



Research Article

# Hydroalcoholic Extract from Rhizomes of *Cynodon dactylon* Improve Hemodynamic and Electrocardiogram Parameters in Myocardial Infarction in Rats

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## ABSTRACT

**Background:** *Cynodon dactylon* is a herbal medicine of interest in Iranian traditional medicine, which is used in cardiovascular diseases such as atherosclerosis and heart failure. The purpose of this study was to evaluate the effects of total extract of *C. dactylon* rhizomes on myocardial infarction and on post myocardial infarction (MI) heart tissue injuries.

**Methods:** Isoproterenol (100 mg/kg) was injected subcutaneously for two consecutive days for induction of MI in rats and *C. dactylon* extract was administered orally twice daily started before isoproterenol injection for 4 consecutive days.

**Results:** Histopathological analysis showed a marked increase in myocardial necrosis in rats with MI ( $p < 0.001$ ). Treatment with *C. dactylon* (200 mg/kg) significantly ( $P < 0.05$ ) decreased myocardial necrosis. Hemodynamic variables were significantly suppressed in MI group and treatment with *C. dactylon* improved the hemodynamic parameters ( $P < 0.05$ ). Our electrocardiogram analysis demonstrated that *C. dactylon* with all doses increased R-Amplitude and R-R Interval ( $p < 0.05$ ,  $p < 0.01$ ) which were suppressed in MI group. Furthermore in treated groups with 100 and 200 mg/kg, P-R interval was also significantly increased in compared to MI group.

**Conclusion:** This study demonstrated that *C. dactylon* can improve hemodynamic and electrocardiogram parameters in isoproterenol-induced myocardial infarction and thereby suggest that it can be used as a cardioprotective agent in myocardial infarction.

## Introduction

Myocardial infarction (MI), which occurs due to an imbalance between the supply of coronary blood supply and myocardial demand, is currently one of the most common causes of mortality and morbidity in the world. When the myocardial ischemia surpasses the critical point for extended time and blood supply is not rapidly restored, it will result in necrosis and fibrosis in the cardiac tissue and causes electromechanical complications such as ventricular dysfunction and heart failure. It is noteworthy, MI is associated with inflammatory response and in this regard neutrophils have a pivotal role in inflammatory response to tissue injury and production of oxygen-derived free radicals.<sup>1,2</sup> MI is determined by alterations in hemodynamic, biochemical and histopathological factors along with altered arterial pressure indices and heart rate as well as ventricular dysfunction.<sup>3,4</sup>

Herbal medicine was being used for a long time before pharmaceutical drugs came onto the scene. Recently, medicinal plants because of their more safety and less side effects were taken into consideration and can be a

valuable source of assistance for prescription medicines. One of these plants is *Cynodon dactylon* (L.) Pers. (*C. dactylon*; family Poaceae) that also is known as Bermuda grass, Devil's Grass, Couch Grass, Triticum repens, and Indian Doab. In some provinces of Iran (such as Azerbaijan and Kurdistan), *C. dactylon* is named "Chayer" and the aqueous extract obtained from its rhizomes is used in the treatment of cardiovascular disorders such as atherosclerosis and heart failure due to its hypolipidemic and cardiac tonic effects.<sup>5-7</sup> Several studies have been reported anti-diabetic,<sup>8</sup> anti-microbial,<sup>9</sup> hepatoprotective,<sup>10</sup> anti-inflammatory,<sup>11</sup> antioxidant,<sup>12</sup> antiarrhythmic<sup>6</sup> and also angiogenic effects of *C. dactylon*.<sup>7</sup> A study by Garjani *et al.* demonstrated cardioprotective effects of *C. dactylon* on right heart failure.<sup>5</sup> Shabi *et al.* showed negative inotropic and chronotropic actions of *C. dactylon* on isolated frog heart.<sup>13</sup> The results of another study that investigated the effects of different fractions of hydroalcoholic extract of *C. dactylon* on heart failure showed that the methanolic fraction of *C. dactylon* obtained by 40 and 60% methanol

