International Journal of Medical Laboratory 2020;7(4):312-320.

Original Article

Effect of *Peganum Harmala* Seeds Extract on Nitric Oxide in U937 Monocytes and Macrophages

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Article history
Received: 23 May 2020
Accepted: 23 Sep 2020
Available online: 30 Nov 2020

Keywords
Macrophages
Nitric oxide
Peganum harmala
U937

A B S T R A C T

Background and Aims: Nitric oxide (NO) has an essential role in inflammation and has been related to pathogenesis and the progress of numerous inflammatory-based diseases, including some cancers. *Peganum harmala* (*P. harmala*) is a medicinal plant used for the treatment of numerous diseases such as several infections. Also, anti-inflammatory effects of *P. harmala* extracts and its derivatives (harmaline and harmine) by suppressing myeloperoxidase, NO, and other mediators have been demonstrated *in vivo*. In this study, the effect of *P. harmala* seeds aqueous extract on NO production in U937 monocytic cells and peritoneal macrophages has been evaluated *in vitro*.

Materials and Methods: U937 and mice peritoneal macrophages were cultured in Roswell Park Memorial institute-1640 with 10% fetal calf serum. Then, the cells at the logarithmic growth phase were incubated with different concentrations of aqueous extract of *P. harmala* seeds (0.1-1 mg/ml) for 24 hours. Next, NO production was assessed by the Griess method in the culture medium.

Results: *P. harmala* seeds aqueous extract did not significantly affect lipopolysaccharide-induced NO production in U937 cells and peritoneal macrophages after 24 hours incubation time compared with untreated control cells.

Conclusions: These results suggest that the anti-inflammatory effects of *P. harmala* may be mediated through NO-independent mechanism(s). However, further studies are warranted to define the *P. harmala* aqueous extract impact on NO expression in other related normal and cancerous cells.

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[Downloaded from ijml.ssu.ac.ir on 2024-05-07]

[DOI: 10.18502/ijml.v7i4.4803]

Introduction

Nitric oxide (NO) is produced by a family of enzymes named nitric oxide synthetase (NOS) [1]. Nitric oxide has an essential role in inflammation [2] and could be a valuable biomarkers in various inflammatory-based diseases such as asthma [3]. NO is produced by numerous structural and inflammatory cells, including eosinophils, macrophages, epithelial cells, and smooth muscle cells [4]. During inflammation, the concentration of NO increases in the lungs [5]. Moreover, NO has been related to the pathogenesis and progress of several diseases comprising insulin resistance, fatness, and cardiovascular anomalies. Furthermore, the effect of NO on the tumor initiation and development of colon, colorectal, gastric, esophageal, and liver cancers (which are inflammatory-mediated) has been shown [6]. The extent of NO generated at the inflammatory site and time is an important determinant of the NO biological effects. Besides, association of deregulated NO in breast cancer microenvironment and tumor progression through angiogenesis promotion and variation of matrix metalloproteinase/tissue inhibitor matrix metalloproteinase has been reported [7].

Peganum harmala (*P. harmala*), as a medicinal herb, has been widely used for therapy of various diseases such as viral, bacterial, and parasitic infections [8-10]. The anti-inflammatory and anti-tumor activities of *P. harmala* or its alkaloid derivatives such as harmine have been demonstrated [11-14]. The toxicity of alkaloid extracts from *P. harmala* seeds has also been described [15]. Besides, the induction of apoptosis by harmine has been determined [16]. Also, cytotoxicity of *P. harmala* seed extract on malignant hematopoietic cells has been shown *in vitro* [17]. Moreover, cytotoxic and apoptotic activity of a novel harmine derivative has been revealed [18]. Anti-angiogenic effects of harmine in bladder cancer have also been presented [19]. Also, anti-inflammatory effects of harmaline and harmine (the *P. harmala*-derived alkaloids) have been demonstrated by suppressing myeloperoxidase, nitric oxide and other mediators in mice [20, 21].

Leukemia, a kind of malignancy resistant to cytotoxic chemotherapy, has a great reversion rate and a poor prognosis [22]. Meanwhile, inflammation has an essential role in leukemia progression [23, 24], and the positive effects of anti-inflammatory substances in leukemia have been indicated [25]. As the present therapeutic medications for leukemia have not been very effective, and reversion rates are great, other innovative treatment approaches are necessary [26]. Since NO has a significant role in leukemia deterioration by facilitating inflammatory cell migration [27] and immune mononuclear cells have a central role in inflammation and NO generation. In this study, the effect of *P. harmala* aqueous extract on NO production in monocytic leukemia U937 cells and peritoneal macrophages has been evaluated *in vitro*.

