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Original Article: The Role of *Rosa Damascena* Mill. on Acute Hypoxia

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Abstract

Background: In the Rosaceae family, *Rosa damascene* Mill. is an important medicinal plant Studies reported its antioxidant, cardioprotective, and neuroprotective effects that may be related to the anti-hypoxic activity. So, we investigated the anti-hypoxic effects of *R. damascenaare*in this study to evaluate the possible mechanism of plant effectiveness in cardiovascular and neurological disease.
Methods: The *R. damascenaare* flowers were extracted with methanol by maceration method and anti-hypoxic activities were evaluated in haemic, asphyctic, and circulatory models.
Results: In asphyctic hypoxia, extract at 250 mg/kg increased the survival time to 21.53±1.21 minutes, which was significantly lower (P<0.0001) than phenytoin (29.60±1.34 minutes). In haemic hypoxia, extract effects were similar to propranolol (P>0.05) at 125, and 250 mg/kg (15.85±0.69 and 16.19±1.71 vs. 16.44±1.39 minutes, P>0.05). In circulatory hypoxia, extract significantly increased the survival time at 250 mg/kg compared to the negative control (13.64±1.51 vs. 9.79±0.56 minutes, P<0.01) but its effect was weaker than propranolol (16.44±1.39 minutes).
Conclusion: *R. damascenaare* show potent anti-hypoxic activity in the haemic model. Its effects were significant in higher doses in asphyctic and circulatory models.

Keywords: Cardiovascular Diseases, Reactive Oxygen Species, Asphyxia, Ischemia, Stroke.

Introduction

Cardiovascular disease is an important reason for death globally and continues to be one of the top victims in modern society. Various causes, including ischemia-reperfusion damage, can be triggered (Gill, Mestril, & Samali, 2002). Recent studies have shown that ischemic regions undergo apoptosis. According to some studies, oxidative stress modulates apoptosis, and antioxidants play a role in preventing it.
Reactive oxygen species (ROS) contribute to tissue damage. The production of ROS increases lipid peroxidation, increases urinary lipid metabolite excretion, modulates intracellular oxidized states, damages DNA and cell membranes, and affects gene expression. In many types of cells, ROS induces apoptosis. In different systems, antioxidants have been shown to suppress or delay apoptosis by acting as ROS scavengers(Hernanz *et al.*, 2001; Parlakpinar, Sahna, Acet, Mizrak, & Polat, 2005). To date, an association between antioxidant activity and iron chelating activity (M. A. Ebrahimzadeh, Pourmorad, & Bekhradnia, 2008), antihaemolytic activity (M Khalili, Ebrahimzadeh, & Safdari, 2014), nitric oxide radical scavenging potential (M. Ebrahimzadeh, Nabavi, Nabavi, & Pourmorad, 2010), and sun protection factor have been reported(M. Ebrahimzadeh *et al.*, 2014). The difference between insufficient oxygen availability and the need for oxygen influences the hypoxia of the

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heart. It occurs mainly in ischemia ,and resulting in multiple deleterious symptoms and, eventually, death.(Kiang & Tsen, 2006). ROS are produced as a result of hypoxia-induced oxidative stress.(Maiti *et al*., 2006). It is not clear whether there is a link between antioxidant activity and anti-hypoxia but there is some evidence to suggest a link between antioxidant activity and antihypoxia. Some compounds and plants with good antioxidant activity have shown good anti-hypoxic activities (M. A. Ebrahimzadeh *et al*., 2018a; Kaveh, Mohamadyan, & Ebrahimzadeh, 2019; M Khalili, Dehdar, Hamedi, Ebrahimzadeh, & Karami, 2015; Masoumeh Khalili, Ebrahimzadeh, Omrani, & Karami, 2014). It has been shown that antioxidant compounds can scavenge ROS and demonstrate anti-hypoxia properties. Increasingly, natural antioxidants are being used in place of chemical antioxidants.

In solid tumors, blood vessels are abnormally organized, which reduces oxygen and nutrient availability and reduces the survival rate of normal cells, while tumor cells are resistant to these conditions. As a result, hypoxia increases tumor cells' ability to cause metastasis and disease progression. Also, the response to treatment in hypoxic tumor cells is less. Compounds that can change these conditions can have significant effects on preventing the progression and treatment of solid tumors (Bennewith & Dedhar, 2011).