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had the strongest inotropic effect.<sup>14</sup> Najafi *et al.* demonstrated that the hydroalcoholic extract of *C. dactylon* reduces myocardial infarct size and arrhythmias following isolated heart ischemia/ reperfusion.<sup>6,15</sup> Nevertheless, to our knowledge there is no *in vivo* study on the effects of *C. dactylon* extract on isoproterenol-induced myocardial infarction and MI induced left ventricular dysfunction. Therefore, the present study was carried out to assess the potential of *C. dactylon* as a cardioprotective agent in animal model of isoproterenol-induced myocardial infarction. Isoproterenol is a synthetic catecholamine and  $\beta$ -adrenoceptor agonist which is an appropriate rat model for induction of MI for investigating the cardioprotective effects of therapeutic attempts and its subcutaneous injection causes severe stress in the myocardium which results in severe biochemical, functional and structural changes in heart resulting in an infarct like necrosis of the heart muscle in experimental animal and recapitulates to the human MI.<sup>3,16,17</sup>

## Methods

### Plant extract preparation

*C. dactylon* samples were collected from the field (summer for flowering sample and beginning of spring for rhizomes, Maragheh- East Azerbaijan, Iran) and a sample was stored at herbarium of school of Pharmacy, Tabriz, Iran with a Voucher No. TbzFPh3894. The rhizomes of the plant were dried at room temperature in shade and reduced to relatively fine powder. 400 g of this powdered rhizomes were extracted by maceration method with 2 liter of methanol-water mixture (70:30) for three consecutive days. The extraction process was repeated 2 more times and then combined extracts filtered through Whatman paper (No.1) and evaporated under reduced pressure at 40 °C to dryness. Finally the lipophilic compounds of dried extract were washed off with n-Hexane. The final amount of extract was 27 g which was preserved in a refrigerator until it was used.

### Animals

Male Wistar rats (250±20 g) were used in this study. The animals were given food and water ad libitum and were housed in the Animal House of Urmia University of Medical Sciences at a controlled ambient temperature of 22±2 °C with 50±10% relative humidity and a 12-h light/12-h dark cycle. The present study was performed in accordance with the Guide for the Care and Use of Laboratory Animals of Urmia University of Medical Sciences, Urmia-Iran which is in line with National Institutes of Health publication, 8th edition, and revised 2011 (ethical code: IR.UMSU.REC.1393.257).

### Experimental protocol

The animals were randomly divided into five groups each consisting of six rats. For myocardial infarction induction, isoproterenol dissolved in normal saline and was injected subcutaneously to rats (100 mg/kg) once a day for two consecutive days. Rats in group 1 (control) received a

subcutaneous injection of saline (0.5 ml) and were left untreated for the whole period of the experiment. Rats in group 2 (MI) were subcutaneously injected with isoproterenol (100 mg/kg) daily for 2 consecutive days at an interval of 24 h and gavaged with saline for 4 days. Rats in groups 3 to 5 received isoproterenol subcutaneously for two consecutive days and were treated orally using gastric gavages with hydroalcoholic extract of *C. dactylon* at doses of 50, 100 and 200 mg/kg, twice daily started before isoproterenol injection for 4 consecutive days. *C. dactylon* extract was dissolved in saline and gavaged at a volume of 0.25-0.5 ml based on body weight. All rats were left fasten overnight. However, they had free access to water at the last administration of extract. At the end of experiments, the animals were killed by an overdose of pentobarbital and the hearts were removed and prepared for further analysis.

### Histopathological examination of the cardiac tissues

For the histopathologic examination of heart, 72 h after the last injection of isoproterenol the hearts were rapidly dissected out and fixed in 10% formalin. The heart tissues were embedded in paraffin, sectioned at 5  $\mu$ m and stained with Hematoxylin and Eosin (H&E) for evaluation of necrosis. The histopathological changes were scored by two trained persons independently as 1, 2, 3, and 4 for low, moderate, high and intensive pathological changes, respectively.

