; infertility, male; estrogens; spermatogenesis; drug therapy

ÖZET İnfertilite; uzun süreli, düzenli ve korunmasız cinsel ilişkiye rağmen gebeliğin oluşmadığı bir reprodüktif sistem hastalığıdır. Yakın gelecekte ise dünya nüfusunun yaklaşık %15'inin infertiliteden etkileneceği ve bunun çoğunluğunun erkek kaynaklı infertilite olacağı tahmin edilmektedir. Erkek infertilitesinde %90 oranında kusurlu sperm üretimi etkilidir ve infertil erkeklerde, aromataz aktivitesine bağlı östrojen seviyelerindeki artış sonucunda testosteron/östradiol oranının azalabildiği ve spermatogenezin bozulduğu bilinmektedir. Bu nedenle intratestiküler testosteron seviyelerinin artırılması ve bozulmuş spermatogenezin iyileştirilmesine yönelik araştırmalarda aromataz inhibitörleri üzerine odaklanılmıştır. Ancak aromataz inhibitörlerinin etkinliği ve güvenirliliği netlik kazanmadığı için infertilite tedavisinde daha az yan etki ve daha güçlü etkinliğe sahip anti-aromataz bileşikleri alternatif terapötik ajanlar olarak kullanılabileceği düşünülmüştür. Fitoöstrojenler, östrojenik bitkisel kaynaklı bileşiklerdir. Birçoğunun aromataz inhibisyonuna sahip olduğu ve bu şekilde testosteron düzeyini artırdığı gösterilmiştir. Bunun yanında, erkek üreme sistemi üzerindeki etkilerinde östrojen reseptörlerine bağlanmanın dışında spermatogenezi etkileyen farklı mekanizmaların olduğu da bilinmektedir. Bu yüzden amacımız, erkek infertilitesinde anti-aromataz etkinliğe sahip doğal polifenolik bileşikler hakkında son gelişmeleri ve tedavi yaklaşımlarını derlemektir. Literatüre göre en yaygın kullanılan anti-aromataz bileşikler arasında resveratrol, kuersetin, apigenin ve naringenin yer almaktadır. Bu derlemede yer alan tüm bileşiklerin ise erkek infertilitesinde olumlu etkiler gösterdiği belirlenmiştir.

Anahtar Kelimeler: Aromataz inhibitörleri; infertilite, erkek; östrojenler; spermatogenez; ilaç tedavisi

Infertility is a reproductive system disease in which pregnancy does not occur despite long-term, regular and unprotected sexual intercourse. According to data from the World Health Organization, 48 million couples and 186 million people have infertility problems. It is estimated that approximately 15% of the world population will be affected by infertility in the near future.[1] The absence of sperm, morphology, and motility are among the most effective factors in male infertility, and defective sperm

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production is effective at a rate of 90%.[2] In the male reproductive system, leydig and sertoli cells have a vital role in spermatogenesis.[3] It is known that as a result of high aromatase expression, spermatogenesis is disrupted and infertility problems occur. Aromatase is an enzyme of the cytochrome P450 class, encoded by the *CYP19A1* gene, responsible for the conversion of testosterone to estrone and androstenedione to estradiol in estrogen biosynthesis.[4] The dominant role of homeostasis between estrogen and androgen in male fertility also supports the role of the aromatase enzyme in infertility.[5]

Testicular development and maintenance of spermatogenesis are under the control of gonadotropins and testosterone. Estrogen plays a role in the regulation of pubertal growth, spermatogenesis, and gonadal functions.[6,7] In men, estrogen hormone is synthesized in the range of 35-45 µg per day on average as a result of the aromatization of androgen in adipose tissue and testicles.[8] There is a balance between estradiol, the most common form of estrogen, and testosterone, which is maintained by endocrine and paracrine factors.[9] Testosterone and estradiol reduce the production of follicle-stimulating hormone and luteinizing hormone with a negative feedback mechanism on the pituitary and hypothalamus.[10,11] It has been reported that in infertile men, as a result of the increase in estrogen levels due to aromatase activity, the testosterone/estradiol ratio may decrease and spermatogenesis may be impaired.[12] Therefore, therapeutic approaches to increase intratesticular testosterone levels have been developed and focused on aromatase inhibitors.