Mountain or altitude sickness is a pathological condition caused by a decrease in the relative pressure of atmospheric oxygen at altitude. It can cause drowsiness, mental and muscular fatigue, decreased mental efficiency, and decision-making power in the early stages and muscle contractions, seizures, coma, and death in more advanced stages. Antipyretic compounds can be useful in treating this disease (Cui *et al.*, 2018; Hall, 2016).

Recent studies conducted on COVID-19 showed that hypoxia plays an effective role in the mortality rate. Also, anti-hypoxic activity was reported from anti-covid drugs such as dexamethasone. The treatment of this disease may be improved by anti-hypoxic compounds in the future (Hosseinzadeh, Shamshirian, & Ebrahimzadeh, 2021; Shamshirian, Shamshirian, Hosseinzadeh, & Ebrahimzadeh, 2020).

Rose damascene Mill. is one of the important medicinal plants of the Rosaceae family. *R. damascene* is known as Gole-E-Mohammadi in Persian culture (Loghmani-Khouzani, 2007). it is traditionally used for chest and abdominal pains, digestive diseases, constipation and menstrual problems, and (Batool, Kalsoom, Akbar, Arshad, & Jamil, 2018; Mahboubi, 2016).Flavonoids and glycosides, terpenes, and anthocyanins are important compounds found in different parts of the plant. (Davoodi *et al.*, 2017) Vitamins B1, B2, B3,C, A, and K, malic acid, carotenoids, citric acid, tannins, and pectinhave also been reported. (Bikmoradi, Harorani, Roshanaei, Moradkhani, & Falahinia, 2016) Major active phenolic compounds are quercetin, gallic acid, kaempferol, cyaniding,and D-glycoside (Hashempur, Khademi, Rahmanifard, & Zarshenas, 2017).*R. damascene* has strong antioxidant, anti-diabetic, anti-inflammatory, anti-aging, relaxant, sedative, neuroprotective, and cardioprotective activities (özkan, Sagdiç, Baydar, & Baydar, 2004).

Due to its active flavonoids and phenolic compounds, *R. damascene* exhibits antioxidant properties. It is used to treat and prevent diseases by inhibiting free radicals(Afsari Sardari, Mosleh, Azadi, Mohagheghzadeh, & Badr, 2019). Its neuroprotective effects are due to the inhibition of hippocampal neurons(Homayoun *et al*., 2015). The cardioprotective activity of *R. damascene*hydro-alcoholic extract can prevent high blood pressure (Homayoun *et al*., 2015) and show dose-dependent ionotropic and chronotropic effects (Boskabady, Vatanprast, Parsaee, & Boskabady, 2013). Based on the good antioxidant, neuroprotective and cardioprotective activities of *R. damascene*, this plant may have shown these effects due to its anti-hypoxic activity, so in this study, we investigated the anti-hypoxic properties of *R. damascene.*

Materials and Methods

Preparation of Plant extract

The *R. damascena are* flowers were purchased from a local market, after preparing the herbarium and determining the herbarium number (identified by Dr Bahman Eslami in Department of Biology, Islamic Azad University of Qhaemshahr, Iran; voucher no:

173-648). The dried powder of the plant was extracted by methanol using the maceration method (3 rounds and each round for 48 hours). The extract was concentrated and dried with a rotary evaporator at 40 ºC (Bakhshi Jouybari, Bekhradnia, Mirzaee, & Hosseinzadeh, 2022) to obtain the methanolic extract of *R. damascena* flowers (MRF).

Animals

Male Swiss albino mice (21 ± 3 g) were housed in polypropylene cages at 44-54% relative humidity and 24 ± 1 ºC, with a 12-hour on/12-hour off cycle (lights on at 8 a.m.). The animals had free access to standard pellets, water, and libitum. Experiments were performed between 9:00 and 15:00 h.A standard pellet diet, water, and libitum access were provided to the animals. The experiments were conducted between 9:00 and 15:00 h. The NIH guidelines of the Laboratory Animal Care and Use were followed in all experiments. A protocol for the experimental study was also approved by the Institutional Animal Ethical Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1398.144). To perform the experiments, the mice were divided into groups of 8.

Asphyctic Hypoxia

Mice were subjected to hypoxia by putting them separately in a firmly closed 300 ml glass container which was placed underwater in an aquarium of 25 ºC. The animals had convulsions and died from hypoxia. The survival time was recorded. Mice received single i.p. injections of 62.5, 125, and 250 mg/kg doses of MRF or phenytoin (50 mg/kg) 30 min prior to hypoxia. The control group was treated with normal saline. As a positive control, phenytoin was used, while as a negative control, normal saline was used. (Hosseinzadeh & Ebrahimzadeh, 2020; Mortazavi, Hosseinzadeh, & Ebrahimzadeh, 2021).

