Biotechnic & Histochemistry

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ibih20

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To cite this article: Taylan Onat, Melike Demir Caltekin, Züleyha Doğanyigit, Can Turkler, Emin Kaymak, Mustafa Kara & Ethem Serdar Yalvac (2021) Activation of cannabinoid 2 receptors by JWH-133 protects against ovarian ischemia-reperfusion injury in rats, Biotechnic & Histochemistry, 96:5, 394-400, DOI: 10.1080/10520295.2021.1905183

To link to this article: https://doi.org/10.1080/10520295.2021.1905183

Published online: 12 Apr 2021.

BIOTECHNIC & HISTOCHEMISTRY
2021, VOL. 96, NO. 5, 394–400
https://doi.org/10.1080/10520295.2021.1905183

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Activation of cannabinoid 2 receptors by JWH-133 protects against ovarian ischemia-reperfusion injury in rats

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ABSTRACT

We investigated the efficacy of activated cannabinoid 2 receptors for alleviating ovarian ischemia-reperfusion injury in rats. Female Wistar albino rats were divided randomly into six groups: ischemia-reperfusion (IRG); ischemia-reperfusion + 0.2 mg/kg JWH-133 (JIRG1), ischemia-reperfusion + 1 mg/kg JWH-133 (JIRG2); ischemia-reperfusion + 5 mg/kg JWH-133 (JIRG3); solvent control, and sham control. Ovarian ischemia was established for 3 h followed by reperfusion for 3 h. Ovarian tissue was investigated using histology, immunohistochemistry and biochemistry. Administration of JWH-133 synthetic cannabinoid reduced nuclear factor kappa-B immunoreactivity as well as TUNEL positivity scores and malondialdehyde levels. These reductions were significant in all cases except for the malondialdehyde levels in the 1 mg/kg JWH-133 group. Activation of cannabinoid 2 receptors by JWH-133 reduced ovarian ischemia-reperfusion injury due to its antioxidant and anti-inflammatory effects.

KEYWORDS

Cannabinoid 2 receptors; inflammation; ischemia-reperfusion injury; JWH-133; oxidative stress

Ovarian torsion is caused by complete or partial rotation of the ovary and fallopian tube together with the vascular structures that supply them. Ovarian torsion is an urgent gynecological condition in women of any age (Houry and Abbott 2001). Ischemia and necrosis can occur following ovarian torsion (Sasaki and Miller 2014). Without early diagnosis, organ death may result. Following surgical detorsion, blood flow resumes and tissue reperfusion begins. Reperfusion injury can occur due to production of reactive oxygen species (ROS), which elicit release of inflammatory agents (Sayyah-Melli et al. 2012); the overall process is termed ischemia-reperfusion (IR) injury. Inflammation is initiated following IR; the nuclear factor kappa-B (NF-κB) pathway plays a key role in this process. As a regulator of proinflammatory cytokine production, such as interleukin 1 and tumor necrosis factor-α, the NF-κB pathway is an important contributor to the inflammatory response (Lawrence 2009).

Cannabinoids can be derived from plants (e.g., *Cannabis sativa*) or synthesized either endogenously or exogenously. The two best known members of the endocannabinoid system (ECS) are anandamide and 2-arachidonoylglycerol. Regardless of the source, cannabinoids bind to similar receptors in humans and produce similar effects on energy metabolism, and on the central nervous, reproductive and gastro-intestinal systems. The ECS includes two types of G-protein coupled receptors, also called cannabinoid type 1 (CB_1) and cannabinoid type 2 (CB_2). CB_1 is found mostly in the brain, while CB_2 is found in the peripheral cells of the immune system (Picone and Kendall 2015). CB_2 also is present in follicular fluid in the ovarian cortex and medulla (El-Talatini et al. 2009).