However, since the efficacy and safety of aromatase inhibitors are not clear, anti-aromatase compounds with fewer side effects and stronger efficacy can be used as alternative therapeutic agents in the treatment of infertility.[13-15] Therefore, our aim is to review the latest developments and treatment approaches to natural polyphenolic compounds with anti-aromatase activity in male infertility.

AROMATASE INHIBITORS

Aromatase inhibitors can be classified in 2 different ways according to their structure (steroidal and non-steroidal) or effects (first, second, and third-generation). Steroidal inhibitors mimic androstenedione substrate and bind aromatase irreversibly (formestane and exemestane). Non-steroidal inhibitors, on the other hand, bind to heme iron in the enzyme structure and inhibit enzyme activity reversibly (anastrozole and letrozole). First-generation aromatase inhibitors (aminoglutethimide) are weak efficacy and non-specific, whereas third-generation aromatase inhibitors (letrozole and anastrozole) are more potent and more specific.[16] The efficacy, specificity, and toxicity of second-generation aromatase inhibitors (formestane and fadrozole) are between the other 2 generations.[17] Letrozole and anastrozole, which are non-steroidal inhibitors classified as the third-generation, are widely used in the treatment of breast cancer and polycystic ovary today.

When aromatization of androgens to estrogens is inhibited as a result of its use in men, the negative feedback effect of estradiol on the hypothalamo-pituitary-gonadal axis is eliminated, resulting in an increase in testosterone levels.[18] Therefore, it can be preferred as an alternative therapeutic way to reduce estrogen levels in the treatment of hypogonadism and gynecomastia.[16] Although its use in male infertility has been reported in many clinical studies and case reports, infertility has not completely disappeared.[17] In addition, many side effects such as loss of libido have been seen in clinical studies, especially for letrozole. In long-term use, it may increase the risk of osteoporosis by decreasing bone mineral density.[18] For this reason, studies on the efficacy and safety of aromatase inhibitors in male infertility continue (Figure 1).

Phytoestrogens are plant-derived compounds that can bind to estrogen receptors due to their estrogen-like chemical structure and are classified into subclasses such as hydroxybenzoic acids, anthocyanins, flavonols, isoflavones, stilbenes, and lignans. It has been reported that it is found in the seeds, roots, stems, leaves, and fruit parts of many plants and therefore is widely consumed in the diet of humans.[19] Due to its anti-inflammatory and antioxidant properties, its use in the treatment and prophylaxis of obesity, diabetes, and cardiovascular diseases is being investigated.[20] It has been reported that there are dif-

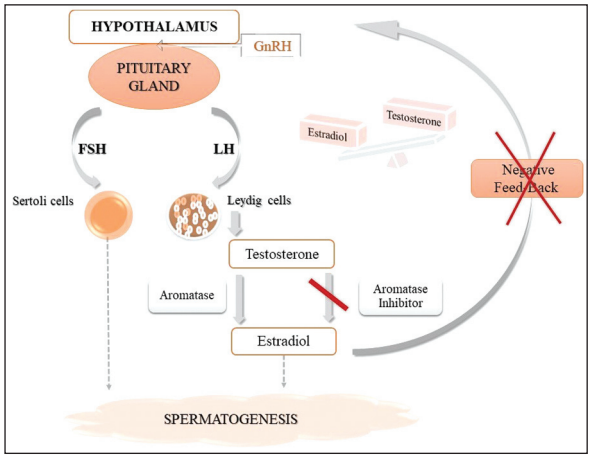

FIGURE 1: Aromatase inhibitors on the hypothalamus-pituitary-gonadal axis.

ferent mechanisms affecting spermatogenesis apart from binding to estrogen receptors in their effects on the male reproductive system.[21] Obtaining both positive and negative results between a regular diet containing phytoestrogen and sperm morphology supports that it is effective through different mechanisms.[22] Studies with phytoestrogens mostly focused on inhibition of aromatase, and some compounds were evaluated in vivo on testicular activity. As mentioned above, although aromatase inhibitors show a better effect profile, they usually cause serious side effects such as decreased bone mineral density, osteoporosis, musculoskeletal disorders, and changes in lipid profiles. Therefore, natural products that have a long history of use in traditional medicine and also exhibit aromatase inhibitory activity may offer increased clinical efficacy and reduced side effects over aromatase inhibitors.