### Hemodynamic measurement

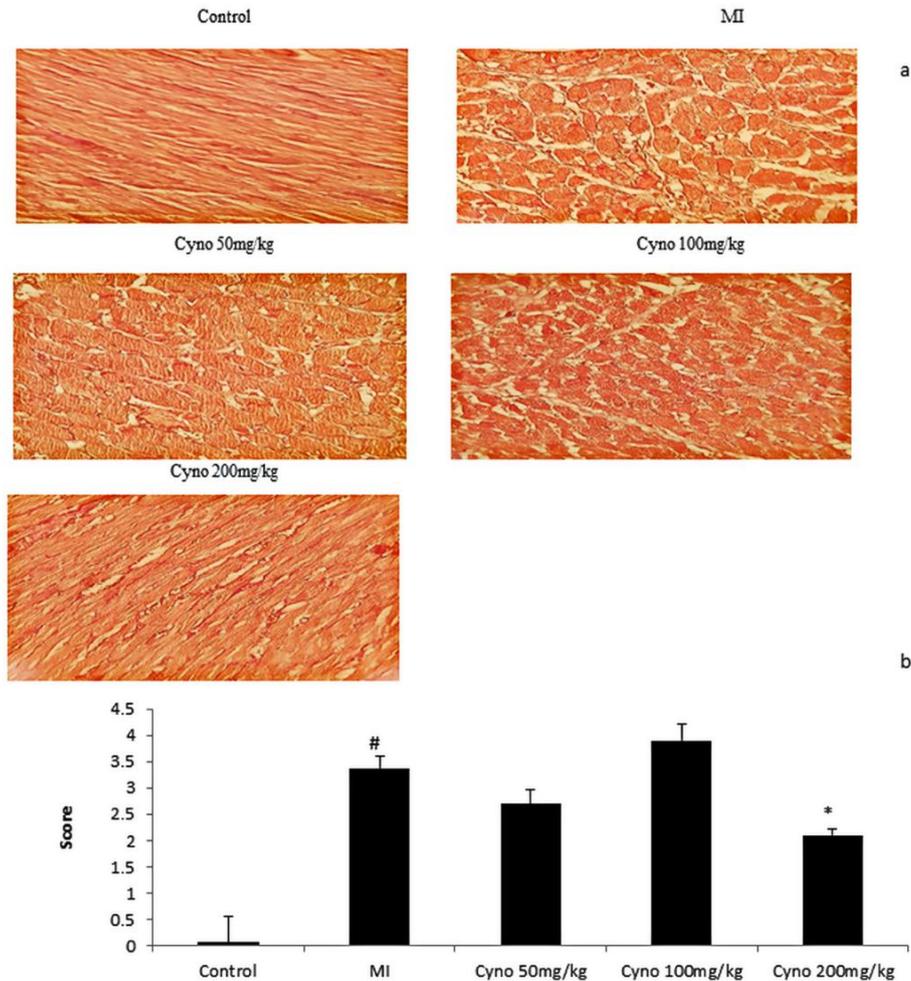
At the end of the experiment, 72 h after the second injection of isoproterenol, the animals were anesthetized by an *ip* injection of a mixture of ketamine (60 mg/kg), xylazine (10 mg/kg), and when the rats no longer responded to external stimuli a standard limb lead II ECG (Powerlab system; AD Instruments, Australia) was recorded and the changes in ECG pattern were examined. For measuring the hemodynamic parameters a polyethylene cannula connected to a pressure transducer was inserted into the left common carotid artery to measure arterial blood pressure (ABP), mean arterial blood pressure (MAP), Developed pressure (DP) and heart rate (HR). All parameters were continuously recorded using a Powerlab system (AD Instruments, Australia).<sup>16</sup>

### Neutrophil counting in blood

Prior to euthanization, in order to determine the number of peripheral neutrophils, blood samples were collected from the hepatic vein. Then fresh blood samples were smeared on the clean lams and stained with Gimsa solution and the percent of neutrophils were counted at 100 $\times$  zooming in optical microscope.

### Statistical analysis

All results are presented as mean±sem. One way ANOVA was used to make comparisons between the groups. If the ANOVA analysis demonstrated significant differences, a Student-Newman-Keuls post test was employed to compare the mean values between the groups.



**Figure 1.** (a) Photomicrographs and grading of histopathological changes of sections of rat cardiac apexes. Heart tissue of MI group shows intensive cardiomyocyte necrosis and increased edematous intramuscular space. Hydroalcoholic extract of *C. dactylon* specially at 200 mg/kg demonstrated a marked improvement. H&E (40<sup>x</sup> magnification). (b) Grading of histopathological changes in the rat's cardiac apex tissues. Grades 1, 2, 3, and 4 show low, moderate, high and intensive pathological changes, respectively. MI: isoproterenol-induced myocardial infarction; Cyno: *Cynodon dactylon*. Values are the mean ± SEM (n = 6 #p < 0.001 from respective control value; \* p < 0.05 as compared with MI group using one way ANOVA with Student-Newman-Keuls post-hoc test.