The ECS may be a therapeutic target for pharmacological agents for treating inflammatory diseases and tissue injuries (Steffens and Pacher 2012). The ECS can initiate apoptosis and autophagy, induce cell cycle arrest, affect inflammatory responses to malignant cells, and block angiogenesis and metastasis (Ayakannu et al. 2013; Pyszniak et al. 2016). Activation of CB_2 receptors has been shown to reduce IR injury in the heart, liver and kidneys (Bátkai et al. 2007; Pacher and Haskó 2008; Çakır et al. 2019a). It has been suggested that activation of CB_2 receptors affects ischemic regeneration (Pacher and Haskó 2008). Although both antioxidant and anti-inflammatory substances have been investigated in various animal models for preventing or reducing the effects of IR (Feizi et al. 2008; Nayki et al. 2018; Turkler et al. 2018; Çakır et al. 2019a), a substance has yet to be developed that can be developed into drug form that can be used safely in humans.

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JWH-133 is a selective CB_2 agonist. Anti–inflammatory, antioxidant and anti-apoptotic effects of JWH-133 have been reported for myocardial IR, neurodegeneration, kidney IR and liver toxicity models (Li et al. 2013; Tutun and Baydan 2018; Çakır et al. 2019a, b). Activation of CB_2 receptors by JWH-133 reduces apoptosis, inflammation and oxidative stress (Feizi et al. 2008; Li et al. 2013). We have found no reports concerning the effects of JWH-133 on ovarian IR; therefore, we investigated the histological, immunohistochemical and biochemical effects of activating CB_2 receptors by JWH-133 for ovarian IR.

Material and methods

Animals

Our investigation was performed in accordance with international guidelines for the ethical use of animals; ethical permission was obtained from the Kobay Experiment Animals Laboratory Industry and Trade Co. (no. 13/09/2018-308). We used 48 180–220 g Wistar albino female rats obtained from Kobay Experiment Animals Laboratory Industry and Trade Co. Animals were maintained at 20–22 °C and 55–65% humidity with a 12 h light:12 h dark cycle prior to the study.

Experimental groups

Rats were divided randomly into six groups of eight: IR group (IRG), IR + 0.2 mg/kg JWH-133 group (JIRG1), IR + 1 mg/kg JWH-133 group (JIRG2), IR + 5 mg/kg JWH-133 group (JIRG3), solvent only control group (control), and a sham surgery group (sham).

Experimental procedure

The rats were anesthetized by intraperitoneal (i.p.) injection of 50 mg/kg of ketamine hydrochloride (Eczacıbaşı, Istanbul, Turkey) plus 7 mg/kg xylazine hydrochloride (Bayer, Leverkusen, Germany). The ventral abdominal area was shaved, disinfected with povidone-iodine and a 2–3 cm longitudinal abdominal incision was made. The uterus and right ovary were exposed and a unilateral right complete ovarian ischemia model was established by occluding the right ovarian vessels using an atraumatic suture (no: 0, polyglactin). Ischemia was maintained for 3 h. One half hour before reperfusion, JWH-133 (Cayman Chemical, Ann Arbor, MI) was administered i.p. at doses appropriate for the experimental groups. The reperfusion period was initiated by removing the suture. Reperfusion was maintained for 3 h. Animals then were euthanized by decapitation under anesthesia. The right ovary was removed, then cut in half. One half was placed in 10% formalin for histologic and immunohistochemical examination; the other half was placed in an Eppendorf tube and stored at −80 °C for biochemical assay.

Histology

The ovarian tissues taken at the end of the experiment were fixed with 10% formalin for 1 week. Tissues then were dehydrated through 50, 70, 80, 96 and 100% ethanol, cleared with xylene and embedded in paraffin wax. Sections were cut at 5 μm and affixed to slides, then deparaffinized, rehydrated and stained with hematoxylin and eosin (H & E) (Doğanyiğit et al. 2020). The stained sections were dehydrated through ascending ethanols, cleared with xylene and mounted with Entellan (Merck, Darmstadt, Germany). The preparations were examined using a BX53 light microscope (Olympus, Tokyo, Japan).

