Journal of Research in Pharmacy

Research Article

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Hydroalcoholic extract of *Arum orientale* ameliorates myocardial infarction induced by isoproterenol in rats

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Received: 30 April 2020 / Revised: 31 October 2020/ Accepted: 23 November 2020

ABSTRACT: *Arum* species have antioxidant, antimicrobial, and anti-cancer effects. However, there is no study on its possible cardioprotective effects. In the present study, the protective effects of hydro-alcoholic extract of *Arum orientale* (A. orientale) on isoproterenol-induced myocardial infarction (MI) were evaluated. For induction of MI the rats were received isoproterenol (100 mg/kg) for two consecutive days, whereas treated groups received 40, 80 and 160 mg/kg/day of hydroalcoholic extract of *A.orientale* intraperitoneally *(ip)* 20 min before each Isoproterenol injection. Isoproterenol-induced MI significantly increased myocardial necrosis and neutrophil infiltration. Histopathological analysis showed that *A. orientale* at dose of 160 mg/kg significantly reduced necrosis and neutrophil infiltration in the heart tissue ($P< 0.046$ and $P<0.048$, respectively). Induction of MI also increased myeloperoxidase (MPO) activity and peripheral neutrophil percent. While *A. orientale* similarly decreased MPO activity and peripheral neutrophils in blood ($P<0.021$ $p<0.042$ respectively) at dose of 160 mg/kg. Administration of the extract markedly decreased serum malondialdehyde level at dose of 80 mg/kg and creatine phosphokinase (CPK) activity with all doses. Our results for the first time reported potential cardioprotective effects *of A. orientale* that partially can be through suppression of inflammatory responses and reduction of lipid peroxidation following MI. However, any suggestions for potential use in MI needs further studies.

KEYWORDS: Arum; Myocardial Infarction; neutrophil; lipid peroxidation; creatine kinase

1. INTRODUCTION

Despite the advances and increase of awareness in personal and public health care, cardiovascular diseases, prevalently myocardial infarction (MI) are of the most common causes of human death globally [1]. MI occurs due to imbalance between coronary blood supply and cardiomyocytes oxygen demand [2] Induction of oxidative stress caused by generation of reactive oxygen species (ROS) in cardiomyocytes is a leading factor in pathophysiology of MI. Myocardial necrosis or cell death due to MI is directly associated to ROS generation [3]. Besides, ROS can trigger signaling cascades, which predominantly produce inflammatory cytokines that results in cardiac depression. In response to MI, an intense inflammatory reaction initiates, which is pivotal for cardiac remodeling and repair after MI [4]. Neutrophils are the key mediators of this process that regulates removal of necrotic cardiomyocytes [5]. Although initiation of inflammatory response is beneficial for cardiac remodeling and healing process after MI, but over-activation of inflammation signaling leads to adverse secondary complications in infarcted heart [4]. Thus, suppression of post-inflammation response seems substantial.

Herbal plants are used in East from ancient times and recently are being popular in western consumers [6]. Arum genus, which belongs to *Araceae* family, is a flowering plant native to western Asia, northern Africa, Mediterranean region and Europe [7]. Arum species are used as herbal remedies in traditional medicine of different countries. These plants have exhibited various pharmacological activities, including antioxidant, anticancer, antimicrobial, and anti-nociceptive activities [8-11]. Arum species have

How to cite this article: Javidmehr A, Abbaszadeh S, Kian M, Hamedeyazdan S, Soraya H. Hydroalcoholic extract of *Arum orientale* improves myocardial infarction induced by isoproterenol in rats. J Res Pharm. 2021; 25(1): 80-88.

https://doi.org/10.35333/jrp.2021.287
ISSN: 2630-6344

antioxidant and free radical scavenging potential owing to presence of polyphenols and flavonoids in these plants [11]. Dietary antioxidants and flavonoids of herbal plants could be beneficial for cardiovascular health [12]. To the best of our knowledge, there is no study hitherto on possible cardioprotective potentials of Arum species. *Arum orientale* (A. orientale) is one of the Arum species, which grows in Iran, and so far, no study conducted on the effects of *A. orientale* on cardiovascular diseases.