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[DOI: 10.18502/ijml.v7i4.4803]

Materials and Methods

Reagents and chemicals

Roswell Park Memorial institute (RPMI)-1640 medium, penicillin, streptomycin, and trypan blue were purchased from Sigma (USA). Fetal calf serum (FCS) was obtained from Gibco (USA), and (3-[4, 5-dimethyl thiazol-2, 5- diphenyltetrazoliumbromide]) (MTT) kit was purchased from Invitrogen (USA). Flasks, microtiter plates, and tubes were bought from Nunc (Falcon, USA). *P. harmala* seeds were obtained from the local market.

Preparation of *P. harmala* seeds extract

100 g of certified *P. harmala* desiccated seeds were hewn and boiled in 1 liter distilled water. Next, the solution was clarified and dried out by dehydration. The dried extract was then liquefied in RPMI-1640 and filtered by 0.2 µm filters and put at -20°C until the following tests. The freezed extract was diluted in RPMI-1640 medium to make the needed concentrations previous usage in experiments.

Cells

Human leukemic monocytes (U937, NCBI C130) were bought from National Cell Bank of Iran, Pasteur Inst. of Iran, Tehran. The cells were maintained in RPMI-1640 medium complemented with 10% FCS in 5% CO_2 at 37˚C.

Isolation of peritoneal macrophages from BALB/c mice

BALB/c mouse peritoneal macrophages were prepared according to the Schon-Hegrad method [29]. Briefly, RPMI-1640 was injected into the peritoneum of the mice in a sterile condition. Subsequently, peritoneal lavage was collected and centrifuged at 300 g. Then, the supernatant was discarded, and cell mass was resolved in RPMI-1640 containing 10% FCS. Next, 2×10^5 of these cells were added to each well of a 96-well plate, and the plates were incubated at 37°C for 4 hrs. During incubation, macrophages adhere to the plate. After incubation time, non-adherent cells will be washed off.

Cell culture and treatment

Leukemic cells were cultured in RPMI-1640 medium supplemented with 10% FCS, penicillin (100 IU/ml) and streptomycin (100 µg/ml) at 37˚C in 5% CO2.

The cells were proliferated in 25 cm^2 flasks and passaged when they got 90% convergence. Through passaging, the old medium was replaced with fresh medium. The cells were detached by pipetting alongside the flask bottom by a suitable pipette several times. Then, the cells were sub-cultured in other flasks with fresh medium. After passage, the viability was above 95% according to trypan blue experiment. Next, the cells were distributed at a concentration of 2×10^5 cells/well. Subsequently, the leukemic cells and peritoneal macrophages were separately incubated with different concentrations of *P. harmala* seeds aqueous extract (0.1-1 mg/ml) followed by stimulation with lipopolysac-charide (LPS), 4 µg/ml for 24 hours. All experiments were done in triplicate. After incubation, the supernatants were collected and centrifuged at 1500 rpm for 5 minutes. The supernatants were reserved at -80°C for the next experiments.

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Nitric oxide assay

NO production was estimated by the Griess method in the culture medium [30]. Basis of this colorimetric technique is establishing colors from diazotization by nitrite in an acidic medium and its combination with naphthyl ethylenediamine in Griess substance. Briefly, 50 µL of cell supernate was added to 50 µL of Griess reagent (25 µL of 0.1% solution of N-(1-Naphthyl) ethylenediamine dihydrochloride (Sigma-Aldrich, St. Louis, MO) and 25 µL of 1% sulfanilamide solution (Fluka) in 2.5% H_3PO_4. After 10 minutes in the dark, samples absorbance were read at 570 nm. The amount of $NaNO_2$ was calculated by comparison with a standard curve ranging from 0 to 100 µM of $NaNO_2$. Non-treated cells were used for control.

Trypan blue dye exclusion assay

The trypan blue dye exclusion assessment is a drop-out of color by viable cells and taking up via dead cells. Viability is evaluated by calculating viable and dead cells. The viable cells' ratio to the whole number of cells is considered viability proportion [31]. This study was approved by the Ethical Committee of Shahed University, Tehran, Iran.

Statistical analysis

Effect of the *P. harmala* seeds aqueous extract on each cell line was performed in three independent experiments (n=3), and the results were expressed as mean±standard error of the mean (SEM). Statistical comparisons between groups were made by analysis of variance (ANOVA). $P < 0.05$ was considered significant. For statistical analysis and graph making, the software SPSS 16.0 and Excel 2003 were used correspondingly.