Immunohistochemistry

Expression of p-NF-κB protein in the ovarian tissue was assessed using the avidin-biotin peroxidase method (Çakır et al. 2019a). Briefly, sections were dewaxed and hydrated, then subjected to antigen retrieval using citrate buffer, pH 6, in a 600 W microwave oven for 5 min. Sections then were treated with 3% methanolic hydrogen peroxide to block endogenous peroxidase activity and Ultra V block solution (TA-125-HDX; Thermo Fisher Scientific, Waltham, MA) was applied to prevent nonspecific staining. Sections then were incubated overnight at 4 °C with primary antibodies (BT-MCA1291; Bioassay Technology Laboratory, Shangai Korain Biotech Co., Shangai, China) diluted 1:50. Biotinylated secondary streptavidin-horseradish peroxidase (TA-125-HDX; Thermo Fisher Scientific) and diaminobenzidine chromogen (TA-060-HDX; Thermo Fisher Scientific) were applied. Sections were counterstained with Gill's hematoxylin. Sections were dehydrated through an alcohol series, cleared with xylene and mounted with Entellan (Doğanyiğit et al. 2020). The sections were examined using a BX53 light microscope (Olympus, Tokyo, Japan). Immunoreactivity levels were assessed using the Image J program. Ten different areas were evaluated for each slide.

Biochemical analysis

A commercial rat malondialdehyde (MDA) assay kit (201–11-0157; Sunred Biological Technology Co., Ltd., Shanghai, China) was used according to the manufacturer's instructions to assay MDA in the ovarian tissue. Results were recorded as nmol/ml MDA.

TUNEL for identifying apoptosis

The number of apoptotic cells was counted in sections using an In situ cell detection apoptosis fluorescein kit (In Situ Cell Death Detection Kit; Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions. Briefly, sections were deparaffinized with xylene, rehydrated through an alcohol series to water, then washed twice with phosphate-buffered saline (PBS) for 5 min. Antigen retrieval was performed using 0.01 M 5% sodium citrate buffer, pH 6.0, at 37 °C in a 600 W microwave oven for 5 min. Sections were cooled at room temperature for 10 min, washed twice with PBS for 5 min each, then incubated with the TUNEL reaction mixture from the kit in a humid chamber at 37 °C for 60 min. The sections then were counterstained with DAPI, mounted in glycerol sealing solution and observed using a BX53 fluorescent microscope (Olympus). We counted apoptotic cells in 50 areas using fluorescence microscopy at 200 x. The total number of TUNEL positive apoptotic cells in 50 different areas was counted by using the Image J program. (Doğanyiğit et al. 2020).

Statistical analysis

The SPSS 22 statistical software package (SPSS Inc., Chicago, IL) was used for statistical analysis. Data are means ± SD. Group comparisons were performed using a one way ANOVA test. The *post hoc* Tukey test was used for binary comparisons. Values for $p \leq 0.05$ were considered significant.

Results

Histology

Sections of ovary of the control and sham groups contained follicles with normal histology at various stages of development (Figure 1). In the IR group, the number of corpora lutea was increased and atretic follicles were observed in some areas. Follicles exhibiting atresia were observed in sections of ovarian tissue of the JIRG1 group; more normal follicles were observed in the sections of the JIRG2 and JIRG3 groups.

Immunohistochemistry

Immunohistochemical staining is illustrated in Figures 2 and 3. p-NF-κB expression was increased significantly in the IRG animals compared to all other experimental groups ($p < 0.05$ for all comparisons). p-NF-κB expression levels were decreased significantly in the JIRG2, JIRG1 and JIRG3 groups compared to the IRG group ($p < 0.0001$ for all comparisons) (Figure 3).

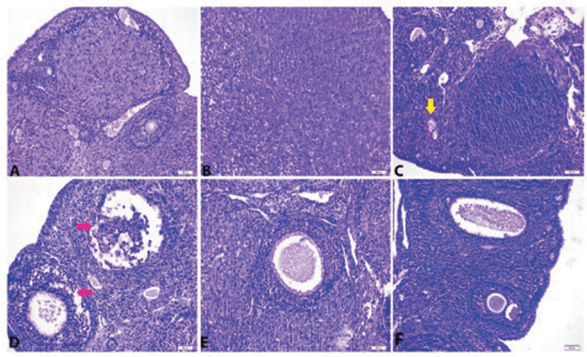


Figure 1. Ovarian tissues stained with H & E. A) Control. B) Sham. C) IRG. D) 0.2 mg/kg JWH-133. E) 1 mg/kg JWH-133. F) 5 mg/kg JWH-133. Yellow arrow, atretic follicle; pink arrows, degenerating follicle destined for atresia. x 200.

