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Role of Hyperoside on Ovarian Tissue Damage Created by Ovarian Torsion Detorsion

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Abstract: Here, hyperoside (HYP) was investigated against ovarian tissue injury induced by bilateral ovarian torsion detorsion (T/D) model. 18 Sprague Dawley female rats were grouped as sham, T/D and T/D+HYP. Sham group, abdominal incision was performed and repaired with no additional intervention. T/D group, T/D model was established. T/D+HYP group, HYP was administered by oral gavage prior to detorsion. Following detorsion, rats were sacrificed and the ovarian tissues were excised. Oxidant parameters elevated and antioxidant values declined in T/D group compared to sham group. HYP treatment decreased oxidant biomarkers and increased antioxidant mediators. After all, HYP prevented ovarian tissue injury generated by T/D model in rats. © 2020 NTMS.

Keywords: Hyperoside, Ovarian Torsion Detorsion, Ovary, Rat.

1. Introduction

Ovarian torsion (O/T) may reduce ovarian reserve through damaging ovarian tissue and therefore it is an gynecological emergency, especially during reproductive period (1). Several clinical conditions lead to O/T which diminishes or blocks ovarian blood flow and results in tissue injury (2). Detorsion leads to ischemia reperfusion (I/R) injury by enhancing reactive oxygen species (ROS) production which aggravates the ischemic injury (3). Early diagnosis has importance for the viability of ovaries and keeping fertility (4, 5).

Antioxidant molecules play role in overcoming the harmful effects of ROS (6). Malondialdehyde (MDA) indicates tissue injury and it is generated as a result of lipid peroxidation. It ruins enzymatic activity and permeability of cell membrane (7).

Total oxidant status (TOS) is a significant parameter on evaluating oxidative damage (8). Total antioxidant status (TAS) reflects whole antioxidant activity.

Therefore, ratio between TOS and TAS determines oxidative balance (9). Different agents have been examined to alleviate or eliminate I/R-induced oxidative injuries in various organs (10-14).

But the role of hyperoside (HYP) against ovarian torsion detorsion (T/D) injury has not been investigated yet. HYP is a flavonoid (15) performs against oxidative stress through its anti-ischemic, anti-inflammatory and antiapoptotic activities (16-18). HYP prevented I/R-induced myocardial injury (19). HYP protected against oxidative damage in lung cells induced by H_2O_2 (20). HYP also performed protection against I/R-induced liver damage (18).

Here, it was aimed to determine potential beneficial effects of HYP against oxidative damage induced by ovarian T/D.

2. Material and Methods

2.1. Experimental Animals and Ethical Approval

This study was carried out with the permission (Protocol number: 07.11.2019-207) of Atatürk University Experimental Animals Local Ethics Committee. The animals were supplied by Atatürk University Experimental Animal Research and Application Center and here was also preferred for the experimental steps. Animals were held in regular cages via appropriate laboratory conditions.

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They were fed with standard pellet feed and water but fasted 12 hours prior to experiment to avoid anesthesia related complications.

2.2. Groups and Torsion Detorsion Model

Rats were immobilized in supine position. Abdominal regions were barbered, cleaned and anesthesia was administered prior to surgical procedure. Povidone-iodine was used for the disinfection step. 60 mg/kg intraperitoneal (i.p.) ketamine (Ketalar®, Pfizer, İstanbul) and 10 mg/kg i.p. xylazine hydrochloride (Rompun®, Bayer, İstanbul) were applied as anesthesia to animals. HYP was obtained from Sigma Aldrich Co. 18 Sprague Dawley female experimental rats were randomized as: Sham group: 1-2 cm incision, a median laparotomy, was performed on abdominal area and then it was repaired. T/D group: Following the incision, as described in sham group, torsion was established by rotating ovaries and related structures in clockwise 360 degrees and they were fixed by microvascular clamps. Following 3 hours, clamps were removed providing blood flow for 3 hours in detorsion phase. Incisions were repaired by silk 3/0 suture. T/D+HYP group: All procedures of T/D group were carried out and 20 mg/kg HYP was given to the rats as i.p. prior to detorsion. After the experiment, rats were sacrificed. Ovarian tissues were excised and held at -80ºC until the biochemical analysis.

2.3. Biochemical Analysis of Ovarian Tissues

Firstly, all ovarian tissue samples were homogenized and then all biochemical analyses were performed. Interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) were gauged through appropriate kits (Elabscience, Wuhan, China).

MDA level was gauged through a previous described method (21). Superoxide dismutase (SOD) activity was determined via protocol presented by Sun et al (22). Myeloperoxidase (MPO) activity was demonstrated using a foreknown method (23). TAS and TOS values were determined by commercial kits (Rel Assay Diagnostics).

Oxidative Stress Index (OSI) was measured as: OSI=[(TOS, μmol H_2O_2 equivalent/L)/(TAS, mmol Trolox equivalent/L)×10].

2.4. Statistical Analyses

SPSS package program was preferred for the evaluation of the results. One-way ANOVA test was used for data and Tukey test was used for the results that with no distribution. All results were demonstrated as Mean±Standard Deviation (SD) and p value was accepted significant when $p<0.05$ level.