Haemic Hypoxia

The haemic hypoxia test was performed based on previous reports and with some modifications [18, 41]. Mice were injected with sodium nitrite ($NaNO_2$) at a dose 360 mg/kg i.p. after the i.p. administration of 62.5, 125, and 250 mg/kg doses of MRF. Each animal's survival time (in minutes) is defined as the time between the induction of hypoxia and death. The Control group was treated with normal saline (10 ml/kg) and propranolol (20 mg/kg) was used as the positive control(Hosseinzadeh & Ebrahimzadeh, 2020; Hosseinzadeh *et al*., 2021; Mortazavi *et al*., 2021).

Circulatory Hypoxia

The circulatory hypoxia test was performed based on previous reports and with some modifications. A NaF (150 mg/kg) solution was administered i.p. to mice thirty minutes after 62.5, 125, and 250 mg/kg doses of MRF were injected i.p. Antihypoxic activity was estimated in minutes as the survival time. Normal saline (10 ml/kg) was administered to the control group, and propranolol (20, and 40 mg/kg) used as the positive control(Hosseinzadeh & Ebrahimzadeh, 2020; Hosseinzadeh *et al*., 2021; Mortazavi *et al*., 2021).

Statistical Analysis

The statistical analysis was performed using GraphPad Prism 8. The data are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was done. To determine the differences in means, the Tukey multiple comparisons test was used. The P-values below 0.05 were considered significant.

Results

In asphyctic hypoxia, MRF at 250 mg/kg increased the survival time to 21.53±1.21 minutes, which was significantly lower (P<0.0001) than phenytoin (29.60±1.34 minutes). At 62.5, and 125 mg/kg, MRF increased the survival time, but its effect was not significant compared to the normal saline (20.08±0.72 and 20.35±1.39 vs. 18.91±1.41 minutes, P>0.05). So, MRF showed weak activity in the asphyctic hypoxia model.

The extract showed potent antihypoxic activity in haemic and circulatory models (Fig. 1 and 2). In haemic hypoxia, MRF effects were similar to propranolol (P>0.05) at 125, and 250 mg/kg (15.85±0.69 and 16.19±1.71 vs. 16.44±1.39 minutes, P>0.05). In 62.5 mg/kg, MRF activity was not significant compared to the negative control (11.25±1.21 vs. 11.13±0.59 minutes, P>0.05).

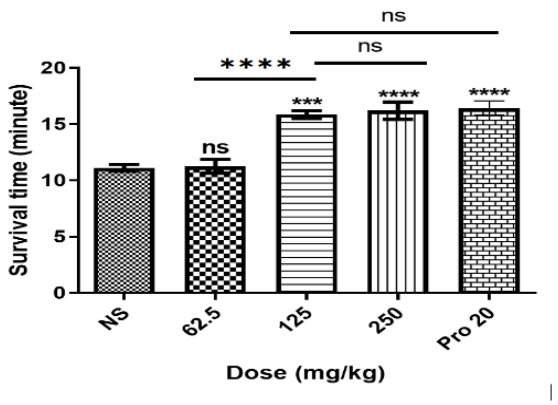

Fig. 1 Antihypoxic activity of MRF in haemic hypoxia. Data are expressed as mean ± SD (n=8), (ns, not significant, P > 0.05, *** P < 0.001, **** P < 0.0001).

In circulatory hypoxia, MRF significantly increased the survival time at 250 mg/kg compared to the negative control (13.64±1.51 vs. 9.79±0.56 minutes, P<0.01) but its effect was weaker than propranolol (16.44±1.39 minutes). At 62.5, and 125 mg/kg, MRF increased the survival time, but its effect was not significant compared to the negative control (10.54±1.52 and 11.58±0.43 minutes, P>0.05).

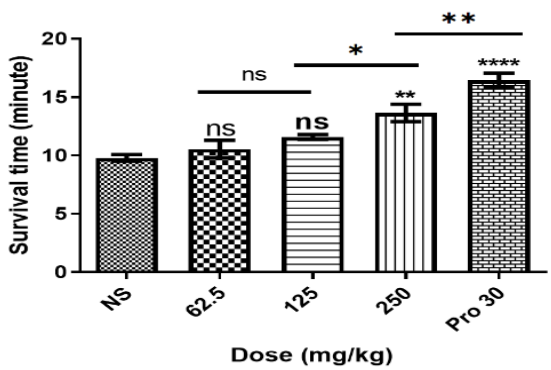

Fig. 2 Antihypoxic activity of MRF in circulatory hypoxia. Data are expressed as mean ± SD (n=8), (ns, not significant, P > 0.05, * P < 0.05, ** P < 0.01, **** P < 0.0001).