Biochemistry

We found significantly increased MDA in the IR group compared to the control group. Although MDA levels were decreased in all drug treated groups compared to the IR group, we found a statistically significant decrease only in the JIRG1 and JIRG3 animals. (Table 1, Figure 4).

TUNEL staining

The number of apoptotic cells was increased significantly in the IRG animals compared to the control group. We found a statistically significant decrease in apoptotic cells in all groups treated with JWH-133 compared to the IR group (Table 1, Figure 5).

Discussion

The ECS commonly is associated with both normal sexual and oocyte maturation, and pathological inflammation and neurodegenerative diseases (Gammon et al. 2005; Di Marzo and Petrocellis 2006; Sun et al. 2013; Çakır et al. 2019b). ECS exerts its effects through cannabinoid receptors, CB_1 and CB_2. We have found no reports concerning the effects of JWH-133 on ovarian IR.

Although ovarian torsion is not common, it is a gynecological emergency that can affect a woman's reproductive health. Surgical detorsion and reperfusion of the ovaries is the predominant treatment (Oelsner et al. 2003). Ovarian reperfusion injury follows resumption of ovarian blood flow; however, reperfusion increases free radicals in the ovarian tissue. Montecucco et al. (2009)

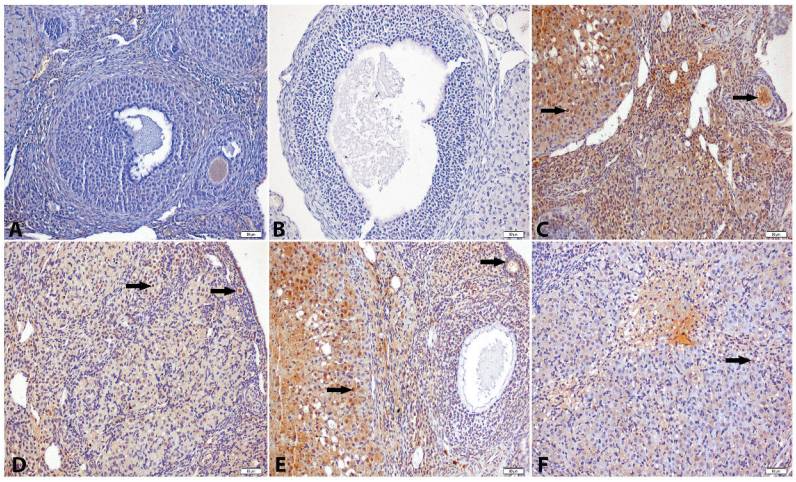


Figure 2. Ovarian tissues stained immunohistochemically for p-NF-κB. A) Control. B) Sham. C) IRG. D) 0.2 mg/kg JWH-133. E) 1 mg/kg JWH-133. F) 5 mg/kg JWH-133.

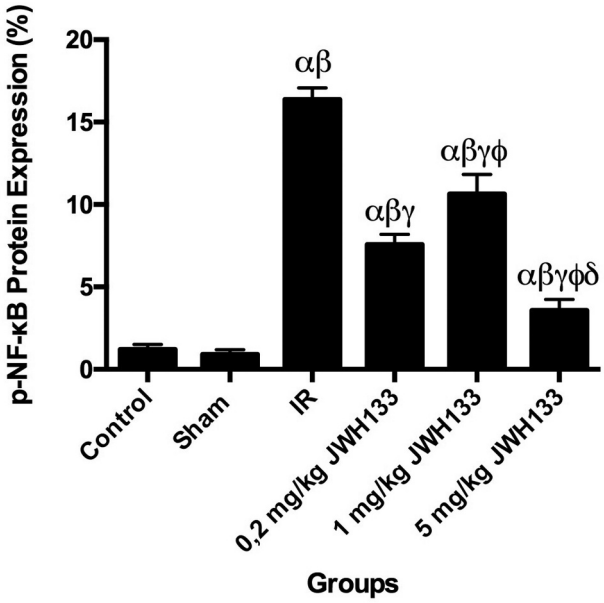


Figure 3. p-NF-kB immunoreactivity data are means ± SD. $^{\alpha}p < 0.05$ vs. control group, $^{\beta}p < 0.05$ vs. sham group, $^{\gamma}p < 0.05$ vs. IRG, $^{\phi}p < 0.05$ vs. 0.2 mg/kg JWH133, $^{\delta}p < 0.05$ vs. 1 mg/kg JWH133.

reported that activation of cannabinoid receptors reduces free radicals.

