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Therapeutic Effects of Hydro-alcoholic Extract of Papaver Rhoeas on Cardiovascular side effect of MIA Induced Osteoarthritis in male Rat

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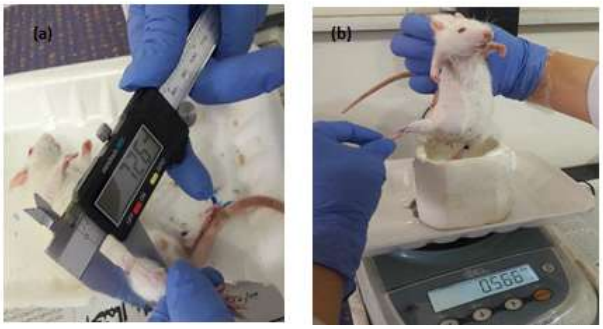
ABSTRACT

In this study 'Therapeutic Effects of Hydro-alcoholic Extract of Papaver Rhoeas on Cardiovascular side effect of MIA Induced Osteoarthritis in male Rat is investigated. OA model in 35 male rats was created by injection of monosodium iodoacetate(MIA) into the right knee joint and then gavage with extract of Papaver Rhoeas for14 days, on day 30 The veins and arteries of the animal were then for injection and then Blood pressure parameters (systolic, diastolic, mean arterial pressure) were recorded and analysis effect of cholinergic and niterergic system .The results were analyzed by SPSS software. The effect of oral extracts of Papaver Rhoeas (200 mg/kg Dosage) on Systolic, diastolic, mean arterial pressure (mmHg) and heart rate (Beat/min) reduced compared with negative group (P <0/05). According to findings, extract of Papaver Rhoeas has a decreasing effect on blood pressure in rats with OA and have been observed at 200mg/kg doses, the least joint damage and the best physiological function of the heart. This effect may be due to inhibition of the niterergic and cholinergic system.

GRAPHICAL ABSTRACT



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INTRODUCTION

Cardiovascular disease (CVD) is one of the causes of death worldwide. In the Western countries, more than one third and in Iran, 50% of the causes of death are among the country. Studies have shown that systemic and chronic inflammation can increase the risk of CVD. Osteoarthritis (OA) or arthritis is also a common degenerative disorder of the joint cartilage, with hypertrophic changes in the subchondral bone, which causes inflammation of the surrounding tissues. Knee osteoarthritis is the most common type and is the most important cause of chronic disability in the elderly. The most common symptom of osteoarthritis is joint pain. Since synovial inflammation plays a role in the initial stages of osteoarthritis, the side effects of OA are the incidence of CVD [1-3]. In addition, the first line of treatment for OA is the use of non-steroidal anti-inflammatory drugs (NSAIDs) which has a serious side effect on cardiovascular disease. Therefore, medicinal plants have modifying effect on blood pressure [4-6].

Papaver Rhoeas L. is one of the plants that has a variety of alkaloids and has a family affinity and similar effects on poppy and due to very small amount of morphine In the extract of this plant, it is called "harmless opium" [7-10]. Various drug properties have been reported, and active ingredients in Papaver Rhoeas include Papaverin, Anthocyanin, Reedin, Adipic acid, Papaveric acid, and Raugenine. Papaverin is one of the opioid alkaloids used to treat regurgitation, especially in the arteries of the heart. Palavering reduces the activity of the sodium-potassium pump. In addition, it inhibits phosphodiesterase enzyme [11-14].

From the late 20th century, the adverse and harmful effects of chemical drugs have led to revert to medicinal herbs. Therefore, the use of alternative methods, such as the use of medicinal plants, can prevent the side effects of it, and since the Papaver Rhoeas plant has a great therapeutic effect on regurgitation, and considering a study on the effect of oral extracts (Gavage) Papaver Rhoeas has not been reported on blood pressure and OA.