Discussion

At the cellular level, hypoxia leads to high levels of oxidative stress. Low oxygen levels are especially dangerous for the brain, which absorbs a significant amount of oxygen.(Warner, Sheng, & Batinić-Haberle, 2004). Because of its high amount of polyunsaturated fatty acids, it is simple to oxidize (Peruche, Ahlemeyer, Brungs, & Krieglstein, 1990). Anti-hypoxia activity manifests in animals' recovery time in a sealed container. Brain tissue loses its anatomical and functional stability due to oxygen deficiency. Consequently, any medicine that allows the brain to survive the effects of ischemia or hypoxia will be of considerable clinical importance. Several various laboratory models have been developed over the last decades that could be used to test the invivo anti-ischemic and antihypoxic drug effects (Peruche *et al.*, 1990). The excessive production of free radicals damages biological materials, howerver, they serve as signaling agents in many normal physiological systems. Hypoxia leads to increased ROS levels due to the accumulation of decreased mitochondrial electron transport equivalents. (Bakonyi & Radak, 2004). The results of ROS can be particularly noticeable in other organs, such as the brain, as it absorbs about one-fifth of the basal oxygen. Treatments to reduce the symptoms of oxidative stress have been improved many times over the years. Antioxidants have been shown to prevent a wide range of diseases. Pharmacologically and medically, polyphenols are potent antioxidants.(Spencer, 2010).

A strong collaboration has been identified between oxidative metabolism and cholinergic activity during the investigations of NaNO2 on brain metabolism (Gibson, Shumada, & Blass, 1978). Chemical hypoxia is caused through the injection of NaNO2 (360 mg/kg, i.p.), which decreases the oxygen-carrying potential of the blood by transforming hemoglobin to methemoglobin. This lethal dosage is injected 30 minutes after phenolic therapy. Immediately after injection of NaNO2, the animals are put in small cages and the time between injection of NaNO2 and cessation of breathing is measured.Several studies have shown that NaF

administration, which induce circulatory hypoxia, ,leads to increased blood histamine levels and decreased oxygen-carrying capacity.The results of the circulatory hypoxia are shown in Fig 2. Compounds showed weak activities in the circulatory model. Certain literature findings that flavonoids improve cerebral blood flow and possess antihypoxic activity confirm our performance (Hertog, Feskens, Kromhout, Hollman, & Katan, 1993). The mode of action of this defensive property may be due in part to the antioxidant activity of these phenolic acids.

As mentioned, *R. damascena* flowers have anthocyanins, terpenes, flavonoids and glycosides. Myrcene, kaempferol and quercetin are the major compounds. Myrcene or β-myrcene is a monoterpene. Its good antioxidant effects have caused anti-cancer effects. Studies show that it is safe up to levels1.23 μg/kg bw/day in humans (Surendran, Qassadi, Surendran, Lilley, & Heinrich, 2021). Kaempferol is a flavonoid with potent anti‑inflammatory activity. Also, it has beneficial effects against obesity and diabetes, cancer, liver injury,protects the cranial nerve and heart function(Ren *et al*., 2019).As a valuable natural flavonoid, quercetin modulates a variety of signaling pathways and targets to demonstrate bioactive properties, such as antibacterial, anticancer and antioxidant properties. (Alizadeh & Ebrahimzadeh, 2022).

So far, the antihypoxic effects of *Allium sativum*(Shahbazee, Mohammadyan, & Ebrahimzadeh, 2019), *Aloysia citrodora* (Hosseinzadeh & Ebrahimzadeh, 2019), *Crataegus microphylla*, *Crataegus pentaegyn*(M. A. Ebrahimzadeh *et al*., 2018b), *Delphinium elbursense*(M. Ebrahimzadeh, S. Nabavi, S. Nabavi, M. Mahmoudi, *et al*., 2010), *Eryngium caucasicum*(M Khalili *et al*., 2015), *Eriobotrya japonica*(Nabavi, Nabavi, Moghaddam, Hellio, & Ebrahimzadeh, 2015), *Hibiscus esculentus*(M. A. Ebrahimzadeh, Nabavi, Nabavi, & Eslami, 2010), *Hypericum scabrum*(Eslami, Nabavi, Nabavi, Ebrahimzadeh, & Mahmoudi, 2011), *Juglans regia*(Nabavi, Ebrahimzadeh, Nabavi, Mahmoudi, & Rad, 2011), *Myrtus communis*, *Sambucus ebulus*(Kaveh *et al*., 2019), *Urtica dioica*(M Khalili *et al*., 2015), *Vicia cracca*(Shahnazi & Ebrahimzadeh, 2017), and many other compounds have been reported.