MDA is a byproduct of lipid oxidation (Del Rio et al. 2005) and MDA levels often are used as a marker for oxidative stress. MDA levels are increased in both ovaries and other tissues following IR (Nayki et al. 2018; Turkler et al. 2018, 2020; Tutun and Baydan 2018). We found that the MDA levels were higher in the IRG than in the other groups. Our finding is consistent with earlier reports (Montecucco et al. 2009; Tutun and Baydan 2018). We found that 0.2, 1 or 5 mg/kg doses of JWH-133 decreased MDA levels; the decrease, however, was not statistically significant for the JIRG2 animals.

Inflammation caused by IR can damage tissue affected by IR. Activation of NF-κB initiates release of proinflammatory cytokines, chemokines and adhesion molecules (Lawrence 2009). NF-κB participates in many inflammatory diseases (Tak and Firestein 2001), so it is a potential pharmacological target (Karin et al. 2004). NF-κB also participates in tissue damage caused by oxidative stress (Guo et al. 2020). Activation of CB receptors improves clinical outcome in inflammatory diseases (Alhouayek et al. 2011). Activation of CB receptors reduces plaque size and immune cell infiltration in atherosclerotic mice, which improves the prognosis for vascular disease (Zhao et al. 2010). CB2RA also exhibits regulatory effects on bone marrow functions. In mice with CB_2 receptor deficiency, the number of neutrophils is increased in the bone marrow (Kapellos et al. 2017). In kidney IR, JWH-133 decreased the expression of NF-κB (Çakır et al. 2019a). Our findings are consistent with the earlier studies.

Table 1. MDA analysis and TUNEL stained cells in ovarian tissue.

	Experimental groups						
Assay	**Control**	**Sham**	**IR**	**0.2 mg/kg JWH-133**	**1 mg/kg JWH-133**	**5 mg/kg JWH-133**	***p***
MDA nmol/ml	2.84 ± 0.34[a]	2.72 ± 0.21[a]	3.63 ± 0.27[b]	2.83 ± 0.24[a]	3.08 ± 0.42[a,b]	2.81 ± 0.56[a]	< 0.001
TUNEL stained cells	0.12 ± 0.34[a]	0.16 ± 0.37[a]	1.45 ± 1.23[b]	0.29 ± 0.46[a]	0.35 ± 0.70[a]	0.35 ± 0.48[a]	< 0.001

Data are means ± SD. Groups indicated by the same superscript are not significantly different.

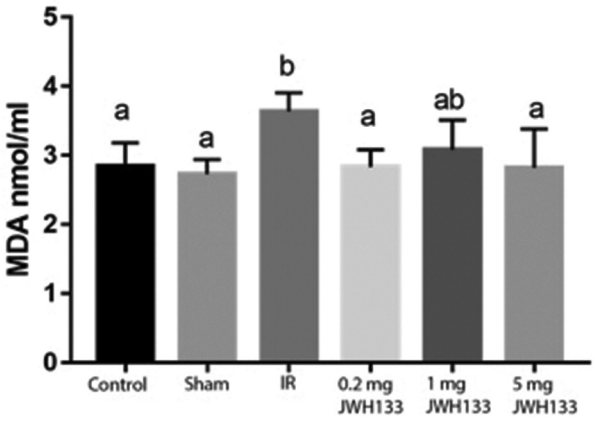
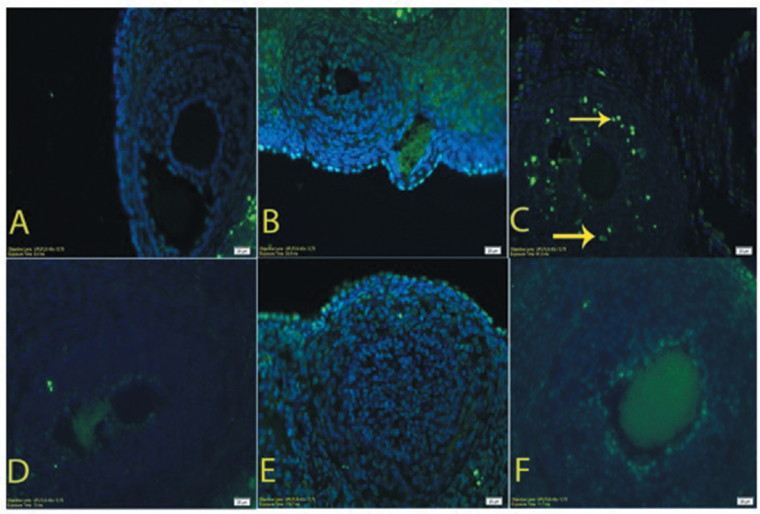