In a study by Abdi et al., They found that the aqueous alcoholic extract of wild anemone could inhibit the acute phase of the formalin test in mice by Opioidergic, Glutamatergic, and Nitrergic mechanisms. Is responsible for inhibiting inflammation in a study, Margulein et al. Showed that the cholinergic anti-inflammatory pathway plays an important role in reducing the inflammatory response in collagen-induced arthritis (CIA) 71. The effect of selective α7nAChR agonist was more effective than nicotine in improving the clinical symptoms of arthritis and reducing the incidence of arthritis in the form of delayed onset of the disease as well as the protective effect against joint destruction and lowering 78TNFα levels in serum and synovial tissue. The results of various studies have shown that the sympathetic nervous system delays the onset of osteoarthritis by activating anti-inflammatory mechanisms.

In this present study, decided to examine the effect of wild anemic extract on hypertension in rats with OA [15-18]. Therefore, at first material and method will describe. At second, Experimental Protocol, statistical analysis and result is written. At the end discussion and conclusion will be described [19-21].

MATERIALS AND METHODS

The Papaver Rhoeas flower was collected from the surrounding area of Shiraz and was identified by a botanical professor at the Faculty of Sciences of the University of Shiraz. To prepare the extracts the plant was then dried and Macerate in 70% ethanol for 72 hours and then incubator at 37 ° C for 72 hours.

Animal groups

35 Wistar male rats divided to the following groups:

Group 1. No OA, and no treatment;

Group 2. No OA but treated with 200 mg/kg Papaver Rhoeas daily for 2 week;

Group 3. MIA induced OA (1 mg Monosodium Iodoacetate in 0.9% saline) by a sterile needle G 27 on the knee joints in maximum flexion. Of course, in the absence of any damage to the subcondolar bone for one time;

Group 4. MIA induced OA as the 3rd group but treat with 10mg/kg celebrex;

Group 5. MIA induced OA and oral administration of 100mg/kg Papaver Rhoeas extract daily gavage for 2 week;

Group 6. MIA induced OA and oral administration of 200mg/kg Papaver Rhoeas extract daily gavage for 2 week;

Group 7. MIA induced OA and oral administration of 400mg/kg Papaver Rhoeas extract daily gavage for 2 week;

Experimental Protocol

35 Wistar male rats (30 days old) with a weight range of 100-150g for one week in light conditions (12 hours of light and 12 hours of darkness) and 22 ± 3 °C and water and food was available, after one week OA were induced in all of the above groups. Anesthesia was done by intraperitoneal administration of ketamine-xylazine (60-5) mg/kg respectively combination and sterilized the right knee of the rat with 100% ethanol and then induced cartilage deficiency by intravenous injection of 1 mg Monosodium Iodoacetate (MIA, MIA; sigma-ALDRICH, USA). After one week osteoarthritis model in each animals Extract of Papaver Rhoeas (100,200,400) mg/kg and celebrex (10 mg/kg) was gavage daily for 14 days. At the end of 4th week each animals were Anaesthetize by IP injection of urethane (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 1.2 g / kg and to prevent aspiration during anesthesia doing Tracheostomy. Then, the veins and arteries convalesce for injection and blood pressure record, respectively. An artery cannula was connected to the pressure transducer and Power Lab device (AD Instruments, Sydney, Australia). The Power Lab device was connected to a computer lab equipped with Lab Chart 7 (AD Instruments, Sydney, Australia). After the surgery, the animal was resting for an hour to get stable position. Then, in each groups, 20 minutes blood pressure was recorded for at first, After surgery to recorded interaction of cholinergic effect, the authors added Acetylcholine (Ach) and Acetylcholine with Papaver Rhoeas extract (Ach+ EX) respectively to all groups and after 1 hour recorded interaction of Nitrergic effect added Nitro-L-Arginine Methyl Ester (LNAME) and Nitro-L-Arginine Methyl Ester with Papaver Rhoeas extract (LNAME+ EX) respectively to all groups.