Isoproterenol (ISO) is a synthetic β-adrenergic receptor agonist which its administration at high doses induces infarct-like lesions in animal models [13]. Therefore, induction of MI in rats by using ISO is a suitable model to evaluate cardioprotective effects of different compounds [14]. In the present study, we evaluated the cardioprotective effects effects of hydro-alcoholic extract of *A. orientale* on myocardial necrosis, neutrophil infiltration, myeloperoxidase (MPO) activity, lipid peroxidation, and creatine phosphokinase (CPK) activity in ISO-induced MI in rats.

2. RESULTS

2.1. Effects of hydro-alcoholic extract of *A. orientale* on myocardial necrosis and neutrophil infiltration

Our histological examination showed regular arrangement of myocardial fibers with no apparent necrosis and neutrophil infiltration in control group. MI group showed widespread subendocardial necrosis and myocardial neutrophil infiltration (Figure 1A). Treated group especially Arum 160 mg/kg significantly reduced myocardial neutrophil infiltration and necrosis (P<0.046) as showed in Figures 1B and C.

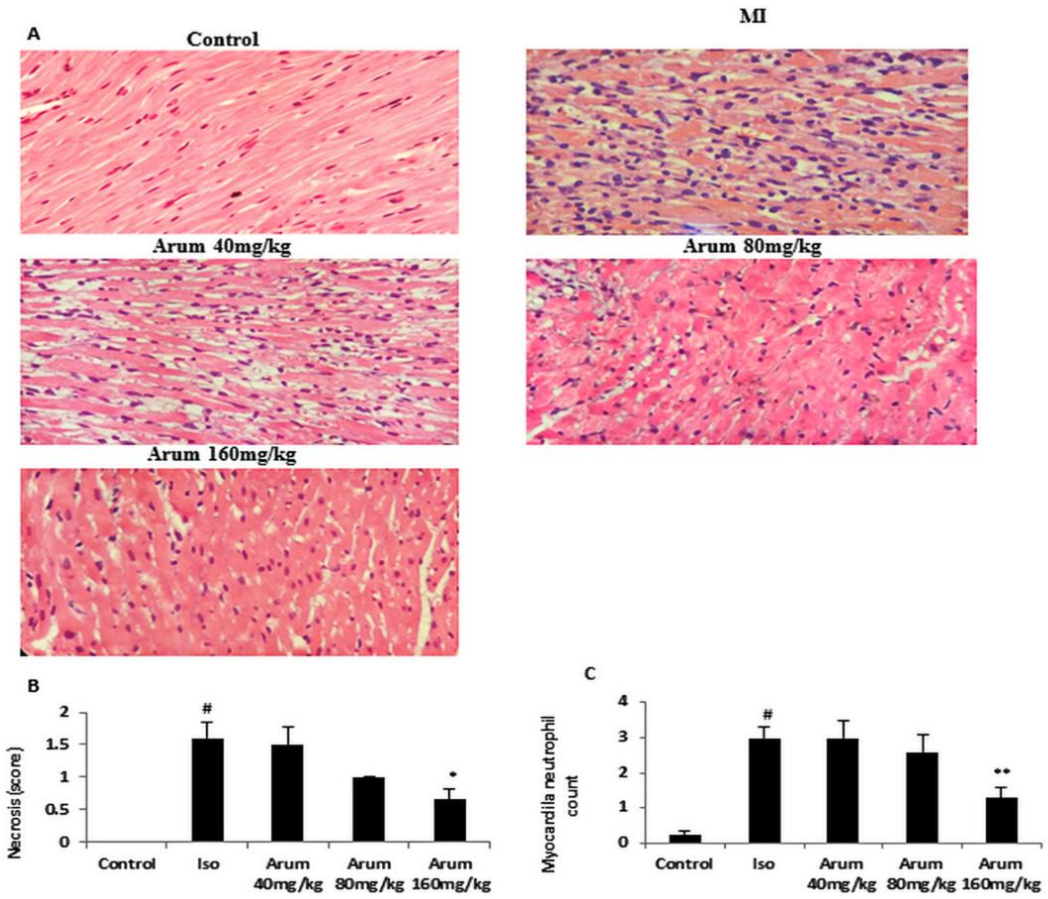

Figure 1. (A) Histopathological observation in the myocardial tissues of the rats treated with hydroalcoholic extract of *A. orientale*. In order to quantify the histological changes, cardiomyocyte necrosis **(B)** and myocardial neutrophil count **(C)** were graded in the rat's cardiac apex tissues after hematoxylin and eosin (H&E) staining (40x magnification). Values are the mean±sem(n = 6). #P<0.001 compared with control group; *P<0.05 as compared with MI group using one way ANOVA with Tukey *post hoc* test.