P<0.05 was considered statistically significant

## Results

### Effects of *Cynodon dactylon* on histopathology of infarcted myocardium

The myocardial fibers were arranged regularly with clear striations in the control group, as shown in Figure 1. There was no evidence of necrosis in the control group. The histological sections of the hearts obtained from MI group demonstrated extensive subendocardial necrosis (Figure 1a). *C. dactylon* extract with dose of 200 mg/kg significantly reduced isoproterenol induced myocardial degeneration and necrosis (p<0.05) (Figure 1a and b).

### Effects of *cynodon dactylon* on the hemodynamic responses

It was observed that mean arterial pressure (MAP) was significantly decreased from 110±7mmHg in control group to 66±9mmHg in the MI group (p<0.01). There was a significant increase (p<0.05) in the mean arterial blood pressure (MAP) of rats treated with *C. dactylon* 50, 100

and 200 mg/kg to 95±4, 98±6 and 97±12 mmHg respectively. It was found that arterial blood pressure (ABP) from 114±13 mmHg in the control group decreased to 72±8 mmHg (p<0.05) in the MI group. *C. dactylon* treatment with doses of 50, 100 and 200 mmHg increased the arterial blood pressure significantly (p<0.05). Isoproterenol alone (MI) reduced developed pressure (DP) from 30±5mmHg in control group to 9±2 mmHg (p<0.01). In the group treated with 50 mg/kg of extract of *C. dactylon* significantly increased developed pressure near to the normal value (p<0.05) (Table 1).

### Effects of hydroalcoholic extract of *Cynodon dactylon* on Electrocardiogram

According to our results, MI group showed a marked (p<0.05) decrease in R-amplitude, whereas treatment with hydroalcoholic extract of *C.dactylon* with doses of 50, 100 and 200 mg/kg/day demonstrated a considerable increase in R-amplitude (p<0.05, p<0.01 and p<0.05 respectively) as compared with MI.

**Table 1.** Effects of hydroalcoholic extract of *C. dactylon* on hemodynamic parameters.

Groups (N=6)	Mean arterial pressure (mm Hg)	Arterial blood pressure (mm Hg)	Heart rate (bpm)	Developed pressure (mm Hg)
Control	110±7	114±13	195±3	30±5
MI	66±9 <sup>#</sup>	72±8 <sup>a</sup>	305±34 <sup>#</sup>	9±2 <sup>#</sup>
Cyno 50 mg/kg	95±4 <sup>*</sup>	109±6 <sup>*</sup>	216±10 <sup>*</sup>	30±5 <sup>*</sup>
Cyno 100 mg/kg	98±6 <sup>*</sup>	110±7 <sup>*</sup>	207±10 <sup>*</sup>	23±4
Cyno 200 mg/kg	97±12 <sup>*</sup>	121±16 <sup>*</sup>	195±16 <sup>*</sup>	16±4

Data are expressed as mean±sem. N=6. <sup>#</sup>p<0.01 and <sup>a</sup>p<0.05 from respective control value; <sup>\*</sup>p<0.05 as compared with MI group using one way ANOVA with Student-Newman Keuls post-hoc test. Cyno: cynodon dactylon; MI: Isoproterenol-induced myocardial infarction

**Table 2.** Effects of hydroalcoholic extract of *C. dactylon* on electrocardiographic parameters.

Groups	P Wave (sec)	QRS complex (sec)	QT interval (sec)	R-R interval (sec)	P-R interval (sec)	R Amplitude (µv)
Control	0.017± 0.002	0.018± 0.004	0.043± 0.002	0.29± 0.006	0.05± 0.002	0.4± 0.05
MI	0.02± 0.001	0.014± 0.001	0.067± 0.01	0.19± 0.029 <sup>a</sup>	0.042± 0.005	0.2± 0.03 <sup>a</sup>
Cyno50 mg/kg	0.022± 0.004	0.013± 0.001	0.066± 0.01	0.27± 0.01 <sup>*</sup>	0.051± 0.002	0.4± 0.03 <sup>*</sup>
Cyno100mg/kg	0.023± 0.003	0.012± 0.001	0.067± 0.009	0.29± 0.013 <sup>*</sup>	0.055± 0.002 <sup>*</sup>	0.5± 0.06 <sup>**</sup>
Cyno200mg/kg	0.021± 0.003	0.013± 0.001	0.076± 0.01	0.31± 0.028 <sup>**</sup>	0.06± 0.001 <sup>*</sup>	0.37± 0.07 <sup>*</sup>