Results

Effect of *P. harmala* seeds aqueous extracts on LPS-induced NO production in U937 cells

In present study, the effect of different concentrations of *P. harmala* seeds aqueous extract on LPS-induced NO production was assessed in U937 cells. Figure 1 shows that *P. harmala* seeds aqueous extract had no significant effect on LPS-induced NO production in U937 cells at used concentrations after 24 hours of incubation time compared with untreated control cells.

Effect of *P. harmala* seeds aqueous extracts on LPS-induced NO production in peritoneal macrophages

The effect of different concentrations of *P. harmala* seeds aqueous extract on LPS-induced NO production in peritoneal macrophages is shown in figure 2. *P. harmala* seeds aqueous extract has not demonstrated any significant effect on LPS-induced NO production in peritoneal macrophages at used concentrations after 24 hours incubation time compared with untreated control cells, as can be seen in figure 2.

Discussion

Natural ingredients are sources of effective mixtures that can help prepare new active therapy [31, 32]. Medicinal plants have been broadly used for the treatment of many tumors, including leukemia [33-37]. The anti-leukemic effects of several medicinal herbs have been associated with their anti-inflammatory properties [38, 39].

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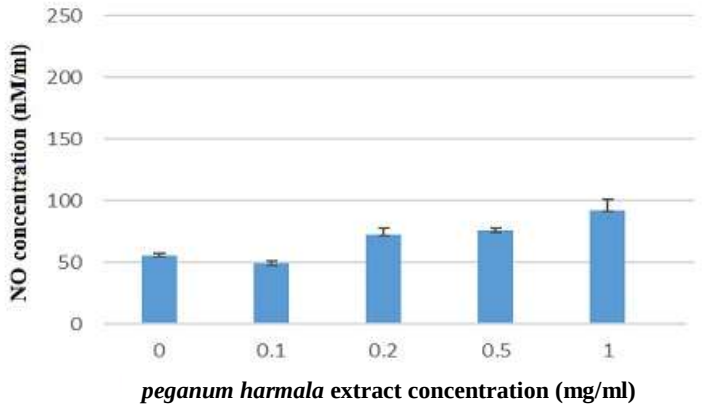

Fig. 1. Effect of *peganum harmala* seeds aqueous extracts on LPS-induced NO production in U937 cells. The U937 cells (2×10^5 cells/well) were treated with different concentrations of *peganum harmala* seeds aqueous extract (0.1 to 1 mg/ml) in the presence of LPS (4 µg/ml) for 24 hours. At the end of treatment, NO concentrations in the conditional medium were detected by the Griess method. Data are mean±SEM of triplicate cultures. N=3; P<0.05 was considered significant.

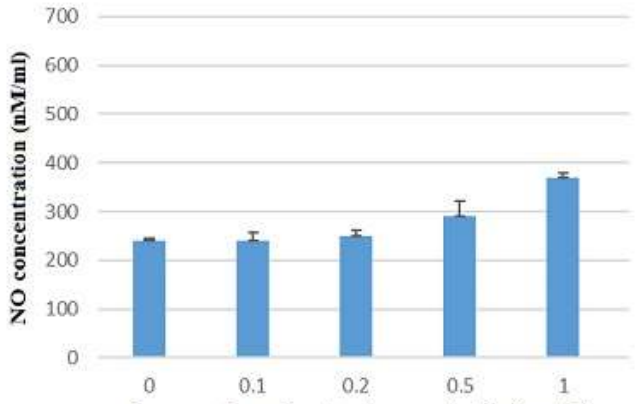

Fig. 2. Effect of *peganum harmala* seeds aqueous extracts on LPS-induced NO production in peritoneal macrophages. The peritoneal macrophages (2×10^5 cells/well) were treated with different concentrations of *peganum harmala* seeds aqueous extract (0.1 to 1 mg/ml) in the presence of LPS (4 µg/ml) for 24 hours. At the end of treatment, NO concentrations in the conditional medium were measured by the Griess method. Data are mean±SEM of triplicate cultures. N=3; P<0.05 was considered significant.

P. harmala is a medicinal plant with known anti-inflammatory and anti-tumoral activities [11-14]. The anti-inflammatory properties of two *P. harmala*-derived alkaloids (harmaline and harmine) have been attributed to their inhibitory effects on myeloperoxidase, nitric oxide, and other inflammatory- mediators production *in vivo* [20, 21]. According to the present study's results, *P. harmala* seeds aqueous extract has no significant effect on LPS-induced NO production in human U937 monocytes/mice peritoneal macrophages.