2.2. Effects of hydroalcoholic extract of *A. orientale* on lipid peroxidation

For determination of lipid peroxidation, malondialdehyde (MDA) level were measured in the serum. MDA levels increased significantly in MI group in compare to control group (P<0.01). Treatment only with moderate dose of the hydroalcoholic extract of *A. orientale* (80 mg/kg) markedly diminished MDA level (P<0.036) that shows this effect is dose–independent (Figure 2).

2.3. Effect of hydroalcoholic extract of *A. orientale* on the activity of myocardial MPO and neutrophil count in blood

ISO injection resulted in an increase in peripheral neutrophil count (P<0.007) and leukocyte infiltration into the myocardial tissue, as measured by an increase in MPO activity (P<0.015). Treatment with the extract was found to reduce the peripheral neutrophil percent (P<0.042) and MPO activity in the myocardial tissue with the most profound reduction at *A. orientale* 160 mg/kg (P<0.021) (Figure 3).

2.4. Effect of hydroalcoholic extract of A. orientale on CPK activity

As can be seen in Figure 4, the total creatine kinase increased significantly in MI group in comparison to control (P<0.000). Treatment with the extract at all three doses caused profound reduction in serum CPK level in comparison to MI group (P<0.000).

3. DISCUSSION

The present study investigated the effects of hydro-alcoholic extract of *A. orientale* on cardiac neutrophil recruitment and necrosis, MPO activity, lipid peroxidation, and CPK activity in ISO-induced MI. Our results showed that administration of *A. orientale* (160 mg/kg) significantly reduced necrosis, neutrophil infiltration and MPO activity in the heart. Treatment with the hydroalcoholic extract of *A. orientale* (80 mg/kg) markedly diminished lipid peroxidation. In addition, treatment with the extract at all three doses reduced serum CPK level in comparison to MI group. According to our findings, treatment with hydroalcoholic extract of *A. orientale* can be cardioprotective in myocardial infarction through its anti-inflammatory and anti-oxidant effects.

Histopathological findings showed that MI induction with ISO caused necrosis in the heart tissue, which is similar to prior studies [15, 17, 18]. The mechanism of necrosis following MI has well elucidated in literatures. Excessive influx of Ca^{2+} increases contractions of myocardium and consequently, increases myocardial oxygen need. These circumstances lead to ATP depletion and leakage of electron from respiratory chain. Released electrons react with oxygen molecules and synthesize ROS, which lead to oxidative damages and finally result in myocardial necrosis [19-21].

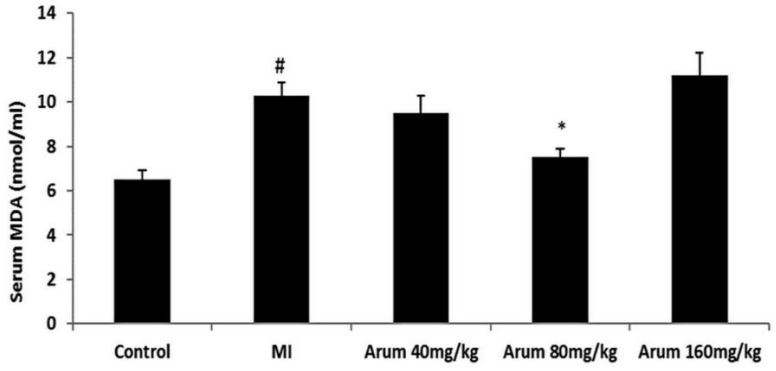

Figure 2. After treatment with hydroalcoholic extract of *A. orientale*, serum MDA levels were measured in rats with isoproterenol-induced MI. Values are mean±sem (n=6). #P<0.05 compared with control group; *P<0.05 as compared with MI group using one way ANOVA with Tukey *post hoc* test.