Data are expressed as mean ± sem. <sup>a</sup>p< 0.05 from respective control value; <sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01 as compared with MI group using one way ANOVA with Student-Newman-Keuls post hoc test. Cyno: cynodon dactyl on MI: Isoproterenol-induced myocardial infarction.

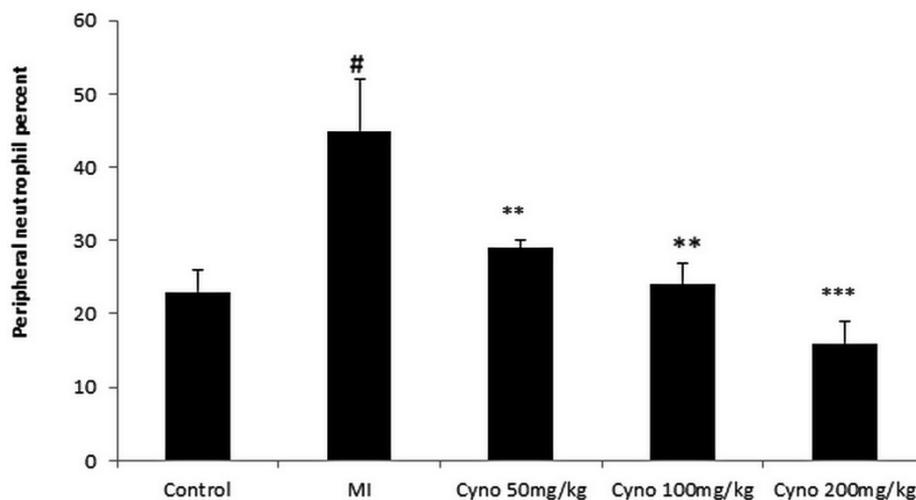
A significant (p<0.05) decrease in the R–R interval and therefore, a significant (p<0.01) increase in the heart rate was observed in the MI group. Treatment with hydroalcoholic extract of *C. dactylon* with doses of 50, 100 and 200mg/kg/day resulted in a significant increase (p<0.05, p<0.05 and p<0.01 respectively) in R–R interval and thus substantially reduced the number of heart beats (p<0.01). Furthermore, treatment with *C. dactylon* 100 and 200 mg/kg/day in compare to MI group increased significantly P-R interval that shows this plant may have A.V node depressant effect (Table 2; Figure 2).

### *The effect of Cynodon dactylon on the peripheral neutrophil count*

Peripheral neutrophil percentage, an indicator of systemic inflammation, was significantly increased from 23±3% in the control group to 45±7% in the MI group (p<0.01). Administration of hydroalcoholic extract of *C. dactylon* with doses of 50, 100 and 200 mg/kg significantly reduced the neutrophil percentage to 29±1%, 24±3% and 16±3% respectively (p<0.01, p<0.01 and p<0.001) (Figure 3).



**Figure 2.** Representative of ECG pattern and changes (recorded from limb lead II) in control, MI and cyno treated rats. MI: Isoproterenol-induced myocardial Infarction; Cyno: *Cynodon dactylon*. (n = 6).



**Figure 3.** The effect of hydroalcoholic extract of *C. dactylon* at the doses of 50, 100, and 200 mg/kg on neutrophil count in blood. Values are mean $\pm$ SEM (n=6). # $p$ <0.01, from respective control value; \*\* $p$ <0.01, \*\*\* $p$ <0.001 as compared with MI group using one way ANOVA with Student-Newman-Keuls *post hoc* test. MI: Isoproterenol-induced myocardial infarction; Cyno: *Cynodon dactylon*.