Figure 4. Assay of MDA in the ovarian tissue of the various experimental groups. Data are means ± SD. Groups indicated by the same letter are not significantly different.

Lower NF-κB immunoreactivity was observed in the JWH-133 groups compared to the IRG animals. The JIRG3 group treated with 5 mg/kg JWH-133 exhibited the least NF-κB immunoreactivity.

Earlier investigations of the histopathology of IR injury emphasized neutrophil invasion, dilated vessels and follicular degeneration (Nayki et al. 2018; Turkler et al. 2018). It has been reported that apoptosis plays a role in injury resulting from IR and that JWH-133 reduced both infarct area and apoptosis in myocardial IR (Li et al. 2013). Prech et al. (2010) used the TUNEL assay and found that apoptosis was increased after IR. We used the TUNEL method to evaluate apoptosis following IR injury to the ovary. The reduced apoptosis that we observed at all three doses of JWH-133 is consistent with previous studies.

Application of JWH-133 reduced oxidative stress, apoptosis and inflammation following ovarian IR damage. We suggest that JWH-133 be investigated further as a potential therapeutic agent for ovarian IR.



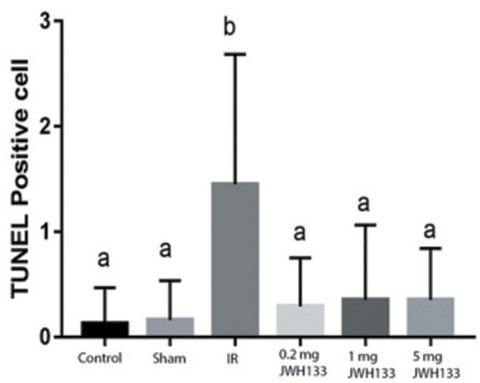


Figure 5. TUNEL stained cells in the ovaries. A) Control group. B) Sham group. C) IR group. D) 0.2 mg/kg JWH-133 group. E) 1 mg/kg JWH-133 group. F) 5 mg/kg JWH-133 group. Yellow arrows, apoptotic cells. G) Number of TUNEL stained cells in the experimental groups. Data are means ± SD. Groups indicated by the same letter are not significantly different. Y axis in TUNEL chart shows the number of TUNNEL positive cells. x 400.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was supported by the Yozgat Bozok University Project Coordination Application and Research Center [6602c-TF/19-249].

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References

Alhouayek M, Lambert DM, Delzenne NM, Cani PD, Muccioli GG. 2011. Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. FASEB J. 25:2711–2721. doi:10.1096/fj.10-176602

Ayakannu T, Taylor AH, Marczylo TH, Willets JM, Konje JC. 2013. The endocannabinoid system and sex steroid hormone-dependent cancers. Int J Endocrinol. 2013:259676. doi:10.1155/2013/259676

Bátkai S, Osei-Hyiaman D, Pan H, El-Assal O, Rajesh M, Mukhopadhyay P, Hong F, Harvey-White J, Jafri A, Hasko G. 2007. Cannabinoid-2 receptor mediates protection against hepatic ischemia/reperfusion injury. FASEB J. 21:1788–1800. doi:10.1096/fj.06-7451com