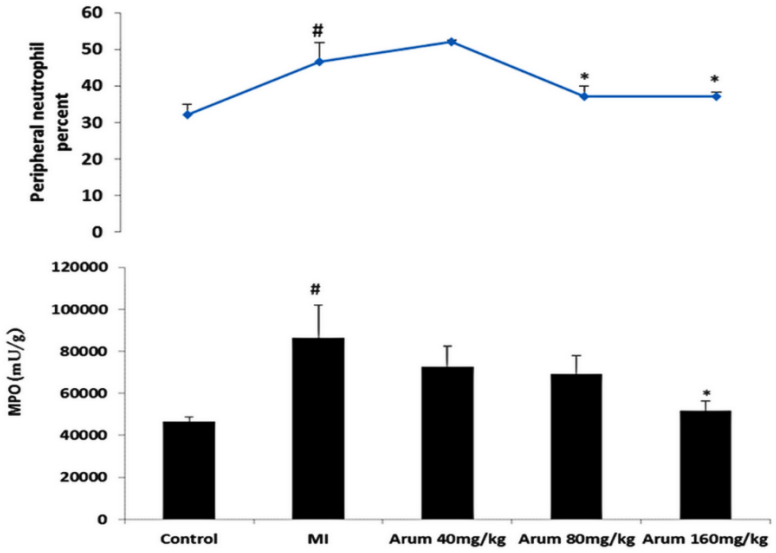

Figure 3. After treatment with hydroalcoholic extract of *A. orientale*, MPO activity (bar graphs) and neutrophil count in blood (line graph) were determined in rats with isoproterenol-induced MI. Values are mean±sem (n=6). #P<0.01 compared with control group; *P<0.05, as compared with MI group using one way ANOVA with Tukey *post hoc* test.

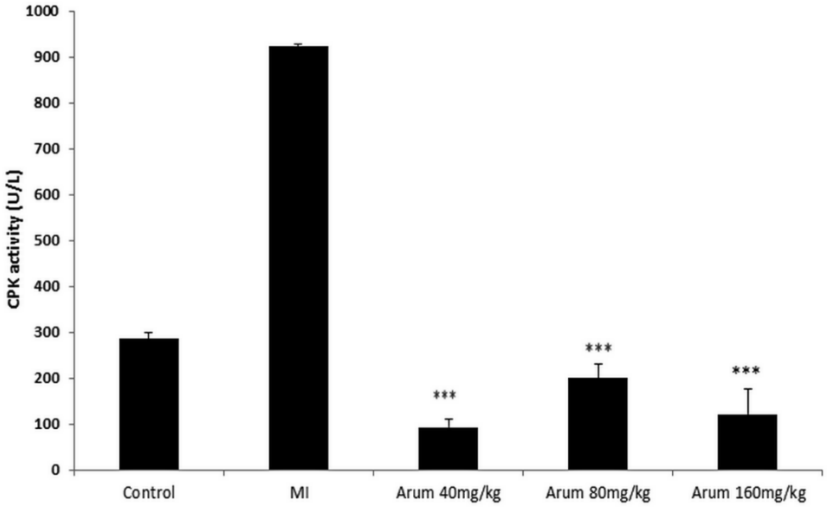

Figure 4. After treatment with hydroalcoholic extract of *A. orientale*, CPK activity was measured in rats with isoproterenol-induced MI. Values are mean±sem (n=6). #P<0.01 compared with control group; ***P<0.001, as compared with MI group using one way ANOVA with Tukey *post hoc* test.

Minimizing of myocardial necrosis is one of the effective strategies to prevail over injuries following MI and optimizing post-MI cardiac healing [15, 22]. Our results showed that administration of *A. orientale* at dose of 160 mg/kg markedly decreased necrosis. Therefore, this plant has advantage on post-MI heart injuries. As mentioned above, excessive activation of post-MI inflammation response negatively affects infarcted heart. Researchers have suggested anti-inflammatory therapy is a good strategy to decrease size of necrosis in infarcted heart [22-24]. Studies on MI canine models revealed that anti-inflammatory treatment reduced size of infarction following MI [25-27]. Considering that induction of inflammation in post-MI heart depends on neutrophils, [5, 28] thereby reduction of neutrophils could be advantageous in minimizing of myocardial necrosis. Evidence have demonstrated that depletion of neutrophils considerably decreased infarcted size and myocardial injury in canine models [26, 27]. Induction of MI in the present study increased peripheral neutrophil percent, serum MPO activity and neutrophil numbers in myocardium. These results indicated occurrence of inflammation following MI and are in line with previous studies [1, 15, 17, 29, 30].