### Discussion

Rhizomes of *C. dactylon* has been widely used traditionally in some parts of Iran and other countries for the treatment of various cardiovascular diseases such as congestive heart failure, arrhythmias and atherosclerosis.<sup>7,18</sup> In the present study, we studied the therapeutic effect of the hydroalcoholic extract of *C. dactylon* on hemodynamic and ECG parameters and also on necrosis and peripheral neutrophil count in isoproterenol-induced myocardial infarction in rats. The results of present study demonstrated that treatment with hydroalcoholic extract of *C. dactylon* alleviated cardiac necrosis and peripheral neutrophil count and also improved cardiac hemodynamic and electrocardiographic parameters. All doses of *C. dactylon* extract increased MAP and ABP and decreased heart rate. Additionally, increased R amplitude, R-R interval and also P-R interval in electrocardiogram. The results of this study for the first time demonstrated that the hydroalcoholic extract of *C. dactylon* had protective effects in isoproterenol-induced myocardial infarction.

Isoproterenol in very high doses causes cardiac ischemia, hypoxia and necrosis with morphological and functional changes in the heart that are very similar to the hemodynamic and pathological changes seen in human MI.<sup>19,20</sup> Isoproterenol induced cardiotoxicity, can be attributed mainly to generation of highly cytotoxic free radicals through auto-oxidation of catecholamines.<sup>21,22</sup> Our ECG data analysis in MI group demonstrated decreased R-Amplitude, R-R interval and P-R interval and increased heart rate. Some studies reported that increased heart rate can cause myocardial necrosis by increasing oxygen consumption.<sup>23</sup>

In 2008, a study by Najafi *et al.* Showed that hydroalcoholic extract of the rhizome of *C. dactylon* had antiarrhythmic effects on ischemia/reperfusion-induced arrhythmias.<sup>6</sup> Another study by Najafi *et al.* in 2009 demonstrated the protective effects of hydroalcoholic extract of *C. dactylon* rhizomes against I/R-induced

injuries. Part of these protective effects was probably due to improved hemodynamic parameters in isolated heart.<sup>15</sup> In 2009, Garjani *et al.* found that *C. dactylon* had positive inotropic effects and improved cardiac function in compensated right heart failure.<sup>5</sup> In 2011, a study was conducted to investigate the anti-inflammatory effects of the aqueous extract of *C. dactylon* in rats. This study also showed that the extract contains phytochemically active components with anti-inflammatory effects.<sup>11</sup> However, little is known about the effects of *C. dactylon* in myocardial infarction. In agreement with the results of the above studies, our study showed that hydroalcoholic extract of the rhizome of *C. dactylon* improves the pattern of electrocardiogram and hemodynamic and also reduced the peripheral neutrophil count and isoproterenol induced myocardial degeneration and necrosis in myocardial infarction.

In 2015, Soraya *et al.* suggested that aqueous extract of *C. dactylon* had an angiogenic compounds, and promotes angiogenesis by stimulating the expression of VEGF as a growth factor.<sup>7</sup> Therefore, the protective effects of this plant on ischemic heart disease and myocardial infarction can be partially attributed to this effect.

Phytochemical analysis of *C. dactylon* showed that its extract contained flavonoids including apigenin, luteolin, orientin and vitexin, sterols and steroidal saponin.<sup>24-26</sup> It has been observed that flavonoids play a role in scavenging oxygen free radicals and are effective antioxidants.<sup>27,28</sup> and also many studies have been done on the anti-inflammatory effects of flavonoids. Flavonoids, in addition to anti-inflammatory activity, can reduce inflammation by inhibiting the production of enzymes involved in inflammation.<sup>11,26</sup> Studies have also shown that saponins in some plants improve cardiac function at an early stages of myocardial infarction.<sup>29</sup> Therefore, these components present in the *C. dactylon* extract may cause cardioprotective effects seen in isoproterenol-induced myocardial infarction.

## Conclusion

Our results indicated that the hydroalcoholic extract from rhizomes of *C. dactylon* can improve hemodynamic and electrocardiogram parameters as well as reduced the peripheral neutrophil count and isoproterenol induced myocardial degeneration and necrosis in myocardial infarction. This suggests that *C. dactylon* can be used as a cardioprotective agent in myocardial infarction.

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## Conflict of interests

Prof. Alireza Garjani is the Editor-in-Chief of Pharmaceutical Sciences. The peer-review process of the submission was supervised by another member of the editorial board. The authors claim no other competing interests.

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