Although there are a few studies in which harmine or harmaline (the *P. harmala*-derived

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alkaloids) decreased the level of NO *in vivo* in mice [20, 21, 40, 41]. All of these researches were carried out *in vivo* and only assessed the effects of *P. harmala* derivatives, not its extracts. However, in the present study, the *P. harmala* seeds aqueous extract effect were assessed on LPS-induced NO production *in vitro* in U937 cells/peritoneal macrophages. For example, in Salahshoor et.al study, suppressing effects of harmine on NO level in nicotine-administrated mice has been demonstrated [20]. The discrepancy between our results and Salahshoor et al. may be due to several facts. This study was performed *in vitro* on monocytes and macrophages, while Salahshoor et al. researched *in vivo*. Moreover, in the present study, the *P. harmala* seeds aqueous extract effect were assessed on LPS-induced NO production in U937 cells/peritoneal macrophages whereas Salahshoor et al. evaluated the harmine (a *P. harmala* -derivative with antioxidant activities) effects. Besides, in present study, for NO production, the macrophages were stimulated with LPS while in Salahshoor et al. study, nicotine was utilized to induce oxidative stress [20]. Also, in another study conducted by Li et al. (2018), inhibition of inflammation, oxidative stress, and NO by harmaline and harmine in mice has been shown. The inconsistency between Li et al. results and this study's results might be due to many factors. This study was performed *in vitro*, but Li et al. carried out their study *in vivo*. Also, in the current study, the *P. harmala* seeds aqueous extract effect on NO production in LPS-stimulated U937 cells/peritoneal macrophages was measured, whereas Li et al. evaluated the harmine and harmaline effects in scopolamine treated mice [21].

Similarly, in another research, decreasing the level of NO in uterine tissues and serum of mice by alkaloid extracts from *P. harmala* seeds has been revealed by Wei et al. (2018). Once again, the contradiction between Wei et al.'s results and ours might be due to several factors. This study was done *in vitro*, while Wei et al. organized their investigation *in vivo*. Besides, in this study, the *P. harmala* seeds aqueous extract influence on NO production in LPS-stimulated macrophages were studied, whereas Wei et al. assessed the *P. harmala* alkaloids effects in mice [40].

Likewise, in another study, intraperitoneal injection of harmine decreased NO level in mice *in vivo*, as reported by Hamsa et al. [41]. Again, the difference between Hamsa et.al results and our data may be due to some factors. This study was done *in vitro*, but Hamsa et al. conducted their search *in vivo*. Also Hamsa et.al evaluated harmine effects in mice *in vivo* while we investigated the *P. harmala* aqueous extract impact on NO production in LPS-induced immune cells *in vitro*.

It is well known that there are several different ingredients in *P. harmala* extracts with different effects [42, 43]. Even some certain *P. harmala* ingredients (harmaline and harmine) exhibit different properties in different conditions. Accordingly, many therapeutic effects of *P. harmala*, including cytotoxicity, apoptosis induction, and anti-tumoral activities, have especially been

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credited to its main alkaloids (harmaline and harmine) [4, 5]. Various studies show that further alkaloids exist in this plant with different pharmacological effects [44]. Furthermore, different cardiovascular effects of *P. harmala* extract or its main active alkaloids (harmine, harmaline, Harman, and harmalol) has been discovered [45].

Although inhibition of NO by harmaline and harmine in mice has been shown [21, 22], the enhancing effect of harmaline and harmine on NO release from endothelial cells has also been revealed [46]. Also, harman (another *P. harmala* constituent) increased NO release in cultured rat aortic endothelial cells, dose-dependently [47], whereas harmalol (a B-carboline derivative of *P. harmala*) has not shown any impact on the production of NO from endothelial cells [46].

Thus, based on the different and sometimes contradictory effects of *P. harmala* constituents, reported by other investigators, the present study results are interpretable. Accordingly, as different components with opposing effects exist in the extract, which may neutralize each other, the difference between each component's effect and the whole extract's effect can be expected.

To the best of our knowledge, up to now, no well-documented study about *P. harmala* aqueous extract effect on NO production in monocytes/ macrophages has been reported *in vitro*. Further studies are required to define the *P. harmala* extracts, and their derivatives impact NO expression in other related normal and cancerous cells *in vitro* and *vivo*. Also, more investigations are necessary to delineate the molecular mechanism(s) of the *P. harmala* extracts and its derivatives properties, for optimizing the current therapeutic methods as well as preparation the valuable natural candidates for development of innovative therapeutic procedures in different diseases including cancers specially leukemia in which present therapeutic medications have not been very successful and relapse rates are high.

Conclusion

P. harmala seeds aqueous extract showed no effect on NO production in monocytic leukemia U937 cells and peritoneal macrophages *in vitro*. Further studies are required to define the *P. harmala* extracts, and its their derivatives impact on NO expression in other related normal and cancerous cells *in vitro* and *in vivo*.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to acknowledge Shahed University for supporting this study.

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