Knee Thickness Measurement

MIA-induced OA, thickness of rat knee was measured with Caliper and will be evaluated on days 1, 7, 14, 21 and 28 (Janet, 2004).the scoring in rats' knee diameters were following: 0.2 to 2 mm (score =01), 2.1 to 0.4 (score =02), 6.1 to 1 (score =03) and 6 to 8 (score =04) (Figure 1-b).

Rat leg weight measurement

Measurement of edema volume in aqueous container placed on the scales at equilibrium mass/specific gravity=volume (V). recording right foot (OA)and left foot(control)weight on days 1,7,14,21 and 28 The extent of edema at time t (measured as V) will be V(t)-V(o). In figure 1 a) Rat knee thickness measurement. b) Evaluation of rat foot weight with osteoarthritis is illustrated.

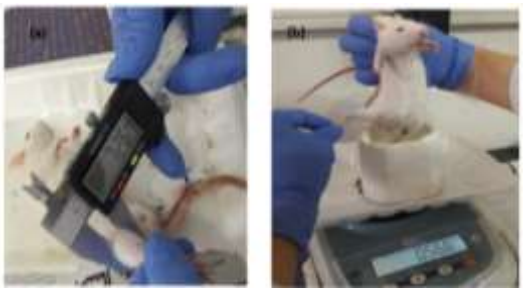

Fig. 1. a) Rat knee thickness measurement. b) Evaluation of rat foot weight with osteoarthritis

Statistical analysis

Statistics software (SPSS version 19.0) was used for statistical analysis. The data Represented mean ± standard error of the mean. Statistical calculations were analyzed by one way ANOVA followed by multiple comparison tests and for analysis of Rat knee thickness and rat foot weight using paired-samples T test. P value <0.05 were considered to be significant (P denoted probability).

RESULTS

As shown in Fig 2, the reduction in arterial pressure in response to oral administration of extracts at dose of 200 mg/kg is more significant than the other doses.

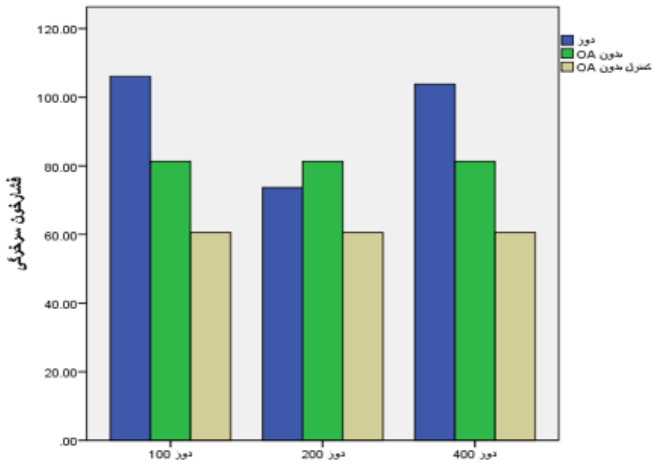

Fig. 2. Mean arterial pressure changes in response to administration of different doses of Papaver Rhoeas extract (100,200,400) mg/kg with compared to the Negative control and Normal groups

Part1. Effect of oral administration of Papaver Rhoeas extract

In Table 1, the mean arterial pressure, systolic, diastolic and Heart rate in the 200 mg/kg group was decrease compare to Negative control group.

Table 1. The effect of oral extracts of Papaver Rhoeas (200 mg/kg) on Systolic, diastolic, mean arterial pressure (mmHg) and heart rate (Beat / min) (N = 5) .