RESVERATROL

Resveratrol was first detected in *veratrum grandiflorum* resins; is a natural polyphenol found in high levels in grapes, blueberries, blackberries, and peanuts. Resveratrol is in the structure of phytoalexin and is synthesized by the stilbene synthase enzyme.[23] It has been reported to have curative effects in many diseases such as obesity, hypertension, stroke, diabetes mellitus, Alzheimer's, and male infertility due to its antioxidant, anti-inflammatory, and antitumoral properties.[24] Recent studies; reported that resveratrol protects fertilization capacity, and regulates sperm motility and morphology by activating adenosine monophosphate-activated protein kinase. However, the molecular effect mechanism showing positive/beneficial effects on sperm parameters has not been fully elucidated.[25,26] Studies evaluating the effects of resveratrol on male infertility are summarized in Table 1. In addition to all these positive aspects, resveratrol also has disadvantages. Despite a great deal of preclinical research, little progress has been made in clinical trials, greatly limiting the application of resveratrol in the situation.[27] The long-term risks and pharmacological mechanisms of resveratrol supplementation are not fully understood, so more randomized controlled trials are needed.[28] In addition, its clinical therapeutic efficacy is greatly limited due to its low absorption rate, rapid metabolism, and low bioavailability. Therefore, various strategies, including nano drug delivery systems, are being developed to increase the bioavailability and pharmacological activity of resveratrol. In addition, extraction of resveratrol from plants is very difficult and costly. It has a low purity rate. Therefore, a way to produce high purity resveratrol from cheap raw materials is sought.[29,30]

CHRYSIN

Chrysin; is a natural flavonoid that is found in high levels in plant extracts, honey, and propolis, and shows antitumoral, antioxidant, anti-inflammatory, and cardioprotective properties.[31,32] It has also been shown to have strong aromatase inhibitory properties and, accordingly, to prevent the decrease in testosterone levels in aged rats. Therefore, it can be applied prophylactically for the testosterone level that decreases with aging.[33,34] In a study on experimental animals, it was reported that it protected the testicular antioxidant capacity and increased semen quality in rats.[31] Studies evaluating the effects of chrysin on male infertility are summarized in Table 2. Like resveratrol, chrysine has several disadvantages that limit its therapeutic use. These include poor absorption, rapid metabolism, short circulatory stability, and poor bioavailability. To overcome the mentioned disadvantages of chrysin, new chrysin formulations such as nanoparticles, nanofibers and liposomes play an important role in enhancing its therapeutic activity.[35]

TABLE 1: The main studies on the effects of resveratrol on male fertility.

Type	Aims	Dose and time	Results	References
Clinical study	In this study, the relationship between obesity and some sperm parameters was investigated and the protective effects of resveratrol in preventing the harmful effects of obesity on spermatozoa were evaluated	Sperm suspensions 2.6, 6, 15, 30, 50, 100 µmol/L; in doses was incubated with resveratrol for 30 minutes	In particular, semen samples from obese men with asthenospermia treated with 0-100 µmol/L resveratrol for 30 minutes showed improvement in sperm motility Resveratrol may have a therapeutic and protective effect against obesity-induced abnormalities in semen	Cui et al.,2016[62]
Clinical study	To evaluate the effect of a multivitamin supplement containing resveratrol on semen parameters in idiopathic male infertility	A multivitamin supplement containing oral resveratrol was given every 12 hours and the patients were evaluated at regular intervals after the treatment	In men with idiopathic infertility, after 3 and 6 months of treatment, resveratrol supplementation has been shown to improve sperm motility and concentration	Illiano et al.,2020[63]
In vivo	To evaluate the effect of resveratrol on the reproductive damage caused by bisphenol A in male mice	20 mg/kg intraperitoneally every day for 5 weeks	It was established that resveratrol protects sperm motility, viability, and oxidative stress indicators against the effects of bisphenol A	Golmohammadi et al.,2021[64]

TABLE 2: The main studies on the effects of chrysin on male fertility.