3. Results

Table 1, 2 and figure 1 represent the biochemical results of ovarian tissue samples. MPO activity, TOS, OSI, TNF-α, MDA and IL-1β levels elevated significantly while TAS value and SOD activity diminished in T/D group when it is compared to sham group. HYP treatment decreased oxidant values, pro-inflammatory cytokine levels and increased antioxidant parameters.

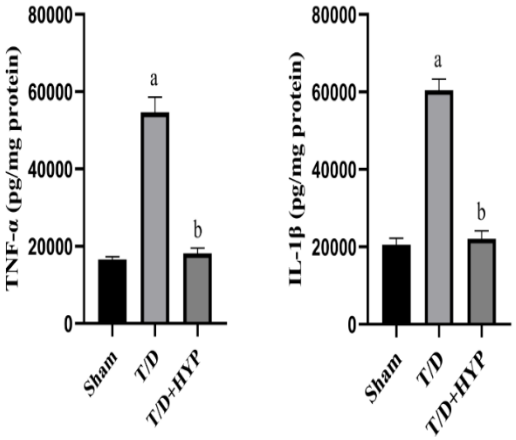

Figure 1: Comparisons of IL-1β and TNF-α levels among sham, T/D and T/D+HYP groups. [a]$p<0.001$ compared to sham group. [b]$p<0.001$ compared to T/D group.

Table 1: Comparisons of Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) levels among sham, T/D and T/D+HYP groups.

Experimental Groups (n=6)	**TAS (mmol/L)**	**TOS (μmol/L)**	**OSI (arbitrary unit)**
Sham	0,73 ± 0,04	5,87 ± 0,81	0,80 ± 0,14
T/D	0,25 ± 0,03[a]	12,17 ± 1,35[a]	4,88 ± 0,68[a]
T/D+HYP	0,72 ± 0,02[b]	6,42 ± 0,77[b]	0,88 ± 0,08[b]

[a]$p<0.001$ compared to sham group. [b]$p<0.001$ compared to T/D group.

Table 2: Comparisons of Superoxide dismutase (SOD), Myeloperoxidase (MPO) activities, and Malondialdehyde (MDA) levels among sham, T/D and T/D+HYP groups.

Experimental Groups (n=6)	**SOD (U/mg protein)**	**MPO (U/g protein)**	**MDA (µmol/g tissue)**
Sham	428,36 ± 29,92	235159,09 ± 20761,28	53,68 ± 4,43
T/D	148,61 ± 7,80[a]	736561,96 ± 55587,92[a]	136,17 ± 12,36[a]
T/D+HYP	408,87 ± 26,12[b]	269082,17 ± 35651,37[b]	66,57 ± 4,30[b]

[a]$p<0.001$ compared to sham group. [b]$p<0.001$ compared to T/D group.

4. Discussion

O/T describes the spinning of ovaries and related structures. During O/T, blood flow is interrupted, ischemia and even necrosis occur in tissues (24). Reperfusion leads to ovarian tissue damage even more than ischemia (25, 26). O/T treatment mainly depends on the protection of ovaries after detorsion (2). Therefore, proactive measures are carried out against tissue injury (27).

I/R injury pathogenesis includes various factors including ROS formation, cytokine release and inflammation (28). It has been proven that oxidative stress causes tissue damage in various animal models (29-32). Various factors including MPO, TOS, TAS and MDA play role in oxidative stress determination. MDA is commonly used to indicate oxidative stress during I/R injury (33-35). Neutrophil infiltration is a part of I/R injury and MPO reflects the neutrophil activity (36). I/R enhances MPO activity in ovarian tissues (37). Neutrophil activation and release of pro-inflammatory cytokines such as TNF-α, IL-1β are enhanced during I/R (38). Exposing to I/R results in increase in TNF-α, IL-1β levels (39, 40). ROS plays role in I/R-related tissue injury (41).

TOS, OSI and TAS values act as oxidative stress indicators and have been used for this purpose in various studies (42, 43). TAS and TOS demonstrate oxidant and antioxidant equilibrium. TAS is an indicator for all antioxidant activity while TOS is limited with ROS (44, 45). SOD catalyzes superoxide free radical conversion into molecular oxygen and superoxide free radical. SOD protects tissues through neutralizing free radicals (46).

HYP prevented H_2O_2-related apoptosis and oxidative stress in granulosa cells by diminishing MDA levels and supporting SOD activity (47). HYP inhibited free radical formation in a previous study (48). Piao et al showed that HYP decreased ROS production besides enhancing antioxidant activity (20). Different agents which performe feature anti-inflammatory, antioxidant and radical scavenging effects have been examined against various I/R injuries (49). In this study, oxidative stress created in ovarian tissues through ovarian T/D model and the potential beneficial properties of HYP were examined against tissue injury. HYP administration was successful on reducing oxidative damage in ovarian tissues caused by ovarian T/D model.

5. Conclusions

HYP is an effective agent against ovarian tissue injury caused by ovarian T/D model via its antioxidant and anti-inflammatory effects. It reduced ovarian tissue injury and became a candidate for therapies against ovarian T/D induced tissue injury.

Conflict of interest statement
None
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