Parameters / Group	heart rate (Beat / min)	mean arterial pressure (mmHg)	Systolic (mmHg)	diastolic (mmHg)
Normal	296.30±25.81	107.78±5.75	126.09±4.76	98.63±3.88
Negative Control	364.39±12.41	128.91±5.46	164.99 ± 5.55^{a}	110.87±4.88
Positive Control	344.85±18.63	149.44±17.50	135.75±14.07	137.35±17.63
200 mg/kg Dosage	316.97±27.21	101.31 ± 7.36^{b}	114.95 ± 5.44^{b}	85.87±3.88

P<0.05 as compared negative group to Normal group; b. P<0.05 as compared the 200 mg/kg dose group with negative group.

According to table 1, the systolic, diastolic and mean arterial pressure and Heart rate increase to negative control compare to the normal group and all parameters decrease in 200 mg/kg dosage compare to the negative control group and in positive control except systolic pressure increase all parameters.

Part 2. Cholinergic Effect

According to Table 2, decreased systolic, diastolic and mean arterial pressure in response to ACH and ACH + Ex compared to negative and normal groups, but the Heart rate variable in both ACH and ACH + Ex groups increased compare to normal group.

Table 2: The effect of acetylcholine on Systolic, diastolic, mean arterial pressure (mmHg) and heart rate (Beat / min) (N = 5).

parameter / Group	HR (Beat / min)	MAP (mmHg)	Systolic (mmHg)	diastolic (mmHg)
Normal	296.30±25.81	107.78±5.75	126.09±4.76	98.63±3.88
negative group	364.39±12.41	128.91±5.46	164.99 ± 5.55	110.87±4.88
Ach	337.04±15.98	70.63 ± 4.33[a]	92.57 ± 6.32[a]	59.46 ± 4.40[a]
Ach + Ex	347.85±23.63	63.40 ± 8.17[b]	73.02 ± 7.61[b,c]	54.61 ± 8.02[b]

a. P<0.05 as compared to ACH group and normal group;
b. P<0.05 difference between ACH + Ex;
c. P <0.05 as compared ACH + Ex with normal group.

Part3. Niterergic effect

According to Table 3, systolic, diastolic and mean arterial pressure were decreased in response to LNAME and LNAME + Ex in compare with normal group but heart rate in both groups, LNAME and LNAME +Ex increased compared to the normal group.

Table 3. The effect of LNAME on Systolic, diastolic, mean arterial pressure (mmHg) and heart rate (Beat / min) (N = 5).

parameter / Group	HR (Beat / min)	MAP (mmHg)	Systolic (mmHg)	Diastolic (mmHg)
Normal	296.30±25.81	107.78±5.75	126.09±4.76	98.63±3.88
negative group	364.39±12.41	128.91±5.46	164.99 ± 5.55	110.87±4.88
LNAME	372.29 ± 7.24[a]	72.33 ± 2.91[a]	91.64 ± 2.80[a]	62.67 ± 3.19[a]
LNAME+ Ex	374.77 ± 11.11[b]	70.00 ± 2.71[b]	88.96 ± 2.82[b]	60.53 ± 2.90[b]

a. P<0.05 as compared to ACH group and normal group;
b. P <0.05 as compared ACH + Ex with normal group. Rat knee diameter and weight

Part4. Rat knee Diameter (ml) and weight

Effect of Celebrex and oral extract of Papaver Rhoas in 200mg/kg dose on knee inflammation as shown in table 4. As show in Table4, rat knee diameter increased in the celebrex administration group from day one until 14 and then in 21 day is similar range with compare to control group and rat knee weight increased from day one until 7 and then in14 day is similar range with compare to control group.

Table 4. Diameter and weight of the rat's knee in the Clebrex and 200mg/kg dose groups.