Type	Aims	Dose and time	Results	References
In vivo	To evaluate the possible protective effects of chrysin and flunixin meglumin in copper-induced testicular damage	Chrysin (50 mg/kg) was administered orally for 21 days	Chrysin and flunixin meglumine have a protective role in copper-induced testicular and spermatological damage in rats	Parlak et. al., 2021[34]
In vivo	To investigate the protective effects of chrysin against zearalenone, which causes reproductive toxicity in male mice	Animals were administered chrysin at 5 or 20 mg/kg orally for 10 days	Chrysin played a protective role in the testicles of mice by attenuating zearalenone-induced toxic effects	Del Fabbro et. al., 2019[65]
In vivo	The effects of chrysin on testicular injury caused by lead acetate were studied	Animals were administered chrysin at 25 or 50 mg/kg orally for 7 days	Lead acetate has been shown to cause a decrease in sperm motility and an increase in the percentage of dead sperm. On the other hand, chrysin reduced this damage to sperm parameters It was concluded that chrysin may be a natural substance that can be used in testicular toxicity	Ileriturk et al., 2021[66]

APIGENIN

Apigenin, also known as 4,5,7-trihydroxy flavone, is a potential therapeutic agent with antioxidant, anti-inflammatory, antibacterial, and antiviral properties that has been investigated in the treatment of cancer due to its high anti-tumoral activity.[36-39] By inhibiting the aromatase enzyme, apigenin can cause changes in semen parameters, androgen levels, and the hypothalamo-pituitary-gonadal axis in the male reproductive system. Therefore, it can be used as a therapeutic agent in male infertility alone or in combination therapy.[40] Antioxidant activity of apigenin has been demonstrated in rat testis tissue.[41] Its protective effects in the male reproductive system are thought to affect testosterone secretion through the cyclic adenosine 3',5'-monophosphate (cAMP)-dependent protein kinase-A (cAMP) signaling pathway.[42] Therefore, it is necessary to elucidate the molecular mechanisms of action on different pathways. Studies evaluating the effects of apigenin on male infertility are summarized in Table 3.

The low solubility and poor bioavailability of apigenin limit in vivo studies. Various drug delivery systems, including liposomes, micelles, nanoparticles, and nanogels, have been used to increase the solubility of apigenin and prolong the pharmacological duration of action. Moreover, for apigenin to be used as an effective therapeutic agent, it is necessary to determine its exact dose and further clinical trials are needed for this. In addition, the duality functions of apigenin should be considered due to the functional variation between antioxidant and prooxidant activities depending on the cell/tissue type and experimental models.[43]

NARINGENIN

Naringenin is a natural flavanone commonly found in many citrus fruits, especially grapefruit.[44] The high antioxidant capacity and reactive oxygen species (ROS) scavenging activity of naringenin was confirmed in invivo and in vitro experimental models.[45,46] It has also been shown to be effective in the treatment of diabetes, atherosclerosis, and insulin resistance due to its effects on lipoprotein metabolism.[47] Due to the various pharmacological activities of naringenin, it continues to be investigated in many areas including sepsis, fibrosis, and cancer in the literature.[48,49] In an in vivo study using the Ehrlich ascites tumor model, it was shown that naringenin decreased the expression of aromatase.[50] Demonstration of naringenin's anti-aromatase activity has led to its prophylactic and therapeutic use in male infertility like other phytoestrogens.[51] In a study by Al-Oanzi et al., it was shown that naringenin's anti-inflammatory and antioxidant activity in testicles improves diabetes mellitus-based sexual dysfunction.[52] Thanks to its anti-aromatase and antioxidant activity, naringenin can be used as an adjuvant in male

TABLE 3: The main studies on the effects of apigenin on male fertility.