Çakır M, Tekin S, Doğanyiğit Z, Çakan P, Kaymak E. 2019a. The protective effect of cannabinoid type 2 receptor activation on renal ischemia–reperfusion injury. Mol Cell Biochem. 462:123–132. doi:10.1007/s11010-019-03616-6

Çakır M, Tekin S, Doğanyiğit Z, Erden Y, Soytürk M, Çiğremiş Y, Sandal S. 2019b. Cannabinoid type 2 receptor agonist JWH-133, attenuates okadaic acid induced spatial memory impairment and neurodegeneration in rats. Life Sci. 217:25–33. doi:10.1016/j.lfs.2018.11.058

Del Rio D, Stewart AJ, Pellegrini N. 2005. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis. 15:316–328. doi:10.1016/j.numecd.2005.05.003

Di Marzo V, Petrocellis LD. 2006. Plant, synthetic, and endogenous cannabinoids in medicine. Ann Rev Med. 57:553–574. doi:10.1146/annurev.med.57.011205.135648.

Doğanyiğit Z, Okan A, Kaymak E, Pandır D, Silici S. 2020. Investigation of protective effects of apilarnil against lipopolysaccharide induced liver injury in rats via TLR 4/HMGB-1/NF-κB pathway. Biomed Pharmacother. 125:109967. doi:10.1016/j.biopha.2020.109967

El-Talatini MR, Taylor AH, Elson JC, Brown L, Davidson AC, Konje JC. 2009. Localisation and function of the endocannabinoid system in the human ovary. PLoS One. 4:e4579. doi:10.1371/journal.pone.0004579

Feizi A, Jafari MR, Hamedivafa F, Tabrizian P, Djahanguiri B. 2008. The preventive effect of cannabinoids on reperfusion-induced ischemia of mouse kidney. Exp Toxicol Pathol. 60:405–410. doi:10.1016/j.etp.2008.04.006

Gammon CM, Freeman GM Jr, Xie W, Petersen SL, Wetsel WC. 2005. Regulation of gonadotropin-releasing hormone secretion by cannabinoids. Endocrinology. 146:4491–4499. doi:10.1210/en.2004-1672.

Guo X, Hong S, He H, Zeng Y, Chen Y, Mo X, Li J, Li L, Steinmetz R, Liu Q. 2020. NFkB promotes oxidative stress-induced necrosis and ischemia reperfusion injury through NRF2-ARE pathway. Free Rad Biol Med. 159:125–135. doi:10.1016/j.freeradbiomed.2020.07.031

Houry D, Abbott JT. 2001. Ovarian torsion: a fifteen-year review. Ann Emer Med. 38:156–159. doi:10.1067/mem.2001.114303

Kapellos TS, Recio C, Greaves DR, Iqbal AJ. 2017. Cannabinoid receptor 2 modulates neutrophil recruitment in a murine model of endotoxemia. Mediat Inflam. 2017:4315412. doi:10.1155/2017/4315412

Karin M, Yamamoto Y, Wang QM. 2004. The IKK NF-κB system: a treasure trove for drug development. Nat Rev Drug Discov. 3:17–26. doi:10.1038/nrd1279

Lawrence T. 2009. The nuclear factor NF-κB pathway in inflammation. C S Harb Perspec Biol. 1:a001651. doi:10.1101/cshperspect.a001651

Li Q, Wang F, Zhang YM, Zhou JJ, Zhang Y. 2013. Activation of cannabinoid type 2 receptor by JWH133 protects heart against ischemia/reperfusion-induced apoptosis. Cell Physiol Biochem. 31:693–702. doi:10.1159/000350088

Montecucco F, Lenglet S, Braunersreuther V, Burger F, Pelli G, Bertolotto M, Mach F, Steffens S. 2009. CB2 cannabinoid receptor activation is cardioprotective in a mouse model of ischemia/reperfusion. J Mol Cell Cardiol. 46:612–620. doi:10.1016/j.yjmcc.2008