Day groups			-1	1	7	14	21
Normal	Knee diameter (ml)	Right	6.05 ± 0.40^{a}	6.08 ± 0.31^{a}	6.04 ± 0.33^{a}	6.03 ± 0.20^{a}	6.04±0.28
		Left	6.03±0.26	6.03±0.16	6.07±0.15	6.04±0.10	6.01±0.14
	Knee weight	Right	1.49 ± 0.50^{a}	1.47 ± 0.44^{a}	1.44±0.33	1.48±0.31	1.46±0.33
		Left	1.44±0.33	1.48±0.34	1.44±0.31	1.42±0.41	1.43±0.44
OA	Knee diameter (ml)	Right	6.05 ± 0.40^{a}	6.08 ± 0.31^{a}	6.04 ± 0.33^{a}	6.03 ± 0.20^{a}	6.04±0.28
		Left	6.03±0.26	6.03±0.16	6.07±0.15	6.04±0.10	6.01±0.14
	Knee weight	Right	1.49 ± 0.50^{a}	$1.47 \pm 0.44a^{a}$	1.44±0.33	1.48±0.31	1.46±0.33
		Left	1.44±0.33	1.48±0.34	1.44±0.31	1.42±0.41	1.43±0.44
Celebrex	Knee diameter (ml)	Right	6.08 ± 0.21^{a}	6.16 ± 0.30^{a}	7.01 ± 0.30^{a}	6.86 ± 0.22^{a}	6.23±0.26
		Left	6.09±0.22	6.08±0.17	6.35±0.14	6.34±0.13	6.21±0.15
	Knee weight	Right	1.46 ± 0.34^{b}	1.47 ± 0.54^{b}	1.73±0.43	1.82±0.41	1.64±0.43
		Left	1.45±0.44	1.49±0.54	1.54±0.41	1.62±0.40	1.49±0.42
200 mg/kg dose	Knee diameter (ml)	Right	6.10 ± 0.33^{b}	6.19±0.20	7.14±0.25	6.79±0.22	6.47±0.19
		Left	6.08±0.26	6.09±0.27	6.30±0.27	6.31±0.26	6.13±0.25
	Knee weight	Right	1.48 ± 0.54^{b}	1.48±0.40	1.79±0.37	1.81±0.37	1.60±0.38
		Left	1.36±0.04	1.35±0.18	1.46±0.17	1.52±0.19	1.44±0.18

a. P<0.05 as compared to right and left foot diameter;

b. P<0.05 as compared to right and left foot weight.

According to Table4, in Papaver Rhoeas extract group (200 mg/kg dose) increased knee weight and diameter from day one until 21compare to control group and least difference was observed on day 21.

4. Discussion

It's be due to the presence of Anthocyanin can reduce the risk of CVD and cause endothelial dysplasia The increase in hypertrophy phosphorylation in protein kinase C and the activation of protein kinase B Akt is due to the improvement of Arterial stiffness, that have a protective effect on the heart.

also This study showed that the Papaver Rhoeas extract can inhibit the process of OA significantly in Monosodium iodoacetate model rat (especially in dose 200 mg/kg) and The increased of edema and weight of joint inhibition of the Papaver Rhoeas extract showed that anthocyanin (is the active ingredient in the Papaver Rhoeas), had the anti-inflammation effect through the mechanism of action in inhibiting the activity of inflammatory cells and pro-inflammation cytokines in sodium iodoacetate model rat The Papaver Rhoeas extract used in the study was according to the previous studies and was explained that Papaver Rhoeas extract caused a significant decrease in proliferation in monkey kidney cancer cell line (IC50=80.07 µg/ml). The scavenging effect of the extract on DPPH• radical was found to be 5.74 µg/ml. The extract's ferric reducing ability of plasma was 2.663 ± 0.002 µg/ml. Also, the extract had more total phenolic content rather than flavonoid contents which make it relatively safe to use and in this study, increased blood pressure (mean arterial pressure, systolic and diastolic pressure) that can be related by the activity of the vagus nervosa, which significantly reduces the rate of heart rate and decreases cardiac contractility that it's similar to Tanaka (2016). On the other hand, acetylcholine released from the intermediate nerve terminals of muscarinic M2 receptors has opened up a series of potassium channels and increased potassium excretion and hyperpolarization of the action potential - producing nodes in the heart. Also, the nicotinic receptor (α7) α7nAChR is present in the synovial tissue. That has been shown for the synovial tissue of patients with OA which can produce topical acetylcholine in Inflammation of the joints is attributed to cholinergic system, which inhibits the production of inflammatory cytokines. In this study decreased systolic, diastolic and mean arterial pressure in response to ACH and ACH + Ex compared to control group, but the reduction of these variables in ACH+ Ex group was higher than ACH group that Indicates the Papaver Rhoeas extract have anti cholinergic effect.