Type	Aims	Dose and time	Results	References
In vivo	To evaluate the possible protective effects of chrysin and flunixin meglumin in copper-induced testicular damage	Animals were administered apigenin at 15 or 30 mg/kg orally for 30 days	Both apigenin and baicalin alone or in low-dose combination reduced testicular damage caused by chlorakinin Both may be promising in the treatment of male infertility	Akilah et al., 2018[40]
In vivo	To evaluate the role of apigenin on acrylonitrile-induced inflammation and apoptosis in germ cells and whether this is via the NF-κB signaling pathway	Animals were administered apigenin at 234 or 468 mg/kg orally for 12 weeks	It was concluded that apigenin could improve testicular maturation and energy metabolism, and inhibit NF-κB activation	Dang et al., 2018[67]
Ex vivo	To examine the protective effects of apigenin isolated from C.cripus in disorders of spermatogenesis due to ROS	Sperm cells were incubated with 2.5, 5, 10, 20 and 40 µM apigenin and cell viability was examined	Apigenin isolated from Carduus crispus can prevent testicular dysfunction due to ROS	Kopalli et al., 2022[68]

NF-κB: Nuclear factor kappa B; ROS: Reactive oxygen species.

infertility by showing an improving effect on sperm parameters. Studies evaluating the effects of naringenin on male infertility are summarized in Table 4.

Although naringenin has many different pharmacological activities, some disadvantages should be considered. Chief among these is the inhibitory effect of the activity of some cytochrome P450 isoforms. If drugs metabolized by cytochrome P450 are taken together with grapefruit, the bioactive substances in citrus will reduce the enzyme activity and change the bioavailability of the drugs. However, the clinical use of naringenin is largely limited due to its low water solubility and bioavailability. In addition, the use of doses that cannot be administered to humans in animal studies is one of the factors limiting its clinical use. Although various approaches such as various enzymatic condensation techniques have been proposed to overcome the disadvantages that limit the clinical use of naringenin mentioned above, it is still not possible to sufficiently dissolve naringenin in water.[53] Therefore, the search for an effective and non-toxic carrier for naringenin will be an important step for clinical applications.

QUERCETIN

Quercetin is a vegetable flavonoid found in many plants and vegetables such as red onions, cabbage, and cabbage. It has strong antioxidant, anti-inflammatory, anti-tumoral, and metal chelating properties.[54] Studies conducted with quercetin in cancer cell lines have shown that the anti-apoptotic effect occurs as a result of inhibition of the PI3K/AKT pathway.[55] It has also been reported to have a role in the prevention of DNA damage due to oxidative stress.[56] Quercetin is known for its various pharmacological activities as well as a ROS scavenger in male infertility. In studies on streptozocin-induced testicular dysfunction, improvement was observed due to its ROS scavenging properties and antioxidant effects.[57] In a different study in the literature; Quercetin and resveratrol have been shown to reduce mitochondrial membrane potential in ram sperm and minimize sperm loss under sperm storage conditions.[58] Due to its anti-aromatase activity, quercetin is thought to contribute to spermatogenesis by increasing serum testosterone levels, improving sperm quality, and improving sexual organ functions.[59] Ranawat et al. reported that high dose quercetin showed pro-oxidant properties, affecting germ cells and impairing spermatogenesis.[60] For this reason, it is necessary to examine dose-dependent activities and to conduct researches that illuminate the mechanisms of action. Several studies evaluating the effects of quercetin on male in-

TABLE 4: The main studies on the effects of naringenin on male fertility.