Allium sativum flowers methanolic extract was able to show excellent antihypoxic effects at 125 mg/kg in haemic hypoxia ($P<0.001$), circulator hypoxia ($P<0.05$) and asphyctic hypoxia ($P<0.001$) compared to the control groups. In asphyctic hypoxia, its antihypoxic effects were almost equivalent to phenytoin (Shahbazee *et al*., 2019).

*Aloysia citrodora*extract at a dose of 250 mg/kg increased the survival time significantly compared to the control group in asphytic hypoxia ($p <0.001$) which was not significantly different from the effects of phenytoin as a positive control ($p>0.05$). On the other hand, the antihypoxic effects of this plant at a dose of 250 mg/kg were not only much more significant than the control group ($p <0.0001$), but also stronger than propranolol as a positive control in circulatory hypoxia model (Hosseinzadeh & Ebrahimzadeh, 2019).

In circulator hypoxia, *Crataegus pentaegyn* fruits extract was more effective at 100 mg/kg than *Crataegus microphylla* fruits extract. It increased the survival time in the experimental group ($P <0.001$). At the same dose, *C. microphylla* fruits extract increased the survival time ($P <0.001$). Both extracts had a significantly affected on survival time, even at a dose of 50 mg/kg in this model ($P <0.01$)(M. A. Ebrahimzadeh *et al.*, 2018b).

Good antihypoxic activity was reported in haemic hypoxia and circulator hypoxia from *Delphinium elbursense* aerial parts hydroalcoholic extract. These effects were strong and dose-dependent. The extract of this plant in the amounts of 1000 mg/kg increased the death time in haemic hypoxia and circulator hypoxia significantly ($P <0.001$)(M. Ebrahimzadeh, S. Nabavi, S. Nabavi, M. Mahmoudi, *et al*., 2010).

Hydroalcoholic extract of *Eriobotrya japonica* flower at a dose of 500 mg/kg in both haemic hypoxia ($p<0.001$) and circulatory hypoxia ($p<0.001$) had significant effects compared to the control group (Nabavi *et al.*, 2015).

Methanolic extract of *Hibiscus esculentus* seed in the amount of 1000 mg/kg increased the time of death in

haemic hypoxia and circulator hypoxia significantly (P <0.001)(M. A. Ebrahimzadeh *et al*., 2010).

However, the *Hypericum scabrum* aerial parts aqueous extract was effective in all three models (asphyctic, haemic, and circulator hypoxia). The extract of this plant increased the survival time in at 7.75, and 62.5 mg/kg, which is very significant. It also prolonged death time perfectly at a dose of 31.25 mg/kg in the other two models (P <0.001) (Eslami *et al*., 2011).

Methanolic extract of *Juglans regia* flowers also had good effects in both haemic hypoxia and circulator hypoxia models. The extract of this plant was able to increase the survival time at 125 mg/kg in haemic hypoxia and 250 mg/kg in circulator hypoxia (P <0.001)(Nabavi *et al.*, 2011).

Methanolic extract of *Myrtus communis* leaves had an amazing effect at a dose of 125 mg/kg in asphyctic hypoxia (P <0.001) compared to the control group and even phenytoin as a positive control. Also, at a dose of 62.5 mg/kg, this extract was able to increase the survival time in circulator hypoxia (P <0.001)(Kaveh *et al*., 2019).

The methanolic extract of *Vicia cracca* aerial parts (at a dose of 200 mg/kg) showed good effects in all three models (P <0.01) (Shahnazi & Ebrahimzadeh, 2017).

In conclusion, MRF showed good anti-hypoxic activity, especially inhaemic and circulatory models. It seems that the reported effects may be due to the wellantioxidant activity of this plant. However, more studies are recommended for the development of anti-hypoxic compounds.

Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

i.p.: Intraperitoneal

MRF: Methanolic extract of *R. damascena* flowers

ROS: Reactive oxygen species