In the current study we demonstrated that, *A. orientale* reduced numbers of neutrophils in the myocardium. In addition, administration of *A. orientale* significantly reduced percent of peripheral neutrophils and MPO activity in infracted heart. Therefore, administration of *A. orientale* hydroalcoholic extract could suppresses inflammation response following MI induction and results in reducing necrosis score in MI-rats. It is noteworthy; this study is the first report on anti-inflammatory effects of *A. orientale*. Our preliminary study (unpublished data) revealed that *A. orientale* possesses alkaloids, flavonoids, saponins, and tannins compounds. Literature have reported these compounds have anti-inflammatory and anti-oxidant activities [31-34]. Therefore, the anti-inflammatory effects of *A. orientale* might be due to the existence of these compounds in its structure. There are few studies on possible effects of *Arum* species on inflammation, which are in contrast with present research. It has been reported that *A. palaestinum* had no anti-inflammatory activity[35]. Another study by Alencar et al. [36] have indicated *A. maculatum* lectin-derived from its tuber has pro-inflammatory effects.

Induction of MI by ISO injection significantly elevated MDA levels of serum that is similar to prior researches [1, 18]. MDA is a biomarker of lipid peroxidation and indicates oxidative damages in cardiovascular diseases [37]. Our results demonstrated that only moderate doses of hydroalcoholic extract *of A.orientale* decreased serum MDA levels that shows dose independent effects. In line with our results, Janakat & Al-Thnaibat [38] showed that aqueous extracts of *A. dioscoridis* has anti-lipid peroxidation activity. These findings could be due to presence of flavonoids and phenolic compounds in structure of Arum species because these compounds have radical scavenging and antioxidant activities[11].

CPK is an enzyme that exist in various tissues including the myocardium and skeletal muscle. Increasing in serum activity of CPK is indicator of cardiac and muscle disorders [39]. Induction of MI in the present study, increased CPK activity in serum that is in parallel with previous reports. However, treatment of animals with *A. orientale* hydroalcoholic extract considerably reduced CPK. As CPK is partially a marker of myocardial damage, [40] these findings indicate cardioprotective potential of *A. orientale*. The lack of phytochemical analysis of the plant to determine effective compound involved in cardioprotection is a limitation of this study.

4. CONCLUSION

To the best of our knowledge, this is the first study reporting potential cardioprotective effects *of A. orientale*. This protection partially can be through suppression of inflammatory responses and reduction of lipid peroxidation following MI. However, any suggestions for potential use in MI needs further studies. Finally, we suggest that the effects of this plant be tested in other animal models of MI.

5. MATERIALS AND METHODS

5.1. Plant collection and extraction

Aerial parts of *A. orientale* were collected from its wild population growing in Aras district, West Azerbaijan, Iran in June 2017. Voucher samples were maintained for reference in the Herbarium of School of Pharmacy, Urmia University of Medical Sciences (No: HUPS-506). The entire plant materials were washed and kept under shade at room temperature till the whole parts became well dried followed by powdering using a grinder (Moulinex, France). Then 130g of plant powder was mixed in ethanol 70% (2.5L) for 24 h at room temperature in order to extract maceration. The extraction process was repeated two more times, Whatman paper filter was used to filter the extract, and eventually ethanol was evaporated by using a rotary evaporator (Heidolph, Germany), at 45°C under vacuum.

5.2. Animals

Healthy adult male Wistar rats (260±20 g, 8-10 weeks old) were used in this study. The animals were obtained from Animal House of Urmia University of Medical Sciences and housed there under standardized conditions (12-h light/dark cycle, temperature 22±1°C and 50±10% humidity) with food and water available ad libitum. All animal experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication, 8th Edition, 2011) and approved by ethics committee of Urmia University of Medical Sciences (ir.umsu.rec.1396.139).

5.3. Experimental procedures

For grouping, the animals were randomly divided into five groups (n=6, each group). In control group, rats received a subcutaneous (*sc*) injection of normal saline (0.5 ml) for two consecutive days. Rats in MI group received an *intraperitoneally (ip)* injection of normal saline for two days and also received (sc) injection of ISO (100 mg/kg/day) for 2 consecutive days at an interval of 24 h. Rats in groups 3 to 5 were *sc* injected with ISO (100 mg/kg/day) and were treated with *ip* injection of hydroalcoholic extract of *A. orientale* at doses of 40, 80, and 160 mg/kg/day for two consecutive days at an interval of 24 h. At the end of experiment, animals were anesthetized by an *ip* injection of a mixture of ketamine (60 mg/kg) and xylazine (10 mg/kg) and blood samples were obtained from hepatic portal vein. Then, animals were euthanized by an overdose of the anesthetics and tissue sampling were done. The overall mortality rate was 25-37%. Actually, the rats who died at the beginning of the study for reasons, such as injections of isoproterenol or anesthetic were excluded from the study.