Type	Aims	Dose and time	Results	References
In vivo	A protective effect of naringenin on possible reproductive damage of phthalates due to oxidative stress	Animals were administered naringenin at 15 or 30 mg/kg orally for 30 days	Reproductive damage such as increase in abnormal sperm count and decrease in sperm motility and histopathological changes in di-n-butyl phthalate in rats was ameliorated by the ntioxidant activity of naringenin	Taşlıdere et al., 2022[69]
Ex vivo	To investigate the effect of quercetin, rutin, naringenin and epicatechin on lipid peroxidation induced in human sperm	20-400 µM	It was concluded that quercetin, rutin, epicatechin and naringenin, which are used against oxidative stress induced in human sperm, are protective against lipid peroxidation, and quercetin is the most effective among them	Moretti et al., 2012[70]
In vivo	To determine the antiretroviral therapy-induced sperm DNA fragmentation and the adjuvant potential of naringenin in testicular toxicity	Animals were administered naringenin at 40 or 80 mg/kg orally for 4 weeks	It has been shown that antiretroviral treatment can impair testicular microanatomy, sperm parameters and sperm DNA in rats, and naringenin has a protective role against these damages	Adana et al., 2018[54]

TABLE 5: The main studies on the effects of quercetinin on male fertility are summarized.

Type	Aims	Dose and time	Results	References
Ex vivo	To investigate the effects and molecular mechanisms of quercetin on sperm function in infertile patients with leukocytospermia	10 µmol/L	Quercetin has been shown to significantly improve sperm motility and acrosome reaction in samples from leukocytospermic patients	Diao et al., 2019[71]
Ex vivo	The effect of cryopreservation on human sperm DNA integrity and subsequently the effect of quercetin on preventing sperm damage during the freeze-thaw process were investigated	Cryopreserved with the addition of quercetin	Cryopreservation has been shown to cause damage to sperm DNA and quercetin has been shown to reduce this damage	Zribi et al., 2012[72]
Ex vivo	To investigate the effect of quercetin on the motility of human spermatozoa in asthenozoospermic cases	0,05-0,1-0,2-0,5-1M	The study showed that quercetin has positive effects on sperm motility depending on dose and time	Karabulut et al., 2020[73]

fertility are summarized in Table 5. The metabolism of quercetin in the body is quite rapid, and as a result, the circulating time and bioavailability of the active quercetin molecule are limited. This creates great differences between the in vitro pharmacological activity of quercetin and its in vivo activity. Also, quercetin has low water solubility, further affecting its therapeutic potential. Since quercetin has a very low solubility in gastric and intestinal fluid, studies are needed to increase its aqueous solubility in order to maintain its levels in the blood and other tissues for a long time. In some studies, the effects of quercetin such as pro-oxidant activity, mutagenicity, genotoxicity, inhibition of enzymes responsible for hormone metabolism and mitochondrial toxicity have been evaluated.[61] Toxicity and safety analyzes are needed for quercetin before it can be applied as a therapeutic molecule in clinics.

CONCLUSION

It has been reported that plant-derived polyphenolic compounds have many pharmacological activities. In particular, research on the mechanism of action on cancer, obesity, diabetes, cardiovascular, and neurodegenerative diseases continues. In male reproductive system diseases, they can be used as pharmacological agents in the treatment of pathological conditions that cause infertility, such as insufficiency of leydig cells, decreased testosterone level, and impaired spermatogenesis. According to the literature, the most widely used anti-aromatase compounds include resveratrol, quercetin, apigenin, and naringenin. All the compounds in this review were found to have positive effects on male infertility. However, it was determined that the studies were based on histopathological or biochemical methods and were insufficient to elucidate the mechanism of action. For this reason, more specific effects should be investigated by molecular methods, different combinations should be tried, various pharmacological forms should be compared and safety studies should be done. Thus, it can contribute to the presence of more effective and safe alternative pharmacological agents in the use of natural resources in the treatment of diseases.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Osman Çiftçi;* ***Design:*** *Yasemin Şahin, Münevver Nazlıcan Zengin;* ***Control/Supervision:*** *Osman Çiftçi;* ***Data Collection and/or Processing:*** *Münevver Nazlıcan Zengin, Yasemin Şahin;* ***Analysis and/or Interpretation:*** *Yasemin Şahin, Münevver Nazlıcan Zengin;* ***Literature Review:*** *Münevver Nazlıcan Zengin;* ***Writing the Article:*** *Yasemin Şahin, Münevver Nazlıcan Zengin;* ***Critical Review:*** *Osman Çiftçi, Yasemin Şahin.*

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