Nayki C, Nayki U, Keskin Cimen F, Kulhan M, Yapca OE, Kurt N, Bilgin Ozbek A. 2018. The effect of rutin on ovarian ischemia-reperfusion injury in a rat model. Gynecol Endocrinol. 34:809–814. doi:10.1080/09513590.2018.1450378

Oelsner G, Cohen SB, Soriano D, Admon D, Mashiach S, Carp H. 2003. Minimal surgery for the twisted ischaemic adnexa can preserve ovarian function. Hum Reprod. 18:2599–2602. doi:10.1093/humrep/deg498

Pacher P, Haskó G. 2008. Endocannabinoids and cannabinoid receptors in ischaemia–reperfusion injury and preconditioning. Br J Pharmacol. 153:252–262. doi:10.1038/sj.bjp.0707617

Picone RP, Kendall DA. 2015. Minireview: from the bench, toward the clinic: therapeutic opportunities for cannabinoid receptor modulation. Mol Endocrinol. 29:801–813. doi:10.1210/me.2015-1062

Prech M, Marszałek A, Schröder J, Filas V, Lesiak M, Jemielity M, Araszkiewicz A, Grajek S. 2010. Apoptosis as a mechanism for the elimination of cardiomyocytes after acute myocardial infarction. Am J Cardiol. 105:1240–1245. doi:10.1016/j.amjcard.2009.12.039

Pyszniak M, Tabarkiewicz J, Łuszczki JJ. 2016. Endocannabinoid system as a regulator of tumor cell malignancy–biological

pathways and clinical significance. Oncol Targ Ther. 9:4323–4336. doi:10.2147/OTT.S106944

Sasaki KJ, Miller CE. 2014. Adnexal torsion: review of the literature. J Min Invas Gynecol. 21:196–202. doi:10.1016/j.jmig.2013.09.010

Sayyah-Melli M, Rashidi MR, Kaseb-Ganeh M, Rashtchizadeh N, Taghavi S, Ouladsahebmadarek E, Ghojazadeh M. 2012. The effect of erythropoietin against oxidative damage associated with reperfusion following ovarian detorsion. Eur J Obstet Gynecol Reprod Biol. 162:182–186. doi:10.1016/j.ejogrb.2012.02.014

Steffens S, Pacher P. 2012. Targeting cannabinoid receptor CB2 in cardiovascular disorders: promises and controversies. Br J Pharmacol. 167:313–323. doi:10.1111/j.1476-5381.2012.02042.x

Sun J, Fang Y, Chen T, Guo J, Yan J, Song S, Zhang L, Liao H. 2013. WIN55, 212-2 promotes differentiation of oligodendrocyte precursor cells and improve remyelination through regulation of the phosphorylation level of the ERK 1/2 via cannabinoid receptor 1 after stroke-induced demyelination. Brain Res. 1491:225–235. doi:10.1016/j.brainres.2012.11.006

Tak PP, Firestein GS. 2001. NF-κB: a key role in inflammatory diseases. J Clin Invest. 107:7–11. doi:10.1172/JCI11830

Turkler C, Kulhan NG, Ata N, Kiremitli T, Cimen FK, Suleyman H. 2018. Ameliorative effect of lutein on ovarian ischemia-reperfusion injury in rats. Brat Lek Listy. 119:713–717. doi:10.4149/BLL_2018_127

Turkler C, Kulhan M, Kulhan NG, Onat T, Yildirim E, Kaplan S, Suleyman H, Dinc K. 2020. The negative effect of desflurane on reproductive capacity in female rats. Brat Lek Listy. 121:62–66. doi:10.4149/BLL_2020_009

Tutun H, Baydan E. 2018. Cannabinoid receptor type 2 agonist JWH-133 deteriorates the liver toxicity induced by cypermethrin. Turk J Vet Anim Sci. 42:211–221. doi:10.3906/vet-1712-13

Zhao Y, Yuan Z, Liu Y, Xue J, Tian Y, Liu W, Zhang W, Shen Y, Xu W, Liang X, Chen T. 2010. Activation of cannabinoid CB2 receptor ameliorates atherosclerosis associated with suppression of adhesion molecules. J Cardiovasc Pharmacol. 55:292–298. doi:10.1097/FJC.0b013e3181d2644d