It also The stimulation of articular chondrocytes by IL-1β or TNF-α has been described to allow the nuclear translocation of NF-κB p65, which then activates the expression of a wide range of catabolic genes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in chondrocytes, resulting in the production of destructive proteases and enhanced degradation of extracellular matrix. Cholinergic system in the arteries by the nitric oxide have a Vasodilation effect.

Previous studies have shown that inhibition of production of NO by L-NAME (inhibitors of NOS) in the vessels leads to increase blood pressure but in our study decreased blood pressure in response to LNAME and LNAME + Ex in compare with

normal group. The reduction of these variables in the LNAME +Ex was higher than the LNAME group, but heart rate In both groups, LNAME and LNAME +Ex increased compared to the normal group and the rate of this increase was higher in the LNAME +Ex that Indicates the Papaver Rhoeas extract have anti-niterergic effect. This finding are consistent with the research by Farokhi et al. (2017) and Reddy et al. (2007).

In conclusion, this study shows that oral administration of Papaver Rhoeas extract improve of OA inflammation side effects by inhibits cholinergic and niterergic system.

Conclusion

In this research shows Therapeutic Effects of Hydro alcoholic Extract of Papaver Rhoeas L on Blood Pressure of MIA Induced Osteoarthritis in male Rat. Hypertension is one of the most common and most prevalent diseases in the world today. Chronic inflammation is one of the risk factors for cardiovascular disease (CVD). Since synovial inflammation plays a role in the initial stages of osteoarthritis (OA), therefore, the side effects of OA are the incidence of CVD. One of the most appropriate methods for treating this disease is the use of medicinal herbs such as Papaver Rhoeas that have effect in blood pressure modifying. The present research shows Therapeutic Effects of Hydro-alcoholic Extract of Papaver Rhoeas L on Blood Pressure of MIA Induced Osteoarthritis in male Rat.

There is strong evidence that OA is an important risk factor for cardiovascular disease, also the first line of treatment for OA is the use of non-steroidal anti-inflammatory drugs (NSAIDs) Which has a serious side effect on CVD research about medicinal plants such as Papaver Rhoeas L that reduce inflammation in OA and modifying effect on blood pressure now discuss about this effect. In this study, a OA rat model induced by monosodium iodoacetate. Then in order to formed OA evaluate diameter and weight of the rat's knee on day 1, 7, 14 and 21and show that diameter and weight in OA group increase compare to normal group.

This study showed that systolic, diastolic, mean arterial pressure and heart rate increased in OA group (negative control) compared to normal group and Huston et al (2015) showed a relationship between severity of osteoarthritis and cardiovascular disease. As show in this study the treatment by the Celebrex due to increase the systolic, diastolic and mean arterial pressure and Heart rate compare to the normal group. However, oral administration of Papaver Rhoeas extract reduced the arterial pressure, systolic and diastolic pressure and increased heart rate compared to normal group and OA group. It can be due to the effect of oral extracts on cardiac output or changes in peripheral vascular resistance. Since oral extracts reduce systolic pressure compared to control and it can reduce cardiac output by decreasing volume Impact and ultimately reduced cardiac contractility. This effect may be due to the presence of palavering in Papaver Rhoeas. Also, the study by Marco et al as shown that the benefits of phosphodiesterase-2 inhibition are the effectiveness of diastolic function of the left ventricle, which is similar to our study.

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Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

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Disclosure Statement

The authors reported no potential conflict of interest.

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