5.4. Histopathological study

At the end of experiment (on day 3) cardiac tissues rapidly were removed and cardiac apex were isolated. Cardiac specimens were fixed in 10% formaldehyde, then were embedded in paraffin, sectioned at five µm with microtome, and stained with hematoxylin and eosin (H&E) for evaluation of necrosis and neutrophil infiltration. Two trained person (at least one pathologist) were quantified histological changes by scoring as follows: 1, 2, 3, and 4 for low, moderate (small multifocal degeneration with slight degree neutrophil infiltration), high (extensive degeneration and/or diffuse neutrophil infiltration), and intensive (necrosis with diffuse neutrophil infiltration) pathological changes, respectively (40x magnification)[15].

5.5. Malondialdehyde (MDA) measurement

For determination of serum lipid peroxidation, as a marker of oxidative stress, blood samples were taken from portal vein and serum was separated with centrifugation at 3000 rpm for 5 min. Lipid peroxidation was quantified by determination of MDA levels. In brief, 0.5 ml of isolated serum was added to 2.5 ml of 20% trichloroacetic acid (TCA). Then 1ml of 0.6 % thiobarbituric acid (TBA) was added, mixed, and then warmed for 30 min in a boiling water bath followed by rapid cooling. Then 4 ml of n-butyl alcohol was added and centrifuged at 3000 rpm for 15 min. MDA content in the plasma was determined from the absorbance at 535 nm by spectrophotometer. N-buthyl alcohol was used as a blank. The results were presented as nmol/ml plasma [16].

5.6. Neutrophil counting in blood

In order to determine the number of neutrophils in blood, fresh blood samples were smeared on the clean slides and the percent of neutrophils were counted at 100× magnificationin optical microscope after Gimsa staining [15].

5.7. MPO Assay

For quantifying the activity of neutrophils in cardiac tissue, MPO was measured. Briefly, cardiac tissues were homogenized in 50 mM potassium phosphate buffer (pH=6) containing 0.5% hexadecyl-trimethyl ammonium bromide (HTAB) to solubilize the enzyme. The tissues were then freeze-thawed three times and sonicated for 20 s and centrifuged at 11,000×g for 30 min at 4 °C. Then, 100 µl of the upper clear supernatant was added to 2.9 ml solution of 50 mM potassium phosphate buffer (pH 6) containing 0.167 mg/ml of O-dianisidine hydrochloride and 0.0005% H_2O_2. After five minutes, 100 µl of 1.2 M hydrochloric acid was added to stop the reaction. MPO content in the myocardial tissue was determined from the absorbance at 460 nm by spectrophotometer (Cecil 9000, UK). The results were expressed as miliunits of MPO in gram tissue[15].

5.8. CPK Activity

CPK activity was measured according to the instructions provided in a commercially available assay kit (Pars Azmun, Iran).

5.9. Statistical analysis

Data were presented as mean±sem. One-way ANOVA was used to make comparisons between the groups. If the ANOVA analysis indicated significant differences, a *Tukey post hoc test* was performed for

pairwise comparison. SPSS 16 were used for statistical analysis. Any differences between the groups were considered significant at P<0.05.

Acknowledgements: The present study was supported by a grant from the Research Vice Chancellors of Urmia University of Medical Sciences, Urmia, Iran.

Author contributions: Concept- H.S.; Design- H.S.,A.J., S.A.; Supervision- H.S.; Resource- H.S.; Materials- H.S., S.H.; Data collection and processing- A.J., S.A., S.H.; Analysis and Interpretation- H.S.; Literature Search- A.J., S.A., M.K.; Writing – A.J., S.A., M.K.; Critical Reviews – H.S., A.J., S.A., M.K., S.H.

Conflict of interest statement: None declared.

Ethics committee approval: All experiments conducted in this study were approved by ethics committee of Urmia University of Medical Scienceswith the approval number of ir.umsu.rec.1396.139 on 2017.

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